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Acute Bacterial Meningitis at Boston City Hospital during 12 Selected Years, 1935–1972

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Data are presented on the occurrence of and mortality rate from acute bacterial meningitis at Boston City Hospital during 12 years between 1935 and 1972 selected in relation to the introduction of potent antibacterial agents. The most frequent causative organisms were *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae,* but large proportions were caused by other gram-positive cocci and gram-negative bacilli. The greatest reduction in mortality rate after antibiotics became widely used was in patients with meningococcal and influenzal meningitis who were ≤ 19 years old. Less striking reductions occurred in cases of other etiologies in patients ≤ 59 years old, but in those ≥ 60 years old, the mortality rate remained high, and the proportion of cases of meningitis in that age group more than doubled. Comparisons with similar data on all bacteremic infections are presented.

The occurrence and mortality of cases of bacteremic infections due to clinically important pathogens at Boston City Hospital (Boston, Mass.) during 12 selected years between 1935 and 1972 were reported recently [1]. Striking changes occurred in the incidence of all bacteremic infections and in the relative incidence of those due to some specific bacterial pathogens over the nearly four decades of that study. During that period numerous antibacterial drugs that are highly active therapeutically against narrow, broad, and medium spectrums of bacterial infections were introduced and became extensively used in hospitals, and most of them also were used by physicians outside of hospitals. A similar study of the occurrence, mortality, and some other important features of bacteriologically authenticated cases of acute pyogenic meningitis at the same hospital during the same 12 selected years is reported in this paper.

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Materials and Methods

The hospital records were examined of all patients admitted to the Boston City Hospital during the 12 selected years in whom a clinical diagnosis of meningitis was made and bacteriological examination of cerebrospinal fluid (CSF) revealed a significant bacteriological pathogen. The years were chosen to reflect the impact of the successive introduction and widespread use of major new and effective antibacterial agents on the ecology of serious bacterial infections: 1935, before sulfonamides; 1941, after sulfonamides; 1947, after penicillin and streptomycin; 1951, after the first tetracycline, chloramphenicol, polymyxin, and bacitracin; 1953, after erythromycin; 1955 and 1957, before kanamycin and penicillinase-resistant and "expanded-spectrum" penicillins; 1965, 1969, and 1972, after cephalosporins and gentamicin.

For this study records (including autopsy records) were analyzed of those patients in whom the results of cytological and chemical studies of the CSF and whose clinical and/or anatomical features were consistent with the diagnosis of acute bacterial (pyogenic) meningitis. The results of bacteriological examinations of all other specimens submitted from these patients were also obtained from the Laboratory of Medical Microbiology of the hospital. Although specimens of blood had been submitted for culture during

life or at autopsy in nearly all of the patients, the results were considered unsatisfactory in some because cultures were contaminated, and in others because there was too long an interval between the times that the blood and the diagnostic CSF were obtained for culture, or because one or both of the specimens were obtained after appropriate antibacterial therapy. A large number of cases that were included in an earlier report [2] covering the first seven selected years ending in 1957 are excluded from the present study because closer scrutiny of the available data indicated that the etiologic agent and/or the diagnosis of purulent meningitis in each case could not be authenticated according to the criteria used in this report. However, all of the cases due to *Streptococcus pneumoniae,* nonenterococcal β-hemolytic streptococci, *Neisseria meningitidis,* or *Haemophilus influenzae* in that earlier report did satisfy these criteria and are included here.

A few patients whose smears of CSF were positive and cultures showed no growth, generally after some antibacterial therapy, but whose blood cultures were positive for a morphologically compatible organism were included as having meningitis due to the same organism. Adequate anaerobic cultures were not done throughout most of the years of the study so that essentially only facultative aerobic or microaerophilic bacteria were identified. All streptococci other than β-hemolytic streptococci or enterococci were classified for convenience as viridans streptococci. Serological typing of pneumococci and meningococci was done by capsular swelling with type- or group-specific antisera. Isolation and identification of bacteria were done by, or under the direction of, A. Kathleen Daly and Alice McDonald (Boston City Hospital).

Meningitis was considered to be community-acquired (C-A) if the first positive culture of CSF was obtained on or within 48 hr after admission to the hospital. The meningitis was considered to be hospital-acquired (H-A) if symptoms and/or signs of meningeal irritation began after admission to the hospital, or if CSF on admission was normal and showed no growth, but specimens subsequently obtained were positive. In 12 (2%) of the cases, blood cultures taken before appropriate therapy was instituted were positive (10 for *S. pneumoniae* and one each for *N. meningitidis* and *H. influenzae*), and a gram stain of the first CSF sample obtained later showed morphologically compatible organisms. The 30 cases of meningitis in babies born in the hospital and those that occurred after neurosurgical operations were considered to be H-A. The therapy used in these cases was reviewed and, in general, could be considered as appropriate at the time but will not be considered.

Results

A total of 572 patients with acute bacterial (purulent) meningitis satisfied the criteria for inclusion in this study. The distribution of causative organisms identified in the initial positive culture of CSF in these cases during each of the 12 selected years of the study is shown in table 1. The total number of authenticated cases increased during the first three years from 46 in 1935 to 82 in 1947 but then ranged between 42 and 54 during the next seven selected years (to 1965) and declined steadily after that to 38 and 22 cases in 1969 and 1972, respectively. The number of patients admitted annually to Boston City Hospital declined progressively after 1951 but most rapidly after 1965 [1]. The highest incidence of authenticated bacterial meningitis was 2.1 cases per 1,000 admissions in 1947, but the rate fluctuated after that and declined in the last three years to 1.1 per 1,000 in 1972. The most frequent organisms were *S. pneumoniae* (pneumococcus), *N. meningitidis* (meningococcus), and *H. influenzae;* together they accounted for 65.5% of all cases. *Staphylococcus aureus* and β-hemolytic streptococci, other than enterococci, together accounted for 12.7% of cases. However, more than half of the cases due to hemolytic streptococci but only one-seventh of those caused by *S. aureus* occurred during the first two years selected for the study. Viridans streptococci, *Staphylococcus epidermidis,* and enterococci together accounted for 7% of the total.

Escherichia coli was the most frequent of the gram-negative bacilli (gram-negative rods by current taxonomy) identified in the first positive culture of CSF; *Pseudomonas aeruginosa, Proteus* species, *Klebsiella pneumoniae, Enterobacter* species, and *Herellea vaginicola* (*Acinetobacter calcoaceticus*) ranked next in that order.

Table 1. Numbers of patients with acute bacterial meningitis at Boston City Hospital during 12 selected years, 1935–1972.

Causative organism	No. of patients for indicated year												Total no. of patients (12 years)	Percentage who lived	Percentage of 572 patients	Percentage of 289 patients who lived
	1935	1941	1947	1951	1953	1955	1957	1961	1963	1965	1969	1972				
Streptococcus pneumoniae	21	20^{3}	22^{4}	24^{7}	14^{7}	16^{7}	5^{3}	17^{6}	16^{9}	18^{5}	13^{7}	7^{3}	193^{61}	31.6	33.7	21.1
Hemolytic *Streptococcus**	8^{2}	9^{2}	2	1^{1}	0	0	0	2^{2}	3	4	1^{1}	1	31^{8}	25.8	5.4	2.8
Viridans streptococci	2	2	2^{1}	2^{1}	1	0	3^{2}	2^{1}	0	2^{2}	1	0	17^{7}	41.2	3.0	2.4
Enterococcus	0	0	3^{1}	1^{1}	2^{1}	0	1^{1}	1	1	0	0	0	9^{4}	44.4	1.6	1.4
Staphylococcus aureus	1	5^{1}	6^{3}	5^{1}	2^{1}	7^{3}	3^{1}	2^{1}	5^{2}	2	3^{1}	1^{1}	42^{15}	35.7	7.3	5.2
Staphylococcus epidermidis	2^{2}	2^{1}	4^{4}	1	0	2^{2}	1^{1}	0	0	0	1^{1}	0	13^{11}	84.6	2.3	3.8
Neisseria meningitidis	4^{1}	9^{8}	14^{11}	9^{8}	13^{11}	14^{12}	15^{14}	5^{4}	6^{4}	4^{3}	5^{5}	2^{2}	100^{83}	83.0	17.5	28.7
Haemophilus influenzae	5^{1}	6^{3}	14^{11}	3^{3}	6^{6}	5^{5}	8^{8}	10^{10}	7^{7}	9^{8}	4^{4}	5^{5}	82^{71}	86.6	14.3	24.6
Escherichia coli	1	3^{1}	6^{1}	1^{1}	1	1^{1}	3^{1}	2^{1}	0	5	0	1	24^{6}	25.0	4.2	2.1
Klebsiella pneumoniae	0	0	2	0	0	0	0	0	1^{1}	2^{1}	2	2^{1}	9^{3}	33.3	1.6	1.0
Enterobacter	0	0	0	0	1^{1}	1	0	0	2^{1}	0	0	1^{1}	5^{3}	60.0	0.9	1.0
Proteus	0	0	1^{1}	2	1^{1}	0	0	1^{1}	1	3^{1}	4^{3}	0	13^{7}	53.8	2.3	2.4
Pseudomonas aeruginosa	1^{1}	0	1	1	2^{1}	2^{1}	1	0	1	2^{1}	1	2^{1}	14^{5}	35.7	2.4	1.7
Others (single)†	0	0	2	0	0	1	0	0	2^{1}	2^{1}	2^{1}	0	9^{3}	33.3	1.6	1.0
Mixed infections‡	1	0	3	2	0	0	2^{1}	1^{1}	0	1	1	0	11^{2}	18.2	1.9	0.7
Total§	46^{7}	56^{19}	82^{37}	52^{23}	43^{29}	49^{31}	42^{32}	43^{27}	45^{25}	54^{22}	38^{23}	22^{14}	572^{289}	50.5	100	100
Survival rate (%)	15.2	33.9	45.1	44.2	67.4	63.3	76.2	62.8	55.6	40.7	60.5	63.6	50.5			
Rate per 1,000 admissions‖	1.17	1.30	2.13	1.32	1.14	1.41	1.25	1.36	1.36	1.65	1.48	1.04				

NOTE. Superscripts indicate numbers of patients who lived.

*1963: one group B and one group G. 1965 and 1969: group B.

†1947: one each *Salmonella enteritidis* and *Salmonella typhimurium*. 1955: *Listeria monocytogenes*. 1963: *Herellea vaginicola (Acinetobacter calcoaceticus)*. 1965: one *H. vaginicola* (lived) and one *Serratia marcescens*. 1969: one *L. monocytogenes* (lived) and one *H. vaginicola*.

‡More than one organism in the first positive sample of cerebrospinal fluid, as listed in table 2, but not included among the individual organisms.

§Mean = 48^{24} for the 12 selected years.

‖Mean = 1.39 for the 12 selected years.

Mixed infections, with more than one organism identified in the first positive culture of CSF, occurred in 11 patients; the organisms and some relevant data in those cases are listed in table 2.

Superinfections with organisms other than those in the original positive culture of CSF were demonstrated in 35 patients, generally after initiation of antibacterial therapy. The original and the superinfecting organisms identified in these cases and some other relevant data are listed in table 3. The superinfecting organisms included gram-negative bacilli in 26 cases, staphylococci in 15, streptococci in 10, and more than one organism in 13 cases. The initial infection was present on admission (C-A) in 17 of the patients, but in 18 it was acquired in the hospital (H-A). In nine of the latter, the superinfection occurred in the last few hours of life and was considered a "terminal" event. Of the 35 patients, 28 (80%) died, as compared with 44 deaths among the 81 originally H-A cases (54%) who were not superinfected ($\chi^2 = 5.8$; $P < 0.05$).

Survival after meningitis. Table 1 also lists (as superscripts) the number of patients in each category who survived and were discharged from the hospital; these include the patients with residual neurological defects which are not considered in detail in this report. The rate of survival among all cases increased more or less steadily each year from about 15% in 1935 to 76% in 1957, but in the last five selected years, it ranged between 41% and 64%. The highest survival rates were in patients with meningitis due to *H. influenzae* (87%), *N. meningitidis* (83%), and *S. epidermidis* (11 survivors among 13 patients, 85%). There was only one death among 57 patients with *H. influenzae* meningitis during the last nine selected years of this study, and nearly all of the patients who died of meningococcal meningitis after 1935 had fulminating disease (Waterhouse-Friderichsen syndrome) and died within 36 hr after admission.

Among the 41 patients with pneumococcal meningitis admitted in the two years before penicillin became available, only three (7%) survived; after that the rate of survival in different years ranged between 18% and 66%, and most of the fatalities occurred within the first two days. Of the 42 patients with *S. aureus* meningitis, 36% survived; among the 31 cases due to nonenterococcal hemolytic streptococci, 26% survived, and of the 26 patients with meningitis caused by other streptococci, 42% survived. One-fourth of the patients with *E. coli* meningitis survived.

Table 2. Mixed infections detected in culture of initial samples of cerebrospinal fluid (CSF).

Year-case no.	Sex, age (years)	Type of infection*	Organisms in first positive CSF culture	Relevant clinical features†	Outcome
35-8	M, 11/12	C-A	*Streptococcus pneumoniae* type 6 + *Staphylococcus aureus* + *Escherichia coli*	Terminal; burns	Died
47-59	M, 60	H-A, 11	Hemolytic *Streptococcus* + *S. aureus* + enterococcus	After neurosurgery (9)	Died
47-61	F, 63	H-A, 141	*S. aureus* + enterococcus	Addict; endocarditis?	Died
47-82	M, 94	H-A, 6	*S. aureus* + enterococcus	Acute and chronic pyelonephritis	Died
51-3	M, 12 days	C-A	*E. coli* + viridans *Streptococcus*	Meningomyelocele (infected)	Died
51-55	M, 84	C-A	*Enterobacter aerogenes* + *Proteus*	Infected cerebral infarct	Died
57-24	M, 39	H-A, 5	*S. aureus* + *E. coli*	*S. aureus* sinusitis; *E. coli* otitis	Died
57-28	M, 46	H-A, 7	*E. aerogenes* + *Proteus*	Fractured skull, after neurosurgery (6)	Lived
61-5	F, 6/12	H-A, 65	*E. coli* + *Proteus*	After neurosurgery (6)	Lived
65-42	F, 67	H-A, 22	*S. pneumoniae* + hemolytic *streptococcus*	Cancer of maxilla	Died
69-41	M, 26	C-A	*Klebsiella pneumoniae* + *Enterobacter cloacae* + *E. coli*	Diabetic coma, brain abscess	Died

*C-A = community-acquired; H-A = hospital-acquired. Number indicates hospital day of first positive CSF.
†Number denotes days from operation to first positive CSF.

Table 3. Superinfections detected by culture of cerebrospinal fluid (CSF) in cases of bacterial meningitis at Boston City Hospital during 12 selected years, 1935–1972.

Year-case no.	Sex, age (years)	Type of infection*	Organism(s) in first positive CSF culture†	Interval (days)‡	Other organisms cultured from CSF†	Relevant clinical feature(s)§	Outcome
35-20	M, 12	H-A, 13	SA	2	SH	After neurosurgery (2), brain abscess	Died
35-22	F, 17	C-A	SH	4, 30	SA, EC	Fracture, after neurosurgery (1), brain abscess	Lived
35-32	F, 39	H-A, 10	HI	24, 29	EC + SE, Pr	Sinusitis, after neurosurgery (10), brain abscess	Lived
35-36	F, 50	H-A, 2	SV	52	EC	SBE, embolus, terminal	Died
35-44	M, 65	C-A	SV	2	EC + SA	Brain abscess, lung abscess	Died
41-9	M, 1 2/12	C-A	HI	10	SV	After three negative CSF cultures	Lived
41-23	M, 27	H-A, 22	SH	9	SA	After neurosurgery (18)	Died
41-44	M, 56	H-A, 19	SP, 8	8	PA	Acute bacterial endocarditis, terminal	Died
47-9	M, 4/12	C-A	SP, 33	6	Enc	Terminal	Died
47-13	M, 6/12	C-A	NM, B	1	SA + EC	Waterhouse-Friderichsen syndrome, terminal	Died
47-36	M, 27	C-A	HI	22	Enc	Pituitary tumor	Died
47-52	F, 56	C-A	SA	2	Enc + Pr	Otitis, brain abscess	Died
47-59	M, 60	H-A, 11	SH + SA	3	EC + SV	After neurosurgery (2)	Died
47-62	M, 63	H-A, 5	EC	1, 3	SA, SE	Osteomyelitis of skull	Lived
47-63	M, 64	C-A	SP, 7	6	UGN	Terminal	Died
51-25	M, 42	H-A, 3	SP, 18	13	SA + EC + Enc	Acute bacterial endocarditis, terminal	Died
51-27	M, 54	C-A	SP	8	SA + PA	Necrotizing pneumonia, terminal	Died
51-28	M, 50	H-A, 43	PA	17	SA	Head injury, after neurosurgery (1)	Died
51-51	F, 72	H-A, 12	SA	1	EC	Terminal	Died
51-52	F, 78	C-A	SP	1	SA + EC + EA	Peritonitis, terminal	Died
53-28	F, 61	C-A	SP, 20	1	EC	*E. coli* in both lungs	Died
55-26	M, 41	C-A	SP, 13	3	EC + Enc + EA	Operated brain tumor 10 months earlier	Died
55-28	F, 46	C-A	SP, 29	1	PA	Perforated gastric ulcer	Died
55-30	M, 55	H-A, 32	SA	5	EA	After neurosurgery (27)	Died
55-35	M, 67	H-A, 19	SE	18	Pr	After neurosurgery (4)	Lived
57-19	M, 2 1/2	C-A	NM	7	Pr		Lived
57-28	M, 48	H-A, 7	EA + Pr	10	SA	Compound fracture, after neurosurgery (1)	Lived
61-10	M, 2	C-A	SP	19	Enc + EA	Terminal	Died
61-25	F, 42	H-A, 5	SV	4	SA	After neurosurgery (1), brain tumor	Died
63-26	M, 47	H-A, 10	HV	8	SA	Skull fracture, after neurosurgery (4)	Died
63-29	M, 41	H-A, 9	Enc	5	EA	Chronic pyelonephritis	Died
65-6	F, N‖	H-A, 9	EC	12	Enc + EA	Meningomyelocele	Died
65-34	F, 59	C-A	SP, 3	5	SA	Terminal	Died
69-1	F, 2/12	H-A, 62	EC	17	SA	Peritoneal shunt (15)	Died
69-29	M, 42	C-A	SP, 10	12	SM	Terminal pneumonia and bacteremia	Died

*C-A = community-acquired; H-A = hospital-acquired (refers to first positive culture of CSF). Number is hospital day of first positive CSF culture.

†SA, *Staphylococcus aureus;* SH, hemolytic *Streptococcus,* not group D; HI *Haemophilus influenzae*; SV viridans *Streptococcus*; SP, *Streptococcus pneumoniae*; NM, *Neisseria meningitidis*; EC, *Escherichia coli*; PA, *Pseudomonas aeruginosa*; SE, *Streptococcus epidermidis*; EA, *Enterobacter aerogenes*; Pr, *Proteus* species; HV, *Herellea vaginicola (Acinetobacter calcoaceticus)*; Enc, enterococcus; UGN, unidentified gram-negative bacilli; SM, *Serratia marcescens*. Number or letter after species designation represents serologic type or group.

‡Days between CSF cultures with indicated results.

§Numbers in parentheses indicate days from operation to first positive CSF culture.

‖N = newborn.

but the rate of survival was higher (42%) among the 48 patients with infections due to other gram-negative bacilli, which include seven of the nine species listed as "other organisms." Only two (18%) of the 11 patients with mixed infections and seven (20%) of the 35 patients with superinfections survived.

H-A bacterial meningitis. Among the 572 patients with authenticated acute bacterial meningitis, 134 were considered to have acquired their

initial meningeal infection in the hospital. Including the 35 patients with superinfections, 29.6% of the cases could be considered H-A. The distribution of the "primary" H-A cases in each year according to the causative organism identified in the first positive culture of CSF is shown in table 4. The proportion of cases that were H-A in the different years of the study varied between 12% in 1955 and 31% in 1963 and averaged 23.3% for the 12 years. The proportion varied more widely among cases with different etiology. Only 1% of the cases of meningococcal meningitis and 6% of the cases of pneumococcal meningitis and of those due to *H. influenzae* were H-A, whereas from nearly one-half to about two-thirds of those due to hemolytic streptococci, staphylococci, *E. coli,* and *K. pneumoniae* and more than three-fourths of those caused by enterococci and by several gram-negative bacilli were H-A.

Occurrence and significance of bacteremia. Bacteremia among the patients studied is summarized in table 5. Nearly two-thirds of the patients in this study had reports of satisfactory blood cultures; the proportion with satisfactory cultures was lowest (55%) among those with meningitis due to gram-negative bacilli or miscellaneous organisms, highest among those with meningitis due to *H. influenzae* or *S. pneumoniae* (77% and 71%, respectively), and about 60% in those with meningitis due to other gram-positive cocci or *N. meningitidis.*

It is interesting that, among all the patients with meningitis due to gram-positive cocci (in-

Table 4. Cases of acute bacterial meningitis acquired during hospitalization at Boston City Hospital during 12 selected years, 1935–1972.

	No. of patients in indicated year(s)								
Causative organism	1935	1941	1947	1951–1957 (four years)	1961–1972 (four years)	Total no. of patients (12 years)	Percentage who survived	Percentage of cases*	Percentage of survivors†
Streptococcus pneumoniae	4	3	2	1	2^1	12^1	8.3	6.2	1.6
Hemolytic *Streptococcus*‡	3^1	6	0	0	6^2	15^3	20	48.4	37.5
Viridans streptococci	1	1	0	1	2	5	0	29.4	0
Enterococcus	0	0	2^1	3^3	2	7^4	57.1	78	100
Staphylococcus aureus	1	4^1	2^1	10^3	9^4	26^9	34.6	61.9	60.0
Staphylococcus epidermidis	1^1	1^1	3^3	2^2	1^1	8^8	100	61.5	72.7
Neisseria meningitidis	0	0	0	0	1^1	1^1	100	1.0	1.2
Haemophilus influenzae	3^1	0	1^1	1^1	0	5^3	60	6.1	4.2
Escherichia coli	0	1	3	1	7^1	12^1	8.3	50	16.7
Klebsiella pneumoniae	0	0	0	0	4^2	4^2	50	44	67
Enterobacter	0	0	0	1	3^2	4^2	50	80	66.7
Proteus	0	0	1^1	3^1	7^4	11^6	54.5	84.6	85.7
Pseudomonas aeruginosa	0	0	1	6^2	5^2	12^4	33.3	85.7	80
Herellea vaginicola (Acinetobacter calco-aceticus)	0	0	0	0	3^2	3^2	66.7	75	100
Others (single)§	0	0	1	0	1^1	2^1	50	33	100
Mixed infections‖	0	0	3	2^1	2^1	7^2	28.6	63.6	100
Total#	13^3	16^2	19^7	31^{13}	55^{24}	134^{49}	36.6	23.4	17.0
Survival rate (%)	23.1	12.5	36.8	41.9	43.6	36.6			
No. with superinfections**	3^1	2	2	6^2	5	18^3	15.8	54.3	50

NOTE. Superscripts indicate numbers of patients who lived.

*Refers to all cases with the same causative organism(s) (listed in table 1).

†Refers to all survivors among cases with the same causative organism(s).

‡1961–1972: two group B (one lived) and one group G (lived).

§1947: *Salmonella typhimurium.* 1961–1972: *Listeria monocytogenes.*

‖More than one organism in the first sample of CSF (as listed in table 3).

#Mean = 11^4 for the 12 selected years.

**Superinfections in patients whose meningitis was originally hospital-acquired.

Table 5. Occurence of bacteremia in patients with acute suppurative meningitis at Boston City Hospital during 12 selected years. 1935–1972.

Organism(s) in initial positive culture of CSF	No. of patients with satisfactory blood culture (%)*	Same organism in blood culture†		
		Positive	No growth	Percentage positive
Streptococcus pneumoniae	137 (24)	81/116 (76)	16/21 (76)	85
Other gram-positive cocci	67 (12)	26/42 (62)	15/25 (60)	63
Neisseria meningitidis‡	59 (10)	13/45 (29)	0/14§	76
Haemophilus influenzae	63 (11)	5/54 (9)	1/9 (11)	86
Gram-negative bacilli and miscellaneous	45 (8)	28/32 (88)	7/13 (63)‖	71
Total	371 (65)	153/289 (53)	39/82 (48)	78

*Blood was obtained within two days of the first positive culture of cerebrospinal fluid (CSF). Numbers in parentheses are percentages of all patients.

†Among satisfactory blood cultures. First two columns are given as number of deaths/number of patients (percentage).

‡Of the 43 cases of meningococcal meningitis at Boston City Hospital during September 1940 to August 1942 reported by Smith et al. [3], the blood cultures were satisfactory for 32, of which 16 (50%) were positive for *N. meningitidis*.

§$\chi^2 = 3.64$.

‖$\chi^2 = 4.37; P < 0.05$.

cluding *S. pneumoniae*) and *H. influenzae*, the mortality rate was about the same in those with blood cultures positive for the same organism as was demonstrated in CSF and in patients whose blood cultures yielded no growth. However, among the 45 cases of meningococcal meningitis with meningococcemia, there were 13 deaths (29%), nearly all fulminating cases of Waterhouse-Friderichsen syndrome, whereas there were no deaths among the 14 patients with meningitis due to *N. meningitidis* in whom the blood culture showed no growth. Also, the mortality rate in patients with meningitis with bacteremia due to gram-negative bacilli or miscellaneous organisms was higher (88%) than in the corresponding cases with negative blood cultures (63%).

Meningococcemia without meningitis. The occurrence of cases of bacteremic infections with *N. meningitidis* was not specifically analyzed in the recent report on bacteremia at Boston City Hospital during the 12 selected years 1935–1972 [1]. There were 46 such cases; seven (15%) of these patients died, all with fulminating cases of Waterhouse-Friderichsen syndrome.

Serological groups of N. meningitidis. Specific serologic typing of strains of meningococci was performed irregularly. The results in those strains that were classified are listed in table 6; 43

Table 6. Specific serologic groups of *Neisseria meningitidis* identified in cases of meningitis and of meningococcemia without meningitis at Boston City Hospital during selected years.

Year(s)*	Cases of meningitis			Cases of meningococcemia without meningitis			Total
	Group A	Group B	Group C	Group A	Group B	Group C	
1941	1	0	0	0	0	0	1
1941–1942†	20	6	3	6	1	0	36
1947	4	0	0	1	1	0	6
1965‡	0	2	0	0	0	0	2
1969	2	1	2	0	2	3	10
1972	0	2	0	0	1	0	3
Total	27	11	5	7	5	3	58

*In the years through 1947, groups A, B, and C were identified as groups I, II, and III, respectively.

†Cases reported by Smith et al. [3]. During these years strains from seven cases of meningitis and from one case of meningococcemia failed to react with antisera of any of the three groups.

‡Of 46 strains isolated in 1964 (38 from nasopharyngeal cultures, five from cerebrospinal fluid, two from blood, and one from conjuctival exudate), all but one were group B [4].

of the strains were from CSF of patients with meningitis, and 15 were from the blood of patients with meningococcemia without meningitis. Group A (formerly type I) was predominant in the early years and included 32 (74%) of the 43 strains classified during those years. During the last three selected years, group B (formerly type II) was the most frequent and accounted for eight of the 15 strains, and groups A and C accounted for two and five strains, respectively. In a separate study of strains of *N. meningitidis* isolated at this hospital during 1964, all but one of 46 strains were identified as group B. These strains included only five strains isolated from CSF and two from the blood of patients without meningitis; the others were from nasopharyngeal cultures, except one which was from conjunctival exudate [4].

Types of pneumococci. Specific serotyping was carried out on the strains of *S. pneumoniae* isolated from all but seven of the 193 cases of pneumococcal meningitis. Specific types were identified for strains from 158 patients, whereas 23 strains, all isolated in 1961 and 1963, were identified only with pooled antisera. Seven strains were not subjected to typing, and only five failed to react with any of the single or pooled type-specific antisera.

The results are listed in table 7. Thirty-three different serotypes were identified among the 158 strains classified with the type-specific antisera. The seven most frequent were types 3, 4, 8, 18, 6, 2, and 12, in that order, and together accounted for 51% of the strains with specific types.

Endocarditis and meningitis. We previously reported the changes in etiology and mortality of bacterial endocarditis for selected years between 1933 and 1965 [5]. In the present study, a diagnosis of acute or subacute vegetative bacterial endocarditis was made during life or at autopsy in 21 of the patients with bacterial meningitis. The causative organisms were *S. pneumoniae* in 13, superinfected with *S. aureus* in one and with enterococcus in one; *S. aureus* alone in two, mixed with enterococcus in one, and superinfected with *Enterobacter aerogenes* in one; viridans streptococci in two; *S. epidermidis* in one; and *Salmonella enteritidis* in one.

Three of the 21 patients recovered. One of the three had type 4 pneumococci recovered from blood and from a septic joint. A second patient also had *S. pneumoniae* type 4 on repeated occasions and recovered; after repeatedly negative results from blood cultures over a period of four weeks, the patient had a subarachnoid and intraventricular hemorrhage and died. At autopsy there were healed vegetations from which enterococcus but no pneumococcus was cultured. The third patient had subacute bacterial endocarditis with repeated positive blood cultures for viridans streptococci and changing murmurs over several weeks with recovery after prolonged therapy.

Autopsies were performed and confirmed the diagnosis in 17 of the 18 fatal cases. In one patient, a 72-year-old male, cultures of CSF and blood were repeatedly positive for *E. aerogenes* after which they were negative for several days. The patient again became febrile and developed meningitis, with *S. aureus* cultured repeatedly from both blood and CSF over a period of three days before he died.

Cultures from other sites. In a larger proportion of the patients, the causative organism of

Table 7. Specific serotypes of *Streptococcus pneumoniae* identified in the cerebrospinal fluid of patients with meningitis at Boston City Hospital during 12 selected years, 1935–1972.

Type(s) or pool(s)*	No. of patients
3	17
4	15
8	13
18	10
6	9
2, 12	8 each
B	7
9	6
7, 14, 20, 23, 24, C	5 each
10, 13, 19, 34, A, E	4 each
5, 10a, 17, 25, 33	3 each
1, 11, 15, 22, 29, D	2 each
16, 27, 28, 31, 32, 40a, F	1 each
Nontypable	5
Not typed	7
Total	193

*Pooled antisera used without further type speciation (in 1961 and 1963) were obtained from the Center for Disease Control, Atlanta, Ga., and included the following types: A: 1, 2, 7; B: 3, 4, 5, 6, 8; C: 9, 12, 14, 15, 17, 33; D: 10, 11, 13, 20, 21, 24; E: 16, 18, 19, 21, 28; F: 23, 25, 27, 29, 31, 32.

the meningitis was also isolated from sites other than CSF or blood. The number of cases with isolates from the various body sites are listed for each of the etiologic groups in table 8. Most of these isolates were from various parts of the respiratory tract, and many were isolated at autopsy. Most of those from sites other than the respiratory tract were gram-positive cocci (other than pneumococci) or gram-negative bacilli.

Distribution by age and sex and mortality rate. These data are summarized in table 9. Males predominated among cases of all etiologic categories and in each age group, but particularly among young (20–39 years) and middle-aged (40–59 years) adults. However, females predominated among the cases of *H. influenzae* meningitis, and the sexes were evenly distributed in the patients with pneumococcal meningitis who were ≥ 70 years old.

The case-fatality ratio (CFR) for cases of all etiologic categories combined was 35.6% for infants (less than one year old), and 21.1% for children one to nine years of age; thereafter the CFR increased more or less steadily with increasing age. The same general trend was true for both males and females in the various etiologic categories, except that among the cases of meningitis due to gram-positive cocci, including *S. pneumoniae,* the mortality rate was lowest in infants, but the numbers of cases in that age group are small. The mortality rate in the 146 males ≤ 19 years old (35.6%) was significantly higher than in the 113 females of that age group (21.2%) ($P < 0.05$). In the other age groups, CFRs were the same for males and females.

Age distribution and mortality in two etiological categories. In table 10 the mortality in each age group among cases of meningitis due to *N. meningitidis* and *H. influenzae* is compared with that in cases due to all other bacteria for the 12 selected years. Nearly three-fourths of the patients in the first group were under 10 years of age, and only 6% were ≥ 60 years old, whereas less than one-fourth of the second group were younger

Table 8. Isolation of the causative organism from sites or sources other than cerebrospinal fluid (CSF) or blood from patients with meningitis at Boston City Hospital during 12 selected years, 1935–1972.

	Same organism as in CSF					
Site or source*	*Streptococcus pneumoniae*	Other gram-positive cocci	*Neisseria meningitidis*	*Haemophilus influenzae*	Gram-negative bacilli and miscellaneous	Total
Ear or mastoid	16 (3)	9	1	1 (3)	2	29 (6)
Nose and/or throat	25 (4)	9 (1)	12 (6)	23 (12)	9 (3)	78 (26)
Sputum or tracheal aspirate	18 (4)	12 (2)	0	0	12 (1)	42 (7)
Lung(s)	8 (2)	8 (1)	0	1	15	32 (3)
Pleural fluid	7	2 (1)	(1)	0	(1)	9 (3)
Synovial fluid	2	1	1 (1)	0	0	4 (1)
Vegetation (cardiac valve)†	6^{7}	2^{5}	0	0	1	9^{12}
Epidural or subdural fluid	0	6 (1)	0	0	0	6 (1)
Intracerebral abscess	2	4	0	0	4	10
Wound, head	0	9	0	0	4	13
Wound, other	2	12	0	0	3	17
Others	3‡	14 (1)§	1‖	0	22#	40 (1)
Total	89 (13)	88 (7)	15 (8)	25 (15)	72 (5)	289 (48)

NOTE. Data are numbers of patients with cultures positive for the same organism as in CSF. Numbers in parentheses indicate patients with negative culture from that source or with culture positive for a different organism.

*Includes only cultures obtained within a day of culture of CSF and before antibacterial therapy.

†Superscripts indicate additional cases of bacterial endocarditis in which vegetations yielded no growth (at autopsy) following therapy, patient recovered (two cases), or diagnosis was clinical (two cases).

‡Catherized urine, liver abscess, and peritoneal fluid, one each.

§ Feces (predominant or very numerous), four; urine, bone, and cutaneous pustule, two each; kidney, vertebral abscess, cervix, and placenta, one each.

‖Petechia.

#Urine, nine; stool and vagina, three each; prostate and umbilicus, two each; eye, vertebra, and cord sac, one each.

Table 9. Distribution by age and sex and mortality rate among cases of meningitis at Boston City Hospital during 12 selected years, 1935–1972.

Causative organism(s)	Age group (years) <1	1–9	10–19	20–39	40–59	60–69	≥70	Total
Streptococcus pneumoniae								
No. of cases	18	18	4	30	50	31	42	193
Percentage of total	9.3	9.3	2.1	15.5	25.9	16.1	21.8	100
Females (%)	33	22	0	27	30	45	50	35
Deaths (%)	39	61	50	57	78	71	81	68.4
Other gram-positive cocci								
No. of cases	12	11	14	13	31	16	15	112
Percentage of total	11	10	13	12	28	14	13	100
Females (%)	42	45	29	13	35	31	40	34
Deaths (%)	42	45	57	62	68	50	80	59.8
Neisseria meningitidis								
No. of cases	28	35	8	10	10	4	5	100
Percentage of total	28	35	8	10	10	4	5	100
Females (%)	36	49	75	40	70	0	40	46*
Deaths (%)	18	11	0	10	20	25	80	17
Haemophilus influenzae								
No. of cases	30	46	0	3	3	0	0	82
Percentage of total	37	56	0	4	4	0	0	100
Females (%)	53	57	←	17	→			52†
Deaths (%)	17	7	←	50	→			13.4
Gram-negative bacilli and miscellaneous‡								
No. of cases	30	4	1	8	17	11	14	85
Percentage of total	35	5	1	9	20	13	16	100
Females (%)	37	←	31	→	18	27	36	31
Deaths (%)	67	←	38	→	53	73	100	66
All cases								
No. of cases	118	114	27	64	111	62	76	572
Percentage of total	20.6	19.9	4.7	11.2	19.4	10.8	13.3	100
Females (%)	40.7	47.4	41	25	32.4	36	45	38.6
Deaths (%)								
All cases	35.6	21.1	37	50	64	63	84	49.5
Males	40	27	50	52	65	60	88	53.2
Females	29	15	18	44	64	68	79	43.4§

*35% females among fatal cases.

†36% females among fatal cases.

‡Includes all mixed infections of initial positive cerebrospinal fluid.

§No statistically significant differences in mortality rate between sexes for any etiologic categories; however, for all patients ≤19 years old, the mortality rate in males (36%) was higher than in females (22%) ($P = 0.02$).

than 10 years old, and one-third of that group were ≥ 60 years of age. In the first group the mortality rate was 17% in infants (younger than one year old), 8% in children one to nine years old, and 0 in those 10–19 years of age; the mortality rate then rose to or above the rate in infants for those 20–69 years old and to 83% (five deaths in six patients) in those ≥ 70 years of age. In the second group, which included cases of meningitis due to all gram-positive cocci, gram-negative bacilli, and other organisms, the mortality rate was 53% in the infants and rose with increasing age to 85% in those ≥ 70 years old.

Mortality before and after antibiotics became available. Table 11 shows a comparison of CFRs for 1935 and 1941—before penicillin came into use—and for the other 10 selected years. The cases of meningococcal and influenzal meningitis are also separated from those caused by all other bacterial species. Among the former the CFR in patients ≤ 19 years old showed the greatest decline, from 53% in 1935 and 1941 to 7% in the

Table 10. Comparison of mortality rates by age in cases of meningitis due to *Neisseria meningitidis* and *Haemophilus influenzae* with those in cases of meningitis due to other bacterial pathogens at Boston City Hospital during 12 selected years, 1935–1972.

Causative organisms	Age group (years)							Total
	<1	1–9	10–19	20–39	40–59	60–69	≥70	
N. meningitidis and *H. influenzae*								
No. of cases	58	81	8	13	13	4	5	182
Percentage of cases	32	45	4	7	7	2	3	100
Deaths (%)	17	9	0	23	23	25	80	15.4
Other bacterial pathogens								
No. of cases	60	33	19	51	98	58	71	390
Percentage of cases	15.4	8.5	4.9	13.1	25.1	14.9	18.2	100
Deaths (%)	53*	55*	53†	55	70‡	66	85	65.4*

*P <0.001.
†P <0.05.
‡P <0.01.

last 10 selected years; this decline was associated with an increase in the proportion of cases in that age group from 63% to 84% ($P < 0.05$). Among cases in the latter etiologic category, there was a less striking decline in CFR in the same age group, from 79% to 43% ($P < 0.01$), and also a decline in CFR among patients 20–59 years old, from 89% to 58% ($P \approx 0.001$). This decline was associated with a slight decrease in the proportion of patients ≤ 19 years old from 36% to 27% ($\chi^2 = 2$), and in the 20–59 year olds from 47% to 36% ($\chi^2 = 2.63$). There were very few older patients (≥ 60 years) with meningitis caused by *N. meningitidis* and *H. influenzae*, but for meningitis of all other etiologies, the proportion of patients in that age group more than doubled from 17% in 1935 and 1941 to 40% after that ($P < 0.001$), and the mortality rate remained unchanged (77% and 76%, respectively).

Mortality rates in C-A and H-A cases. These data are summarized in table 12. Only a small proportion (5%) of the cases of meningitis due to *S. pneumoniae, N. meningitidis,* and *H. influenzae* were H-A, whereas 54% of those due to other gram-positive cocci and 65% of those due to gram-negative bacilli and miscellaneous organ-

Table 11. Comparison of mortality rates by age in cases of meningitis at Boston City Hospital in two years, 1935 and 1941, and in 10 selected years, 1947–1972.

Years, causative organisms	Age group (years)							Total
	<1	1–9	10–19	20–39	40–59	60–69	≥70	
Two years, 1935 and 1941								
N. meningitidis and *H. influenzae*								
No. of cases	6	7	2	4	3	2	0	24
Percentage of cases	25	29	8	17	13	8		100
Percentage (or no.) of deaths	(4)	(4)	(0)	(1)	(1)	(1)		46
All other bacterial pathogens								
No. of cases	6	15	7	14	23	9	4	78
Percentage of cases	8	19	9	18	29	12	5	100
Percentage (or no.) of deaths	83	73	86	86	91	67	(4)	83
Ten selected years, 1947–1972								
N. meningitidis and *H. influenzae*								
No. of cases	52	74	6	9	10	2	5	158
Percentage of cases	32.9	46.8	3.6	5.7	6.3	1.3	3.2	100
Percentage of deaths	12	4	0	22	20	0	80	10.8
All other bacterial pathogens								
No. of cases	54	18	12	37	75	49	66	311
Percentage of cases	17.4	5.8	3.9	11.9	24.1	15.8	21.2	100
Percentage of deaths	50	33	25	46	64	65	83	60.8

Table 12. Comparison of occurrence of and mortality from community-acquired (C-A) and hospital-acquired (H-A) acute bacterial meningitis at Boston City Hospital during 12 selected years, 1935–1972.

Organism(s) in initial positive CSF culture	No. of deaths/no. of patients (%)		Percentage of H-A cases among		
	C-A	H-A	Patients who lived	Patients who died	All patients
Streptococcus pneumoniae	121/181 (67)	11/12 (92)	2	8	6
Other gram-positive cocci	30/51 (59)	37/61 (61)	53	55	54
Neisseria meningitidis and *Haemophilus influenzae*	26/176 (15)	2/6 (33)	3	7	3
Gram-negative bacilli and miscellaneous	21/30 (70)	35/55 (64)	69	63	65
Total	198/438 (45)*	85/134 (63)*	17	30	23

NOTE. None of the differences in mortality rate between C-A and H-A cases for the separate etiologic categories was statistically significant, but for *S. pneumoniae, N. meningitidis,* and *H. influenzae* combined, $P = 0.02$.
*$P < 0.001$.

isms were H-A. The mortality rate in all C-A cases (45%) was appreciably lower than that in the H-A cases (63%) ($P < 0.001$). However, in C-A cases the mortality rate was lower only in the cases due to pneumococci, meningococci, and *H. influenzae* for which the combined mortality was 41% compared with 71% in H-A cases ($P = 0.02$); among all other patients the mortality rate was about the same in the C-A and H-A cases.

Discussion

A comparison of the changes in the occurrence, etiology, and mortality in patients with acute bacterial meningitis, as reported here, with corresponding changes in all cases of bacteremic infections that occurred in the same hospital during the same selected years, 1935–1972 [1], shows many similarities but also a number of differences. Most striking were the differences in the number of patients and the rate per 1,000 admissions to the Boston City Hospital. The cases of bacteremic infections increased steadily during the first 10 selected years and declined during the last two. The number and rates for cases of meningitis increased during the first three years, stabilized at a lower level over the next seven years, and then declined during the last two years. Figure 1 shows the rates for bacteremia and meningitis for the 12 years. (A logarithmic scale was used for rates to exaggerate [relatively] the low rates of meningitis and dampen those of bacteremia.)

The CFR among all of the bacteremic patients decreased from 58% in 1935 to 31% in 1947, increased gradually to > 40% over the next four selected years, and then remained at about that level until 1972, when it dropped again to 31%. The mortality rate from bacterial meningitis dropped from 85% to 24% between 1935 and 1957, rose over the next three selected years to 59%, and declined to 39% in the last two years. For the 12 selected years the mortality rate in the 7,440 bacteremic patients was 37.6%, and it was 49.5% in the 572 cases of meningitis.

S. pneumoniae was the most frequent organism in bacteremic infections in 1935, accounting for nearly one-third of the cases and 42% of the deaths from bacteremic infections in that year; it

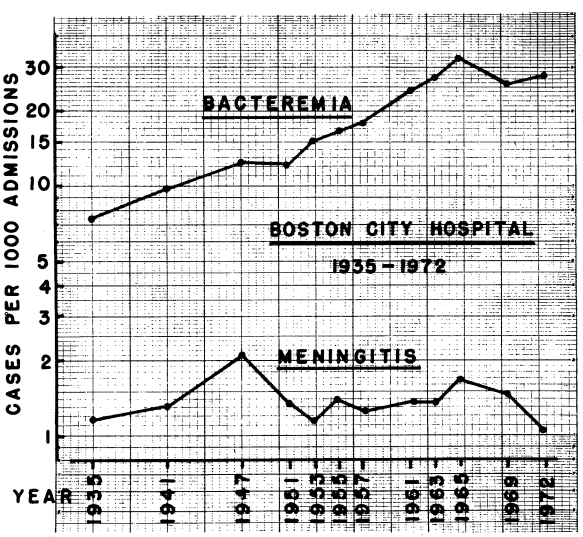

Figure 1. Comparison of incidence of cases of bacteremia and of bacterial meningitis at Boston City Hospital (Boston, Mass.) during 12 selected years.

was then superceded by *S. aureus* and later by gram-negative bacilli but continued to cause 13% –15% of all bacteremias and about 10% of the deaths over the last seven selected years. Among the patients with meningitis, *S. pneumoniae* was the most frequent organism during 11 of the 12 years. None of the 21 patients with pneumococcal meningitis in 1935 survived. Indeed, there had not been a single recovery in 99 cases of pneumococcal meningitis at this hospital between November 1929 and June 1936 [2]. There were three survivors among 20 patients with pneumococcal meningitis in 1941, but in a special study of 10 selected cases in 1937–1938, there were six recoveries in patients treated with sulfonamides in various combinations with specific antiserum and complement [6] as employed earlier by Ward and Fothergill [7, 8] in cases of meningitis due to *H. influenzae*. After 1941 the mortality rate in pneumococcal meningitis improved, but it was > 50% in seven of the last 10 selected years. Among the patients with pneumococcemia, the CFR declined from 78% in 1935 to 25% in 1947; it ranged between 22% and 42% over the next eight years but was only 15% in 1972.

There has been a revival of interest in the specific types of pneumococci in relation to the development of a polyvalent type-specific polysaccharide vaccine [9]. Because there are more than 80 serotypes of *S. pneumoniae*, it became necessary to select the types most prevalent in serious infections such as pneumonia, bacteremia, and meningitis for inclusion in these vaccines. The distribution of types varies in different sites of infection, at different times, in healthy carriers, and in different institutions [10, 11]. In our experience [11] the distribution of specific capsular serotypes in cases of pneumococcal meningitis resembled that among healthy carriers, whereas the distribution in cases of bacteremia and, of course, empyema was more like that among patients with primary (lobar) pneumonia. This finding reflects the greater susceptibility of the meninges to bacteria of relatively low virulence against which the lungs are usually protected to a large degree by the macrophage system or which are noninvasive due to an immune mechanism not operative in the CSF.

S. aureus ranked second among the organisms in bacteremic infections in 1935, but after that it superceded *S. pneumoniae* each year, and the proportion of all bacteremic cases increased from 21% in 1947 to 36% by 1957, after which it declined each year to 12.3% in 1972. There was only one case of *S. aureus* meningitis in 1935 and 1972 and two to seven cases in each of the intervening years. The CFR in the cases of *S. aureus* bacteremia declined from 47% in 1935 to a low of 19% in 1947 and ranged between 33% and 48% after that. The survival rate among the 42 cases of *S. aureus* meningitis for the 12 years was 36%.

β-Hemolytic streptococci other than group D ranked third as a cause of bacteremia in 1935 and accounted for 17% of all bacteremic infections and 21% of deaths from such infections in that year. From 52 cases in that year, the number declined rapidly in the ensuing years, reaching a low of four cases and no deaths in 1955; after that, the number each year varied between 21 and 58 and constituted 4%–7% of all cases of bacteremic infections and of deaths from bacteremic infections. Among the cases of meningitis, hemolytic streptococci ranked second in 1935 and 1941, but there were no cases due to these organisms in three of the selected years (1953–1957), only one or two cases in each of five years, and three or four cases in each of the other two years. There were four survivors among the 17 cases of meningitis due to hemolytic streptococci in the first two years and four survivors among the 14 patients in the last 10 years.

N. meningitidis and *H. influenzae* accounted for only a small proportion of bacteremic infections and of deaths from such infections in each of the 12 years. On the other hand, in five of the 10 selected years after 1947, the number of cases of meningitis due to these two species together exceeded the number of cases of pneumococcal meningitis, but the mortality rate in the 182 cases over the 12 years was 15.4%, and in the 158 cases in the last 10 years, it was 10.8%.

S. epidermidis was excluded from consideration in the report on bacteremia [1], but 13 patients with well-authenticated cases of meningitis due to *S. epidermidis* are included here. Five of the infections followed neurosurgical operations; two were in patients with skull fractures; three were complications of otitis; and one occurred in a patient admitted for subarachnoid hemorrhage

after several specimens of CSF showed no growth. One of these cases of meningitis occurred in a patient who had *S. epidermidis* bacteremia; in another, bacteremia and meningitis were present on admission. There were only two deaths, with a resulting low mortality rate similar to that in meningitis due to *N. meningitidis* and *H. influenzae*.

Among all bacteremic infections, viridans streptococci accounted for about 14% of cases in 1935, 12% in 1941, and 6%–11% in the later years. The CFR in these cases was nearly 50% in 1935, dropped to a low of 11% in 1951, and ranged between 13% and 27% in subsequent years. One to three cases of meningitis due to such streptococci occurred in nine of the 12 years. The mortality rate in the 17 cases was 59%.

Cases of enterococcal bacteremia were not recognized in 1935, and a few cases occurred in 1941 (< 1% of all cases that year), but after that between 2.3% and 6.7% of the cases of bacteremic infection each year were due to enterococci. The mortality rates in these cases ranged between 23% and 61% (median, 40%) in the different years. There were no authenticated cases of enterococcal meningitis in the first two years, nor in four other years; in the other six years there were nine cases with five deaths.

E. coli was the most frequent of the gram-negative bacilli in the cases of bacteremia. About 9% of the cases in 1935 and larger proportions in each of the other years (14% in each of the last three years) were due to *E. coli*. The CFR in these cases ranged from 30% to 49% in the different years. There were no cases of meningitis due to *E. coli* in two of the 12 years, one case in each of five years, and two to six cases in five years. The mortality rate for the 24 cases was 75%.

The most striking change that occurred among cases of bacteremic infection over the 12 selected years was the markedly increased occurrence of cases due to gram-negative bacilli other than *E. coli*. There were very few such cases during the first two years, whereas in subsequent years there were varying numbers due to *Klebsiella, Enterobacter, Proteus,* and *Pseudomonas,* and during the last four years there were also many cases due to *Mima (Acinetobacter), Herellea (Acinetobacter*), and *Serratia*. Gram-negative bacilli including *E. coli* caused one-third or more of the bacteremic cases in each of the last 10 years, and the average mortality rate was 44%. On the other hand, there were relatively few cases of meningitis due to gram-negative bacilli other than *E. coli*– a total of 65 cases in the 12 years with a mortality of 65%. It is of interest that the number and proportions of these cases increased steadily during the last four selected years from 17% of all cases in 1963 to 37% in 1972. A similar, although less striking, increase occurred among all cases of bacteremic infection over the same years [1].

Only rarely was there any difficulty in differentiating H-A from C-A infection among either the bacteremias or the cases of meningitis. Prior therapy in the hospital but not therapy prior to admission presented a problem in diagnosis in an occasional H-A case.

In 1935, 48% of the bacteremias in patients on medical wards and 57% of those in patients on surgical services were H-A. In subsequent years, this proportion among bacteremic patients on medical services was much lower, generally ranging between 20% and 30%, whereas this proportion among surgical patients with bacteremia remained as high or higher (between 60% and 80%) in most of the years. The CFR for all 12 years combined was 32.9% for C-A cases of bacteremia and 46.7% for H-A cases ($P < 0.0001$).

Of all cases of bacterial meningitis, 23% were H-A. The proportion of cases that were H-A was somewhat larger (28%) during the first two years, smaller (12%–19%) during the 1950s, and between 22% and 36% in subsequent years. Most H-A cases followed head injuries or neurosurgical and otorhinological operations, and some were in newborns. Less than 5% of the cases of meningitis due to *S. pneumoniae, N. meningitidis,* and *H. influenzae* were H-A; in contrast, 59% of all other cases were H-A. The CFR in H-A cases of meningitis due to *S. pneumoniae, N. meningitidis,* and *H. influenzae* combined was 72% as compared to 41% among the corresponding C-A cases. Among the cases of meningitis due to other organisms, the CFR was about the same in H-A and C-A cases.

Superinfection of the meninges with species of bacteria not grown in the original diagnostic culture of CSF was demonstrated in 35 patients. The original meningitis was C-A in 17 and H-A in

18 of these patients. Among the C-A cases, *S. pneumoniae* was the original infecting organism in 10, *H. influenzae* in two, and *N. meningitidis* in one, whereas among the H-A cases the original infecting organism was *S. pneumoniae* in two and *H. influenzae* in one, and none was caused by *N. meningitidis*. The original infecting organism (s) in the other cases and all of the superinfecting organisms were either gram-positive cocci other than *S. pneumoniae* or gram-negative bacilli. The mortality rate in the 35 patients with superinfections was 80%; that in the 81 H-A cases of meningitis caused by other gram-positive cocci and gram-negative bacilli without superinfections was 54% ($\chi^2 = 5.8$; $P < 0.05$).

Pathogenic bacteria other than those grown from CSF were cultured from sites other than the nervous system in a large proportion of the cases of meningitis, and many of these organisms were associated with infections of those sites and some also with bacteremia. Some of those other infections anteceded the meningitis, but most of them were superinfections, involving particularly the respiratory and urinary tracts. None of these infections have been considered here, although some of them may have been the cause or a contributing factor in the fatal outcome of those cases.

Comparable changes in age distribution occurred during the years of this study in patients with bacteremia and in those with meningitis. The proportions of infants and children (nine years old or younger) increased after the first two or three years, but more striking increases occurred in the oldest age groups (those $\geq$ 60 years old), among whom the mortality rate was very high in both H-A and C-A cases of both bacteremia and meningitis.

The proportion of males was greater than that of females among the cases of both bacteremia and meningitis, but there was no great sex-related difference in mortality rate.

The data presented here are from a single large municipal hospital and cover essentially the entire antibacterial era. Among cases of both bacteremic infections and bacterial meningitis, the number of cases and rates per 1,000 hospital admissions each year, the distribution of etiologic agents, the proportions that are H-A and C-A, and the CFRs vary considerably in different hospitals and at different times and even vary in the same hospital. No attempt will be made to compare the findings at Boston City Hospital with those in other institutions. Hodges and Perkins [12] recently presented data on acute bacterial meningitis from their hospital for the years 1948–1973 and compared them with those reported from five other widely scattered hospitals, each covering six to 10 years at different times between 1948 and 1970. These data illustrated the wide variations in the distribution of different organisms and mortality rates. Among their own cases, 42% and, in other studies cited, 9%–21% are listed as of unknown etiology. No such cases are included in our study.

Some clinical features, the neurological sequelae, and some aspects of therapy were noted by Hodges and Perkins [12] and in many other reports including the extensive review of experience with meningitis at Massachusetts General Hospital [13]. These aspects have not been considered in this study and will not be discussed. However, one aspect has been studied in some detail, namely the duration of hospitalization [14]; the hospital stay after the diagnosis was established was generally longer in the H-A than in the C-A cases [12]. Analyses of the various therapeutic and prophylactic measures used in these cases were not done; such studies would be required to determine whether they were optimal or whether improvements could be proposed which might reduce the morbidity and mortality and also would be required before controlled studies on the effectiveness of prophylactic and therapeutic measures could be designed and undertaken.

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