MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

April 2, 1970

Jack A. Barnett, M.D.

Meningococcal Disease

Prevalence

In its commonest form, meningococcal disease is a sporadic occurrence in the population with the endemic rate being around 1-2 cases per 100,000 population per year. Historically, major outbreaks have occurred in 10- to 20-year cycles with the peak case rate reaching levels which would project to 3-4000/100,000/year if sustained (Figure 1).

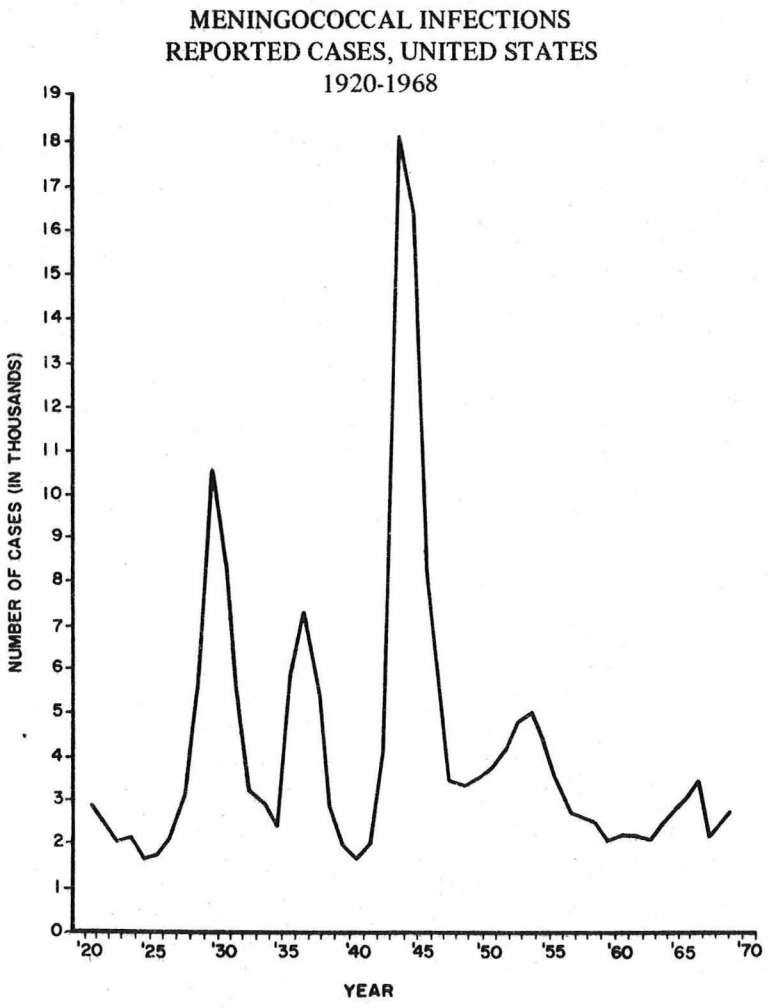


FIGURE 1

In this country the most extensive outbreaks have related to the great wars. There were 5,839 cases with 1,836 deaths in the American army during World War I and 13,922 cases with 559 deaths in World War II. In the latter epidemic there was a major spread to the civilian population and before the epidemic had run its course in 1943 and 1944, some 34,000 cases developed with 4,700 deaths.

During the past several years the infection rate has fluctuated only slightly with some 2000 to 3000 cases being reported annually (Fig. 2).

REPORTED CASES OF MENINGOCOCCAL INFECTION, UNITED STATES, 1960-1967*
MONTHLY RATES PER 100,000 POPULATION ADJUSTED TO AN ANNUAL BASE

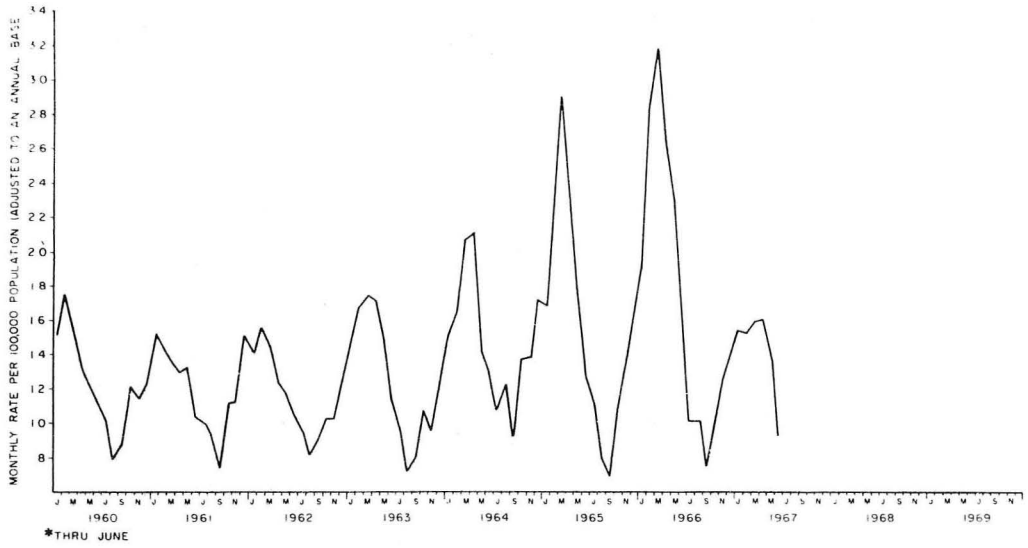


FIGURE 2

There is characteristically a seasonal distribution of rates in the endemic disease with the preponderance of cases occurring in the late winter and early spring months (Fig. 3).

MENINGOCOCCAL INFECTIONS – UNITED STATES
MEAN MONTHLY RATES 1960-1967
MONTHLY RATES 1967-1968 AND 1968-1969

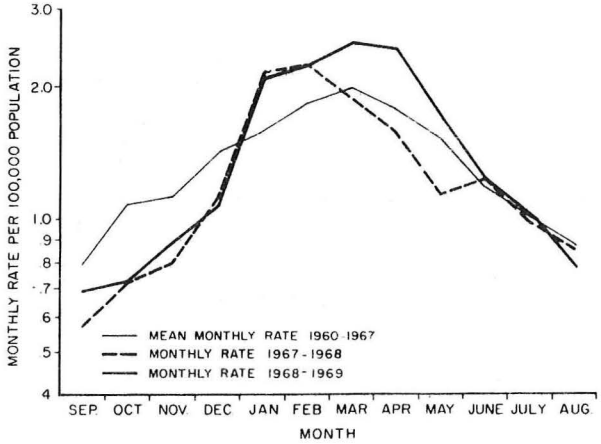


FIGURE 3

Children under 5 years of age regularly account for approximately 50% of the reported meningococcal disease. In 1968, of the 2,237 cases reported in which age was known, 41.5% of the cases occurred in the age group of 4 years and under, 20% in age 5-14, 24.5% in the 15-24 group, and 14% in those 25 years and older. The increased threat to the young person is better expressed by consideration of age-specific attack rates (Table 1).

TABLE 1

Age-Specific Attack Rate of Meningococcal Disease
(# cases/year/100,000 population of that age) (Ref. 2)

Age (years)	Rate
< 1	11.0
1-4	4.0
5-9	1.2
10-14	1.0
15-19	1.5
20-24	2.0
≥ 25	0.3

The overall case fatality rate in World War I was 31.4% and around 10% in World War II. Various civilian studies record the overall rate from 5-10% with the highest rates being seen consistently in patients under 4 years of age and over 40. In 1958, 79% of all meningococcal deaths in this country occurred in patients ≤ 14 years of age (5).

The Organism (Ref. 6-19)

Neisseria meningitidis is a gram-negative diplococcus as it is usually seen in body fluids and conventional growth media. It is biochemically distinguished from Neisseria gonorrheae by its ability to ferment glucose and maltose while the latter utilizes only glucose. The organism is relatively fastidious and is best grown on chocolate agar under increased CO_2 tension at a temperature of 35-37°C. Attempts to isolate the organism from the nasopharynx should utilize ~~Mueller-Hinton~~ Thayer-Martin medium which is essentially chocholate agar containing antibiotics ineffective against the meningococcus but suppressive against other nasopharyngeal flora.

Meningococci can be subdivided into serogroups by use of antisera in techniques involving agglutination, precipitation, fluorescent antibody staining and mouse protection studies. At least four distinct serogroups have been recognized since 1915. Since 1950 the acceptable nomenclature for these serogroups are A, B, C and D (previously I, II, IIα and IV, respectively).

In most clinical studies involving serogrouping it has been noted that non-typable organisms were associated with clinical disease with rare frequency and to a somewhat greater extent with the carrier state (10-15% of cases). More recently different investigators have used more sophisticated immunological techniques to lend identity to some of the previously non-groupable organisms. Slaterus (9)

identified three distinct groups which he termed x, y and z. Using different sources for isolates and a different technique, Evans et al. (10) identifified three "new" serogroups which he termed Bo, 29E and 135. The Bo serogroup seems identical to the y strain of Slaterus; Devine has shown that 29E and z are probably identical (11). The relation of serogroups 135 and x has not been established.

In the Evans study (843 service-associated systemic infections, 1964-1967), the Bo, 29E and 135 strains accounted for only 4.3% of the isolates.

Prior to 1960, all major outbreaks had involved group A organisms which were almost invariably susceptible to sulfadiazine. Endemic disease was attributable to group B and to a lesser extent, group C. In the early 1960s, group B organisms were found to predominate in the major outbreaks in military establishments and it began to appear in civilian cases (Table 2).

TABLE 2

Meningococcal Strains Submitted to NCDC

Serotype	1966		1967		1968	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
A	2	0.3	2	0.5	0	0
B	598	70.6	242	66.0	246	47.4
C	98	12.6	76	20.7	196	37.8
D	2	0.3	0	0	0	0
X	--*	--*	1	0.3	2	0.4
Y	--*	--*	27	7.4	24	4.6
Z	--*	--*	8	2.2	4	0.8
Not typed or nontypable	126	16.3	11	2.9	47	9.0
Total	776	100.0	367	100.0	519	100.0

* This antiserum was not used to group isolates in 1966

Since 1967 group C organisms have appeared in military outbreaks; there has been a parallel increase in its association with civilian cases and at the present time sulfa-resistant group C organisms predominate in both military and civilian cases (Table 3).

TABLE 3

Meningococcal Isolates That Were Inhibited at or Below 1.0 mg per 100 ml Sulfadiazine

Interval	Total		Group B		Group C		All Others	
	Number Strains Tested	Percent Inhibited	Number Strains Tested	Percent Inhibited	Number Strains Tested	Percent Inhibited	Number Strains Tested	Percent Inhibited
Jan. 1966 through Dec. 1966	754	59.3	537	52.4	92	84.9	125	70.4
Jan. 1967 through Dec. 1967	317	56.2	209	49.3	61	62.3	47	78.7
Jan. 1968 through Aug. 1968	426	50.7	192	60.4	164	25.6	70	82.6
Sept. 1968 through Aug. 1969	414	35.3	161	62.1	227	10.6	26	84.6

*Isolates submitted from cases.

Host-Organism Relationships

Infection by the meningococcus may take one of several forms: the "benign" nasopharyngeal carrier state, bacteremia with recovery without therapy, fulminant septicemia with death within hours, chronic septicemia with symptoms waxing and waning over weeks or months, and purulent meningitis which mimics that caused by other pyogenic organisms. There is no convincing evidence that either serogroup has predilection for any one of the clinical states.

Relation of the carrier state to clinical disease. Many investigators have variously estimated the prevalence of nasopharyngeal carrier state of meningococcus.

TABLE 4

Prevalence of Carrier State in Certain Normal Populations

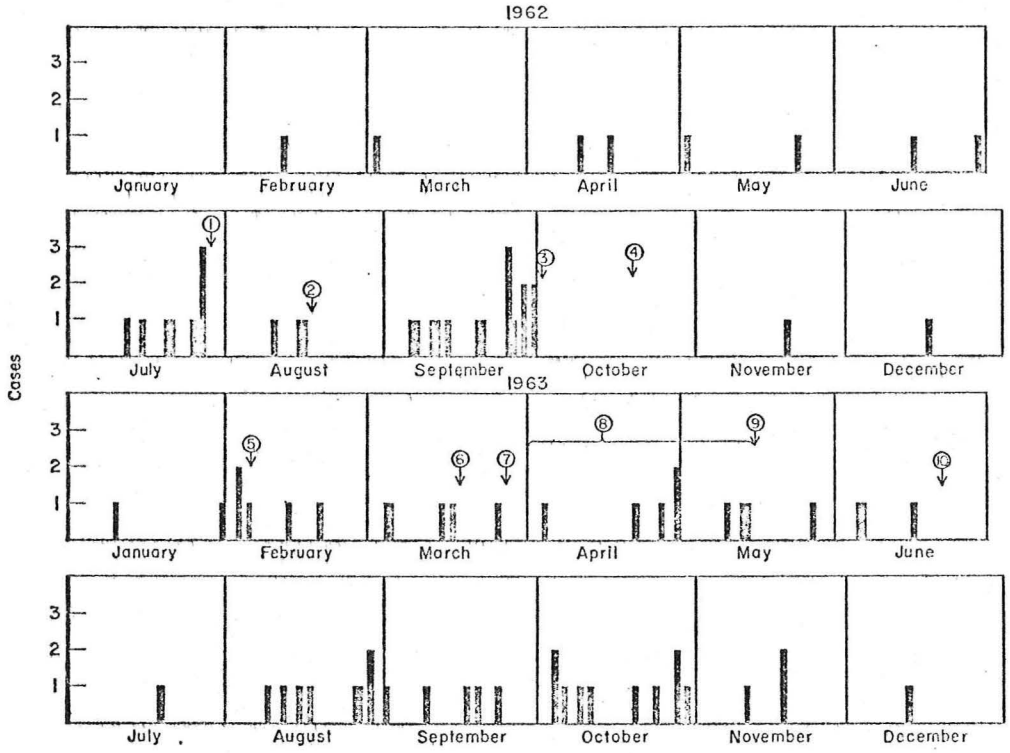
Study	Population	Period	Number	% Carriers
Silverthorne (21)	Medical students	1934	125	12.8
* Silverthorne	Hospital personnel	1934-1936	63	20
Mueller (22)	Boston community	1942-1943	-	18-32
Gauld (23)	New recruits (Ord)	7/63-9/63	400	8.0
Bristow (24)	New recruits (San Diego)	5/63-7/63	488	3.7
Farrell (25)	New recruits (Lackland)	1/65-3/65	583	15.9
Artenstein (26)	New recruits (Dix)	2/66-5/66	950	33.0
Greenfield (27)	"Normal community"-N.Y.	1966	204	3.0

* Multiple cultures over 2-year period. 26 (41%) had positive culture at some time. 11/26 were persistent carriers, 13 were intermittent and 2 had a single positive.

The fact that high carrier rates commonly coexist with outbreaks of clinical disease led to the view that high intensity exposure was the major

factor in determining infection rates and to the dictum that carrier rates above 20% were tantamount to an epidemic. An early challenge to this concept was voiced by Dudley (29), who observed a carrier rate of 13% in the contacts of 5 cases of meningococcal disease at a naval base in 1932 and no clinical disease at the same base during the subsequent year, although the carrier rate averaged 50%. Other authors have had similar difficulties in precisely relating the prevalence of carriers to prevalence of disease (30-33).

Pertinent epidemiological information comes from observations of recent outbreaks (23,24,27,28); Fort Ord is located on the California coast and in 1963 had a total strength of 25- to 30,000 men. New recruits were received daily and at any time 50% of the population consists of basic trainees (first 8 weeks of training). In 1962, '63 and '64, there was an outbreak of meningococcal disease due to the group B organism. (Service criteria for an outbreak: $\geq$ 1 case/10,000 men/week.)



♀ = sulfadiazine prophylaxis

Dates of Onset of Meningococcal Meningitis, Fort Ord, 1962-1963

FIGURE 4 (Ref. 23)

Table 5 shows the change in carrier status in relation to status of training.

TABLE 5

Meningococcal Nasopharyngeal Culture Surveys, July-September, 1963: Prevalence of Infection by Week of Training

Training Status	July 1963						September 1963					
	Number Cultured	Infected Hosts		Group			Number Cultured	Infected Hosts		Group		
		Number	%	A	B	C		Number	%	A	B	C
Reception center	400	30	8	1	22	6*	100	9	9	0	6	3
Pretraining week	50	4	8	0	2	2						
Basic training												
1st week	60	2	3	0	0	2	51	6	12	0	4	2
2nd week	52	7	14	1	3	3	54	8	15	0	8	0
3rd week	48	9	19	0	9	0	51	4	8	0	0	4
4th week	49	8	16	0	7	1	50	12	24	0	10	2
5th week	50	11	22	1	10	0	51	9	18	0	5	4
6th week	51	4	8	0	4	0	52	3	6	0	1	2
7th week	50	11	22	0	9	2	58	9	16	0	9	0
8th week	49	21	43	0	20	1	52	18	35	0	16	2
AIT‡												
12th week							49	17	35	0	14	3
15th week	51	28	55	0	26	2						
17th week							51	24	47	0	24	0
Cadre	59	5	9	0	4	1	38	3	8	0	2	1

* One not grouped

‡ AIT = advanced individual training

In September 1963, group B accounted for 81% of the nasopharyngeal isolates and group C 19%. A and D were not represented. All but 6 of 168 sulfa-resistant strains were group B. 98% of the strains isolated from men who had received sulfa prophylaxis were resistant while in those not receiving prophylaxis only 30% were resistant.

The relation of stage of training to susceptibility to clinical disease is reflected in Table 6 from the Fort Ord experience and Table 7 from the San Diego Naval Training Center experience in 1963 (ref. 24).

TABLE 6

Distribution of 93 Cases of Meningococcal Meningitis in Military Personnel According to Week of Training, Fort Ord, California, 1962-1963

Week of Training	Cases of Meningitis	
	Number	Per Cent
Pretraining	0	
1	5	5.4
2	12	12.9
3	20	21.5
4	10	10.8
5	11	11.8
6	11	11.8
7	11	11.8
8	9	9.7
9	0	
10	0	
11	1	1.1
12	1	1.1
13	0	
14	1	1.1
15	0	
16	0	
Permanent party	1	1.1
Total military	93	100.0
dependents	7	

TABLE 7 *

Cases of Meningococcal Meningitis or Meningococcemia by Military "Age" at Time of Onset

Week of Training at Time of Onset	No. of Cases	Per Cent of Total	Cumulative No. of Cases	Cumulative Per Cent
1	5	15.9	5	15.8
2	6	18.9	11	34.8
3	7	21.0	18	56.2
4	8	25.0	26	81.3
5	1	3.2	27	84.4
6	4	12.5	31	96.9
7	1	3.2	32	100.0
8	0	0	32	100.0
9	0	0	32	100.0

* Ref. 24

In the military environment clinical meningococcal disease is limited to recruits despite persistence of the carrier state in "older" troops (23,24,34,35). In Fort Ord, the nasopharyngeal carrier rate increased some 5-fold above the level seen at induction and the attack rate of clinical disease some 25- to 30-fold over that existent in the "normal population" from which the recruits were drawn. The absence of clinical disease in the more experienced trainees with high carrier rates suggests the period of vulnerability is finite and that host factors, inherent or acquired, are major determinants in the balance between the carrier state and clinical disease.

Additional support for the thesis that vulnerability is finite in fixed populations comes from observations of the outbreak in Barrow, Alaska, in 1964 (28). Five cases of group B meningococcal disease occurred within a 3-week period among 1,450 Eskimos living in 211 native housing units. The outbreak terminated without control measures. Surveys conducted for 2 months after the last case showed the cumulative carrier rate to be almost 50%. The area is quite remote and its previous experience with meningococci was probably nil. It was felt that the disease was introduced by members of a nearby National Guard unit which received some of its replacement personnel from Fort Ord.

Immunity

Several points suggest that immunity should be a decisive factor in host resistance to meningococcal infection: the attack rate is highest in young persons, the period of vulnerability in closed populations seems finite and rather independent of the carrier rate, and epidemics occur in cyclic nature suggesting the need to accumulate susceptible individuals for widespread dissemination to occur. Further, sera from convalescent cases have been shown to possess bactericidal, precipitating and agglutinating activity against the infecting organism (36-38).

The role of immunity was clarified to a great extent by the recent studies of Artenstein's group at Walter Reed (39-44). Notable observations of these experiments include:

1. Presence of bactericidal activity in serum is inversely proportional to incidence of meningococcal disease during the first 12 years of life.
2. Bactericidal activity of serum correlates well with the presence of specific IgG antibodies in serum.
3. Specific and cross-reactive serum bactericidal activity develops within 14 days after development of the carrier state.
4. Bactericidal activity against the epidemic strain was present in the preinfection, baseline serum sample of 5.6% of new recruits who ultimately developed meningococcal meningitis and in 82.2% of those who did not.
5. Of 492 new recruits, 54 (11%) had no serum bactericidal activity against the predominant epidemic strain. 13 acquired the pathogenic strain and 5 developed meningitis (incidence of 38.5%). No cases occurred in the 89% with pre-existent bactericidal activity.
6. A vaccine prepared from group C polysaccharide is effective in reducing acquisition of the carrier state and has a protective effect of 87% against group C clinical disease.

Risk of Secondary Cases in Civilian Populations

TABLE 8

Investigator	Place	Period	# Cases	2° Cases	%*	Families with 2° Cases
Norton (45)	Detroit	1928-29	1,272	89	0.7	3.6%
Bouldan (45)	New York	1905	1,500	88	-	5.9%
ǂ Pizzi (46)	Chile	1941-42	5,885	247	2.5	-
Leedom (47)	L.A.	1965	290	11	-	3.4%

* Ratio of 2° cases to number of contacts of a 1° case

ǂ Pertinent factors:
Only 53 cases in Chile 1932-1940 ∴ little immunity; crowding--7 persons/room, 2.9 persons/bed; unusually cold winter. 2° attack rate was 3.9% in those under 15 and 1.5 in those older.

Interval Between Primary and Secondary Cases (45)

Days	# Instances
1-4	20
5-9	14
10-14	6
15+	6
Total	46

Two studies relate to the risk of exposure of hospital personnel in the management of patients with meningococcal disease:

TABLE 9 (Ref. 28)

Population	Number	Group B Organism in Nasopharynx	
		Number	Per Cent
"Tribe"* and contacts	104	25	24
Hospital contacts of 2 cases from tribe	19	1	6
Medical students	33	0	0
Normal family population	204	7	3

* Tribe: 25 persons comprising 6 related, closely-knit family units. Had 4 cases of meningococcal disease in 12 months.

These studies suggest that in ordinary circumstances the risk of spread to hospital personnel is quite small.

TABLE 10 (Ref. 48)

Exposure Category	# Persons	# With Positive Nasopharyngeal Culture	% Positive
None	42	8	19.1
After therapy of patient	6	1	16.7
Before therapy			
brief	8	2	25.0
extensive	16	3	18.8
	72	14	19.5

Study conducted after admission of patient with meningococcemia. Four persons had organism having serogroup and antibiotic susceptibility pattern of the patient's organism. Only 2 of these had significant exposure to the patient, therefore the maximum infectivity in this study would be 2/30 or 6.6%.

Antibiotic Prophylaxis

The efficacy of sulfadiazine in controlling outbreaks prior to 1960 led to the view that meningococcal infection would never pose a significant problem from the public health standpoint (12,13). The significant appearance of sulfa-resistant strains in the early 1960s prompted intensive searches for an effective agent (50-56). Results from some of the major efforts are shown in Table 11 (ref. 50).

TABLE 11

Comparative Efficacy of Drugs in Reduction of Meningococcal Carrier Rate

Drug	Dose	Duration of Therapy (days)	# Subjects Treated	Carrier Rate (% of Subjects With Positive Cultures)			
				Before Treatment	1 Wk After Treatment	2 Wk After Treatment	4 Wk After Treatment
Sulfadiazine	8 gm total	3	161	57.7	0.6	-	-
Sulfadiazine	3 gm/day	3	100	30.0	0	2.0	-
	2 gm/day	2	100	36.0	3.0	2.0	-
Oxytetracycline	0.5 gm twice/day	4	33	100.0	57.0	100.0	-
	0.5 gm twice/day	8	49	100.0	37.0	90.0	-
Erythromycin	1 gm/day	4	12	100.0	63.6	100.0	-
	1 gm/day	10	28	100.0	53.8	60.0	-
Penicillin G	1,000,000 units twice/day	4	23	100.0	61.5	75.0	-
	1,000,000 units twice/day	10	37	100.0	31.5	66.7	-
Penicillin G	1,500,000 units	10	20	100.0	46.0	75.0	-
Ampicillin	500 mg 3 times/day	10	26	100.0	32.0	38.0	-
Ethoxzolamide	125-375 mg	3	8	100.0	100.0	100.0	-
Procaine penicillin	1,200,000 units/day	2	118	100.0	-	51.0	-
Erythromycin	500 mg 3 times/day	2	7	100.0	-	100.0	-
Rifampin	600 mg/day	4	15	100.0	6.7*	6.7	6.7

* The 6.7% carrier rate in 1st wk is based upon single treatment failure; another subject had 1 of 7 cultures positive for strain originally carried in 1st post-treatment wk; each of additional 2 subjects had 1 of 7 cultures positive for strains of differing serologic reactivity in 1st post-treatment wk; each of latter 3 subjects free of meningococci on all cultures obtained subsequently.

Thus, it can be seen that none of the presently available agents demonstrates acceptable efficacy in eradicating the carrier state. The ability of Rifampin, currently an experimental agent, to dependably suppress the carrier state needs further evaluation.

Clinical Picture and Therapy (Ref. 57-77)

The commonest clinical patterns of clinical meningococcal disease are meningitis, meningococcemia with meningitis, and meningococcemia without meningitis. In one representative series the prevalence of each of these forms was 21%, 29% and 50%, respectively (58). Hypotension is a feature in some 40% of bacteremic cases and a variable number progress to the extensive purpura and unrelenting shock of the "Waterhouse-Friderichson syndrome". Diffuse intravascular coagulation has recently been shown to exist in some bacteremic patients (6 of 19 patients in one series--ref. 66) and in some instances the consequences of this event dominate the clinical course.

Arthritis is a feature in some 5 to 10% of bacteremic cases. Although the condition is occasionally present early in the disease and is associated with positive joint fluid cultures, it is much more commonly seen on the 5th-10th day of therapy and associated with sterile effusions (70-72).

It should be noted that any one of the clinical forms of meningococcal disease can be mimiced by organisms of the tribe Mimeae and the organism resembles neisseria morphologically when viewed in clinical specimens. It is uncommonly sensitive to penicillin (74).

Treatment of Meningococcal Disease

1. Antibiotic Therapy

   Immediate: 1 million units aqueous penicillin intravenously. If evidence of meningococcemia is present this should precede diagnostic studies.

   Sustaining: 15-20 mu aqueous penicillin/day. Continuous infusion yields higher CSF levels than intermittent therapy. Duration 7-10 days.

   Penicillin-sensitive person: Use chloramphenicol 2.0 gm/day. (See Table 12 and ref. 76, 77)

2. Observe for hypotension or other signs of collapsing circulation and institute early therapy (75).

3. Observe for evidence of disseminated intravascular coagulation and if present, therapy with heparin.
   - Thrombocytopenia--may be consequence of action of endotoxin rather than coagulation
   - Prothrombin time--elevated in virtually all patients with meningococcemia--due to decrease in Factor VII and not necessarily related to intravascular coagulation in this syndrome (66).
   - Prolonged PTT and prolonged thrombin time--most reliable indicators.

4. Steroids? No evidence of adrenocortical insufficiency has been demonstrated in gram-negative bacteremia or the "Waterhouse-Friderichson syndrome". They have not been convincingly shown to be effective vasoactive agents in the management of shock.

TABLE 12

Diffusion of Antimicrobial Agents from Blood into Cerebrospinal Fluid

Antimicrobial Agent	Ratio of Levels (Blood to CSF)	
	Normal meninges	Inflamed meninges
Sulfonamides		
Sulfadiazine	1.25 2:1	
Sulfisoxazole	3:1	
Sulfamethoxypyradazine	≤10:1	
Sulfadimethoxine	≤10:1	
Penicillins		
Penicillin G	≤100:1	25:1
Methicillin	Nil-insignificant	10:1
Ampicillin	Insignificant	4:1
Streptomycin	Nil	Significant
Kanamycin	Nil	(?)
Tetracycline		
Chlortetracycline	4:1	2 16:1
Oxytetracycline	Nil-trace	2-16:1
Tetracycline		2-3:1
Demethylchlortetracycline	20-50:1	
Chloramphenicol	1.5:1	1.5:1
Erythromycin	8-64:1	(?)
Cephalosporins		
Cephalothin	≤100:1	1.4:1
Bacitracin	Traces	(?)
Lincomycin	Nil	(?)
Vancomycin	Nil	3-5:1
Polymyxin B	Nil	Nil
Gentamicin	(?)	1.4:1

BIBLIOGRAPHY

Prevalence of Disease

1. National Communicable Disease Center Morbidity and Mortality Report: Annual Supplements Vols. 9-17, 1961-1968.

2. Morbidity and Mortality Weekly Report, Vol. 18, #47, 1969.

3. Eichoff, T. C. Meningococcal infections in the United States: A status report with reference to the state of Louisiana. J. La.. State Med. Soc. 118:485, 1966.

4. Feldman, H. A. Recent developments in the therapy and control of meningococcal infections. Disease-a-Month, February 1966.

5. May, C. D. Circulatory failure (shock) in fulminant meningococcal infection. Pediatrics 25:316, 1960.

The Organism

6. Topley and Wilson. Principles of Bacteriology and Immunity. Wilson, G.S., and Miles, A. A. Williams and Wilkins Co., Baltimore, 1964, pp. 665-678.

7. Rake, G., and Sherp, H. W. Studies on meningococcal infections. III. The antigenic complex of the meningococcus--a type-specific substance. J. Exp. Med. 58:341, 1933.

8. Brannan, S. E. Serological relationships among meningococci. Bact. Rev. 17: 175-188, 1953. (Status to that date)

9. Slaterus, K. W. Serological typing of meningococci by means of microprecipitation. Antonie Van Leuwenhoek J. Microbiol. Serol. 27:305, 1961.

10. Evans, J. R., et al. Prevalence of meningococcal serogroups and description of 3 new groups. Am. J. Epidemiol. 87:643, 1968.

11. Devine, L. F., and Hagerman, C. R. Relationship of serogroups of Neisseria meningitidis. Infection and Immunol. 1:226, 1970.

12. Kuhns, D. M., et al. The prophylactic value of sulfadiazine in the control of meningococcic meningitis. JAMA 123:335, 1943.

13. The transmission and control of meningococcal infections. Am. J. Med. Sci. 209: 69, 1945. Phair, J. J., and Schoenbach, E. B.

14. In vivo and in vitro resistance to sulfadiazine in strains of Neisseria meningitidis. JAMA 186:139, 1963.

15. Eickhoff, T. C., and Finland, M. Changing susceptibility of meningococci to antimicrobial agents. New Eng. J. Med. 272:395, 1965.

16. Alexander, C. E., et al. Sulfadiazine resistant group A Neisseria meningitidis. Science 121:1019, July 1968.

17. Morbidity and Mortality Reports, Vol. 18, #5, 1969.

18. Morbidity and Mortality Reports, Vol. 18, #16, 1969.

19. Morbidity and Mortality Reports, Vol. 19, #9, 1970.

20. Oughton, C. J., et al. Sulfadiazine susceptibility patterns of Neisseria meningitidis group y. Appl. Microbiol. 18:1091, 1969.

Host-Organism Relationships

21. Silverthorne, N. Presence of meningococcus in nasopharynx of normal individuals and bactericidal property of blood against meningococcus. J. Pediatrics 9:328, 1936.

22. Mueller, J. H. The relation of the carrier to epidemic meningitis. Ann. Int. Med. 18:974, 1943.

23. Gauld, J. R., et al. Epidemiology of meningococcal meningitis at Fort Ord. Am. J. Epidemiol. 82:56, 1965.

24. Bristow, W. M., et al. Epidemic meningitis in Naval recruits. Am. J. Public Health 55:1039, 1965.

25. Farrell, D. G., and Dahl, E. V. Nasopharyngeal carriers of Neisseria meningitidis; Studies among Air Force recruits. JAMA 198:1189, 1966.

26. Artenstein, M. S., et al. Acute respiratory disease and meningococcal infection in Army recruits. JAMA 201:128, 1967.

27. Greenfield, S., and Feldman, H. A. Familial carriers and meningococcal meningitis. New Eng. J. Med. 277:497, 1967.

28. Reed, D., et al. An epidemic in an Eskimo village due to group B meningococcus. Part I. Epidemiology. JAMA 196:383, 1966.

29. Dudley, S. F., and Brennan, L. R. High and persistent carrier rates of N. meningitidis, unaccompanied by cases of meningitis. J. Hygiene 34:525, 1934.

30. Rake, G. Studies on meningococcal infection. VI. Carrier problem. J. Exp. Med. 59:553, 1934.

31. Maxcy, K. F. The relationship of meningococcus carriers to the incidence of cerebrospinal fever. Am. J. Med. Sci. 193:438, 1937.

32. Sartell, P. E., and Smith, W. M. Epidemiological notes on meningococcal meningitis in the Army. Am. J. Public Health 34:40, 1944.

33. Aycock, W. L., and Mueller, J. H. Meningococcus carrier rates and meningitis incidence. Bact. Rev. 14:115, 1960.

34. Cook, S. S. The incidence of cerebrospinal fever as related to length of service and season of enlistment. Am. J. Hygiene 23:472, 1936.

35. Sartwell, P. E., and Smith, W. M. Epidemiologic notes on meningococcal meningitis in the Army. Am. J. Public Health 34:40, 1944.

Role of Immunity

36. Houston, T., and Rankin, J. C. The opsonic and agglutinative power of blood serum in cerebrospinal fever. Brit. Med. Bull. 2:1414, 1907.

37. Silverthorne, N., and Fraser, D. T. The action of human blood on the meningococcus. Brit. J. Exp. Path. 15:362, 1934.

38. Thomas, L., et al. Investigation of meningococcal infection. II. Immunological aspects. J. Clin. Invest. 22:361, 1943.

39. Goldschneider, I., et al. Human immunity to the meningococcus. I. The role of humoral antibodies. J. Exp. Med. 129:1307, 1969.

40. Goldschneider, I., et al. Human immunity to the meningococcus. II. Development of natural immunity. J. Exp. Med. 129:1327, 1969.

41. Gotschlick, E. C., et al. Human immunity to the meningococcus. III. Preparation and properties of the group A, group B and group C meningococcal polysaccharides. J. Exp. Med. 129:1349, 1969.

42. Gotschlick, E. C., et al. Human immunity to the meningococcus. IV. Immunogenicity of group A and group C meningococcal polysaccharides in human volunteers. J. Exp. Med. 129:1367, 1969.

43. Gotschlick, E. C., et al. Human immunity to the meningococcus. V. The effect of immunization with meningococcal group C polysaccharide on the carrier state. J. Exp. Med. 129:1385, 1969.

44. Artenstein, M. S., et al. Prevention of meningococcal disease by group B polysaccharide vaccine. New Eng. J. Med. 282:417, 1970.

Risk of Secondary Cases

45. Norton, J. F. Meningococcus meningitis in Detroit: 1928-1929. V. Secondary cases. J. Prev. Med. 5:365, 1931.

46. Pizzi, M. A severe epidemic of meningococcus meningitis in Chile, 1941-1942. Am. J. Public Health 34:231-238, 1944 (March).

47. Leedom, J. M., et al. The problem of sulfadiazine resistant meningococci. Antimicrobial Agents & Chemotherapy, 1966, p. 281.

48. Artenstein, M. A., and Ellis, R. E. The risk of exposure to a patient with meningococcal meningitis. Military Medicine 133:474, 1968.

49. Op.cit., ref. 27

Antibiotic Prophylaxis

50. Dowd, J. M., et al. Antibiotic prophylaxis of carriers of sulfadiazine-resistant meningococci. J. Inf. Dis. 116:473-480, 1966.

51. Bristow, W. M., et al. Op.cit., ref. 24
Gauld, J. R., et al. Op.cit., ref. 23

52. Millar, J. W., et al. In vivo and in vitro resistance to sulfadiazine in strains of Neisseria meningitidis. JAMA 186:139, 1963.

53. Eichoff, T. C., and Finland, M. Changing susceptibility to antimicrobial agents. New Eng. J. Med. 272:359, 1965.

54. Cataldo, J. R., et al. Sulfadiazine and sulfadiazine-penicillin in mass prophylaxis of meningococcal carriers. Military Medicine 133:453, 1968.

55. Artenstein, M. S., et al. Attempted prophylaxis against meningococcal infection using intramuscular penicillin. Military Medicine 132:1009, 1967.

56. Alexander, C. E. Sulfadiazine-resistant group A Neisseria meningitidis. Science 161:1019, 1968.

Clinical Picture--Therapy

57. Smith, E. S. Purulent meningitis in infants and children. J. Pediatrics 45: 425, 1954.

58. Levin, S., and Painter, M. B. The treatment of acute meningococcal infection in adults. A reappraisal. Ann. Int. Med. 64:1049, 1966.

59. Wolf, R. E., and Birbara, C. A. Meningococcal infections at an Army training center. Am. J. Med. 44:243, 1968.

60. Hardman, J. M. Fatal meningococcal infections: The changing pathologic picture in the '60s. Military Medicine 133:951, 1968.

61. May, C. D. Circulatory failure (shock) in fulminant meningococcal infection. An enquiry into the pathogenesis as an approach to rational therapy. Pediatrics 25:316, 1960.

62. Levin, J., and Cluff, L. E. Endotoxemia and adrenal hemorrhage. A mechanism for the Waterhouse-Friderichsen syndrome. J. Exp. Med. 121:247, 1965.

63. Margaretten, W., and McAdams, A. J. An appraisal of fulminant meningococcemia with reference to the Shwartzman phenomenon. Am. J. Med. 25:868, 1958.

64. Black-Schaffer, B., Hiebert, T. G., and Kerby, G. P. Experimental study of purpuric meningococcemia in relation to the Shwartzman phenomenon. Arch. Path. 43:28, 1947.

65. Hjort, P. F., and Rapaport, S. I. The Shwartzman reaction: Pathogenetic mechanisms and clinical manifestations. Ann. Rev. Med. 16:135, 1965.

66. McGehee, W. G., Rapaport, S. I., and Hjort, P. F. Intravascular coagulation in fulminant meningococcemia. Ann. Int. Med. 67:250, 1967.

67. Dennis, L. H., et al. Consumptive coagulopathy in fulminant meningococcemia. JAMA 205:179, 1968.

68. Bachmann, F. Disseminated intravascular coagulation. Disease-a-Month, Dec. 1969.

69. Mammen, E. F., Anderson, G. F., and Barnhart, M. I., Editors. Disseminated Intravascular Coagulation. F.K. Schattauer Verlag, Stuttgart and New York, 1969.

70. Pinals, R. S., and Ropes, M. W. Meningococcal arthritis. Arth. & Rheum. 7:241, 1964.

71. Schein, A. J. Articular manifestations of meningococcic infection. Arch. Int. Med. 62:963, 1938.

72. Beckman, W. W., and Ropes, M. W. Meningococcal arthritis: a clinical study. J. Clin. Invest. 23:950, 1944.

73. Benoit, F. L. Chronic meningococcemia. Case report and review of the literature. Am. J. Med. 35:103, 1963.

74. Donald, W. D., and Doak, W. M. Mimeae meningitis and sepsis. JAMA 200:287, 1967.

75. Barnett, J. A., and Sanford, J. P. Bacterial shock. JAMA 209:1514, 1969.

76. Southern, P. M., Jr., and Sanford, J. P. Meningococcal meningitis--Suboptimal response to cephalothin therapy. New Eng. J. Med. 280:1163, 1969.

77. Sanford, J. P. Pharmacology and modes of action in relation to clinical antimicrobial therapy. Clin. Neurosurg. 14:178, 1967.