

PYOGENIC MENINGITIS — A STUDY OF 303 CASES

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There has been much controversy over the treatment of non-tuberculous bacterial meningitis which has been the subject of many papers and discussions in both paediatric and adult medicine.<sup>1-9,17</sup>

No satisfactory single antibiotic or combination of antibiotics has been generally accepted as ideal, whether given parenterally or orally, in combination with intrathecal therapy or without it. The mortality rate still remains fairly high in most series. The necessity for optimal therapy has been stressed by Banks *et al.*<sup>8</sup> and Alexander,<sup>7</sup> but they do not state what optimal therapy is. Continued study of the problem needs no further justification.

There have been few reports in the South African literature of treatment of meningitis, the most recent being one in 1958<sup>5</sup> and one in 1960.<sup>17</sup>

The cases of non-tuberculous bacterial meningitis at the City Hospital for Infectious Diseases, Cape Town, were studied over the 3-year period January 1955 - December 1957 and were divided into 4 main groups:

1. Meningococcal meningitis — 198 cases.
2. Purulent meningitis (signifying that no organisms were found on a smear stained by Gram's method, or were isolated on culture) — 61 cases.
3. Pneumococcal meningitis — 20 cases.
4. *H. influenzae* meningitis — 24 cases.

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There were also 1 case each of staphylococcal, *S. typhimurium* and *S. paratyphi* C meningitis but these will be excluded from the series, leaving 303 cases for consideration (Table I). It may be pointed out that non-meningococcal cases were admitted to the Infectious Diseases Hospital from general practitioners on the strength of their diagnosis of 'meningitis', and the type of infection, which would have excluded them, was not apparent until the cerebrospinal fluid was examined.

MENINGOCOCCAL MENINGITIS

There were 198 patients in this series, their ages ranging from 1 month to 65 years (Table II). There were 45 patients less than 1 year of age, 94 between 1 and 10 years, and 59 more than 10 years of age (Table I). Of the 198 patients, 98 were male and 100 female; 34 were European, 148 Coloured and 16 African (Table II).

In 191 cases Gram-negative bean-shaped diplococci were seen on direct microscopic examination of the cerebrospinal fluid (96%), and were grown on culture in 64 cases. The organisms were sensitive in all cases to 'chloromycetin', streptomycin, 'aureomycin' and 'terramycin', but over the 3 years there were 12 instances where they were insensitive to penicillin.

At this hospital, until about the middle of 1956, the routine scheme of antibiotic treatment was penicillin with sulphadiazine for a period of 7-10 days. Sulphadiazine was given according to the scheme proposed by Banks.<sup>18</sup>

TABLE I. MORBIDITY AND MORTALITY FIGURES IN 303 CASES OF MENINGITIS

Infection	Age (years)	Cases	Survival	Deaths	Morbidity	Complete recoveries	Survival excluding those who died within 24 hours
Meningococcal	<1	45 (23%)	44 (98%)	1 (2%)	1 (2%)	181 —=90% 198	186 —=98% 189
	1-10	94 (47%)	86 (91%)	8 (9%)	1 (1%)		
	10+	59 (30%)	56 (95%)	3 (5%)	3 (5%)		
	Total	198	186 (94%)	12 (6%)	5 (3%)		
Purulent	<1	10 (16%)	9 (90%)	1 (10%)	0	52 —=85% 61	53 —=96% 55
	1-10	26 (43%)	24 (92%)	2 (8%)	0		
	10+	25 (41%)	20 (80%)	5 (20%)	1 (4%)		
	Total	61	53 (87%)	8 (13%)	1 (2%)		
Pneumococcal	<1	10 (50%)	9 (90%)	1 (10%)	0	16 —=80% 20	17 —=94% 18
	1-10	2 (10%)	2 (100%)	0	0		
	10+	8 (40%)	6 (75%)	2 (25%)	1 (13%)		
	Total	20	17 (85%)	3 (15%)	1 (5%)		
Influenzal	<1	16 (67%)	12 (75%)	4 (25%)	1 (6%)	17 —=71% 24	19 —=83% 23
	1-10	7 (29%)	6 (86%)	1 (14%)	1 (14%)		
	10+	1 (4%)	1 (100%)	0	0		
	Total	24	19 (79%)	5 (21%)	2 (8%)		

TABLE II. RACE, SEX AND AGE DISTRIBUTION IN 303 CASES OF MENINGITIS

Infection	Race distribution			Sex		Age
	European	Coloured	African	Male	Female	Months-Years
Meningococcal .. .. .	34 (17%)	148 (75%)	16 (8%)	98 (50%)	100 (50%)	1 - 65
Purulent .. .. .	13 (21%)	42 (69%)	6 (10%)	39 (64%)	22 (36%)	2 - 52
Pneumococcal .. .. .	3 (15%)	14 (70%)	3 (15%)	12 (60%)	8 (40%)	4 - 40
Influenzal .. .. .	5 (21%)	17 (71%)	2 (8%)	14 (58%)	10 (42%)	3 - 48
Total .. .. .	55 (18%)	221 (73%)	27 (9%)	163 (54%)	140 (46%)	

Because sulphonamides alone are not sufficient<sup>a</sup> and some organisms were reported insensitive to penicillin, chloromycetin was added as a routine antibiotic in the more severe cases from the middle of 1956. Intrathecally, penicillin and/or chloromycetin were given at the initial lumbar puncture if the cerebrospinal fluid was turbid. Lumbar punctures were done daily and intrathecal penicillin or chloromycetin was given until the fluid began to improve macroscopically and on laboratory analysis. From about April 1957, in the majority of cases, only 1 intrathecal injection of 1 or 2 antibiotics was given. Patients with the Waterhouse-Friderichsen syndrome were given intravenous 'solucortef' on admission, followed by cortisone for 8-10 days, with 'eucortone' given for 2 days.

There was a survival rate (Table I) of 94% with 12 deaths, the largest number of fatalities occurring in the 1-10-year group. There were 5 more cases with sequelae, the majority being in the over-10-year group, giving 181 complete recoveries out of 198 cases (90%). Excluding cases dying soon after admission, before therapy had a chance to be effective, there was a total of 189 cases of which 186 survived, giving a corrected survival rate of 98%.

#### PURULENT MENINGITIS

There were 61 patients with purulent meningitis (Table I), their ages ranging from 2 months to 52 years (Table II). Ten of them were below 1 year of age, 26 between 1 and 10 years, and 25 were more than 10 years old (Table I). Of the 61 patients, 39 were male and 22 female, 13 were European, 42 Coloured and 6 African (Table II).

Clinically, the majority appeared to be cases of meningococcal meningitis. Medical students are taught that in purulent meningitis, if no organisms are seen on smear or grown on culture, the likeliest infection is meningococcal. Often there was a history of the patient having received antibiotics before admission to hospital, usually 1 or 2 penicillin injections together with a few sulphonamide tablets. Many meningococci are sufficiently drug-sensitive to disappear from the cerebrospinal fluid on this treatment, whereas *H. influenzae* and *D. pneumoniae* are usually resistant to such minor therapy and are therefore more frequently seen on smear or grown on culture. For these reasons all the so-called purulent meningitides were treated as for meningococcal meningitis.

There was a survival rate (Table I) of 87%, with 8 deaths, the majority of which were in the over-10-years group. There was 1 further case with sequelae, leaving 52 complete recoveries out of 61 cases (85%). Six patients died soon after admission, leaving 55 cases of which 53 survived (96%).

#### PNEUMOCOCCAL MENINGITIS

There were 20 patients whose ages ranged between 4 months and 40 years (Table II); 10 were below 1 year of age, 2 between 1 and 10 years, and 8 over 10 years of age (Table I). Of the 20 patients, 12 were male and 8 female, 3 were European, 14 Coloured and 3 African (Table II).

The Gram-positive diplococcus was found in all cases on microscopy of the cerebrospinal fluid and was grown in 13 out of 19 cases where the CSF was cultured. In the 12 cases where sensitivity was reported all were sensitive to chloromycetin, aureomycin and terramycin; 92% were sensitive to penicillin; and 83% to streptomycin.

The routine therapy at this hospital for pneumococcal meningitis was penicillin, chloromycetin, and sulphadiazine as for meningococcal meningitis. Intrathecal therapy was given daily (in the milder cases penicillin alone, in the more severe cases penicillin and/or chloromycetin), until the cerebrospinal fluid had improved, i.e. the sugar was normal and there were no more than 30-40 cells per c.mm., mostly lymphocytes. Systemic treatment continued for a week thereafter. The average duration of intrathecal therapy was 10 days, and of general therapy, 19 days.

There was a survival rate (Table I) of 85% with 3 deaths, 2 of which were in the group over 10 years of age. The death in the patient below 1 year of age occurred within a few hours of admission. There was 1 case with sequelae, giving 16 complete recoveries out of 20 cases (80%). Excluding the cases dying within a few hours of admission, i.e. 2, there were 17 survivors out of 18 cases, a survival rate of 94%. Taking all the cases below 10 years of age, and excluding the child who died shortly after admission, there were 11 survivors out of 11 cases—a survival rate of 100%.

#### H. Influenzae MENINGITIS

There were 24 patients (Table I), their ages ranging from 3 months to 48 years (Table II). The majority (67%) were less than 1 year old and there was only 1 case over 10 years of age (Table I). Of the 24 patients, 14 were male and 10 female, 5 were European, 17 Coloured and 2 African (Table II).

In 18 cases the organism was seen on direct microscopic examination, and in 20 cases *H. influenzae* was grown on culture. Of 19 cases where the sensitivity was tested all were shown to be sensitive to chloromycetin, streptomycin, and terramycin; 89% were sensitive to aureomycin and only 5% to penicillin.

The routine treatment for this type of infection was chloromycetin, streptomycin, and sulphadiazine, with chloromycetin and streptomycin given intrathecally daily.

Intrathecal therapy was continued as for pneumococcal meningitis. The average duration of intrathecal therapy was 12 days and of general therapy 20 days.

There was a survival rate (Table I) of 79% with 5 deaths, 4 of which occurred in the group less than 1 year of age. There were 2 cases with sequelae, leaving 17 complete recoveries out of 24 cases (71%). Excluding the case which died soon after admission, there were 19 survivors out of 23 cases, i.e. a corrected survival rate of 83%.

## DISCUSSION

Meningococcal meningitis was almost invariably a fatal disease until antimeningococcal serum was introduced many years ago and a few cases were saved. Then came 'prontosil' which saved a few more, followed by sulphapyridine which made an even greater difference. As more sulphamide preparations were introduced the mortality rate fell, as well as the side reactions to the sulphamides. The target then became, not mere survival with or without sequelae, but complete recovery. That is the objective and the problem is how to attain it with the minimum of expense, therapeutic effort, and disturbance of the patient, while avoiding all risk of inadequate treatment.

Sulphonamides are not the final word in therapy of meningococcal meningitis, particularly if given alone.<sup>6</sup> Banks *et al.*<sup>6</sup> stated that the results of treatment of meningococcal meningitis with systemic penicillin and sulphamides and intrathecal penicillin were satisfactory; yet they noted a survival rate of only 70-76%. Cathie and Simpkins<sup>7</sup> treated 51 cases of meningococcal meningitis with penicillin and sulphamides, with 2 deaths (4%) and 6 cases with sequelae (12%), i.e. a survival of 96% and recovery of 84%. The present series shows survival of 94% and complete recovery in 92% of meningococcal infections. In the group of presumptive meningococcal cases, here classed as purulent meningitis, the figures are 87% and 85% respectively. A recent South African series<sup>8</sup> of comparable unidentifiable purulent cases in children, showed a recovery rate of 91%. It would seem that the remaining difficulty is the simplification of the treatment, since, with an infection of such potential virulence and rapidity, it is probably impossible to expect much further statistical improvement.

In pneumococcal meningitis most series overseas, including adults, report mortalities varying from 10% to 60%.<sup>10-15</sup> In Zilberg's series,<sup>9</sup> the mortality rate was 27% in infants and children. In the present series the overall mortality rate was 15% and excluding cases dying shortly after admission, it was 6%. Furthermore, excluding cases over 10 years of age, where the mortality rate is higher than in young children,<sup>15</sup> the survival rate was 100%. In the present series of 20 cases there was a complete recovery rate of 80%. This could probably be improved.

Meningitis due to *H. influenzae* remains a serious disease in spite of the advent of antibiotics and chemotherapeutic agents.<sup>3,4,5</sup> In Zilberg's series, the mortality rate was 26%,<sup>8</sup> in the present series, 21%. Only 71% made a complete recovery.

In searching for possible ways of improving on these results, the clinical manifestations and complications of the meningitides were reviewed. These features are shown

TABLE III. COMPLICATIONS ARISING IN 303 CASES OF MENINGITIS

Complication	Type of meningitis			
	Meningococcal	Purulent	Pneumococcal	Influenzal
Purpura .. ..	47 (24%)	14 (23%)	—	—
Herpes .. ..	25 (13%)	8 (13%)	1 (5%)	—
Arthritis .. ..	10 (6%)	4 (7%)	—	—
Waterhouse-Friderichsen .. ..	9 (5%)	7 (12%)	—	—
Coma .. ..	6 (3%)	2 (3%)	3 (15%)	4 (17%)
Cranial-nerve palsies .. ..	9 (5%)	4 (7%)	4 (20%)	5 (21%)
Hemiplegia .. ..	3 (2%)	1 (2%)	3 (15%)	4 (17%)
Eye complications .. ..	6 (3%)	—	—	—
Sulphonamide haematuria .. ..	2 (1%)	1 (2%)	—	—
Drug eruption .. ..	2 (1%)	1 (2%)	1 (5%)	1 (4%)
Fits .. ..	5 (3%)	—	3 (15%)	—
Stupor .. ..	—	—	—	4 (17%)
Mental deficiency .. ..	—	—	—	2 (8%)
Subdural effusions .. ..	—	—	2 (10%)	1 (4%)
Abortion .. ..	—	1 (2%)	—	—
Venous thrombosis .. ..	—	1 (2%)	—	—
No. of cases .. ..	90 (45%)	35 (57%)	11 (55%)	14 (58%)

in Table III. Apart from confirming other workers' conclusions<sup>2-6,8,10</sup> that coma and paralysis are of bad prognostic significance, the scrutiny does not seem helpful.

The duration of illness before admission gives more hope for the future. It is evident from Table IV that

TABLE IV. DURATION OF HISTORY IN DAYS

Infection	Overall		In those who died (average)
	Variation	Average	
Meningococcal .. ..	Hours - 14	3	3-5
Purulent .. ..	1 - 10	3	3
Pneumococcal .. ..	1 - 27	7	13-5
<i>H. influenzae</i> .. ..	1 - 28	11	22

in the meningococcal and purulent types, the illness had been shorter than in the other two. In these types there was also little or no difference in the duration of illness in those who recovered and those who died. In pneumococcal and haemophilus infections, however, the deaths occurred in those who had been ill for a much longer time than the average for each group as a whole. It would appear possible, therefore, that greater suspicion of meningitis as a cause of illness might lead to earlier diagnosis and treatment and to considerable improvement in the outlook. The treatment must be applied in time and, so applied, it is demonstrably efficient.

None of these types of meningitis would appear to be avoidable, e.g. by immunization techniques. The therapeutic approach obviously gives hope of complete recovery for patients who have neither a fulminating illness nor one of long duration before treatment. The degree to which the treatment can be simplified remains to be seen and will be considered in another paper. The relative paucity of recent publications on the subject should not be interpreted as an indication that the non-tuberculous bacterial meningeal infections are no longer a menace. They are dangerous, but not because of any lack of therapeutic armament. Lumbar puncture, properly carried out, should

be a painless and minor procedure from both the patient's and the doctor's point of view and there is no reason why, in the presence of doubt as to the diagnosis, a specimen of spinal fluid should not be regarded in much the same way as a specimen of urine, particularly in infants and young children. Pandy's test for increased globulin content can be done at the bedside and a positive result would indicate the need for further immediate investigation. There is no other simple procedure for the certain detection of meningitis in its early stages. From the figures given it is obvious that in the pneumococcal and influenzal types of infection, earlier diagnosis is the key to more successful treatment.

#### SUMMARY

1. At the City Hospital for Infectious Diseases, Cape Town, 303 cases of pyogenic meningitis were studied over a 3-year period. They are reported in 4 groups—meningococcal, purulent, pneumococcal and haemophilus infections.

2. The survival rates were 94, 87, 85 and 79% respectively. Complete recovery was found in 90, 85, 80 and 71%.

3. Scrutiny of the clinical and therapeutic factors indicates that adequate treatment is now available but that delay in its application is a vital handicap.

4. Earlier suspicion and diagnosis of the illness is essential.

My thanks are due to Dr. E. D. Cooper, Medical Officer of Health, Cape Town, and Dr. H. Ackermann, Superintendent of the City Hospital for Infectious Diseases, Cape Town, for kind permission to publish these findings; to Dr. R. Rabkin and Dr. C. Cavadas for their cooperation; to Prof. F. J. Ford for his kind help and encouragement, and to Miss C. Freeseaman for preparation of the tables.

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