The treatment of pyogenic meningitis

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The mortality of bacterial meningitis lies between 10 and 15% (Mathies, Leedom, Thrupp, Ivler, Portnoy, and Wehrles, 1965), in spite of susceptibility of the common causative organisms to a wide range of antibiotics. This naturally prompts a search for more efficient therapy and as new antibiotics are introduced they are used with more or less enthusiasm. My purpose here is to report a personal series and compare the results with those treated differently.

MATERIAL AND METHODS

The present series of 210 cases is concerned with the four major groups of pyogenic meningitis—meningococcal, haemophilus, pneumococcal, and unknown (those from whom no organism was recovered from the cerebrospinal fluid (CSF) nor seen on direct film). It includes 99 cases previously reported (McKendrick, 1954) and 111 cases seen in the last nine years. Treatment of the meningococcal and pneumococcal cases was similar in the two groups, except that chloramphenicol replaced streptomycin in the last 29 haemophilus patients and was added to the penicillin-sulphadiazine schedule in the last 22 cases of unknown aetiology. The results of the two groups are virtually identical.

Treatment schedules for the last 111 cases were as previously described (McKendrick, 1962) namely:

(1) Intramuscular penicillin and intramuscular sulphadiazine immediately after spinal tap and blood culture in all cases. Intrathecal penicillin was injected routinely in the appropriate dose at all diagnostic punctures which produced a purulent CSF.

MENINGOCOCCAL INFECTIONS (1) Sulphadiazine in maximum doses, 0.3 g/kg/day (in divided doses 4-hourly) up to 9 g/day for an adult for one to two days, followed by two-thirds of this dose daily for a further five or six days. The drug was given intramuscularly until vomiting ceased, usually within 12 to 24 hours, and then by mouth. (2) Penicillin G intramuscularly 4-hourly for two to seven days, usually 0.5 Mu.

Three patients who developed late septic complications—pericarditis in two and arthritis in one—also received cephaloridine for seven to 14 days.

HAEMOPHILUS INFLUENZAE (1) Sulphonamides in maximum doses as for meningococcal infections.

(2) Chloramphenicol 200 mg/kg/day (in divided doses 6-hourly) for a minimum of two days, the dose being

reduced to 50-75 mg/kg to complete 10 days (maximum doses 4 g/day). The sodium succinate preparation was used intramuscularly as required. This dose schedule does not apply to infants under 4 weeks of age.

PNEUMOCOCCAL INFECTIONS (1) Penicillin G intramuscularly together with crystalline penicillin intrathecally daily for at least five days in a dosage of 5,000 u. from 0 to 3 months, 10,000 u. from 3 months to 2 years, and 20,000 u. for all patients over 2 years. (2) Sulphonamides as for meningococcal infections.

UNKNOWN (1) Penicillin, sulphonamides for seven days, plus chloramphenicol with the dose reduced to 50 mg/kg early in the course and finishing in under seven days if clinical progress is satisfactory. All but one patient in this category had had antibiotics before admission to hospital.

Apart from pneumococcal cases receiving daily intrathecal therapy no further lumbar puncture was performed in any case unless progress was unsatisfactory. Intravenous fluids were not a routine of treatment, feeds being given by mouth or nasal tube. Continued vomiting rarely led to the need for parenteral fluids, the only indications for which were considered to be shock, gastric bleeding, or stage II dehydration. About 15% of patients required parenteral fluid therapy early in their illness.

STEROIDS These were not used routinely. An excessive exudate—CSF cells greater than 30,000/cm or a high or rising protein level—or the development of focal signs 36 hours or later after starting treatment were considered to be indications for steroid therapy.

Bacteria were seen or cultured in all bacteriologically proved cases except two, which are included in the meningococcal series because of their typical clinical picture and rash. Patients with Waterhouse-Friderichsen syndrome have not been included, but cases of meningococcal septicaemia with meningitis have. The only other case excluded from the series is one of haemophilus influenzae meningitis occurring as a terminal infection in a man of 54 suffering from leukaemia. No case has been excluded because of early hospital death. Two of the five fatal pneumococcal cases died within 12 hours of admission.

RESULTS

The overall mortality together with its relation to age in the bacteriologically proved cases is shown in Table I.

TABLE I

CASES (WITH DEATHS IN PARENTHESES) RELATED TO AGE AND TYPE OF MENINGITIS

Aetiology	0-4	5-9	10-19	20-29	30 and over	Total cases and deaths	Mortality rate (%)
<i>Meningococcus</i>	56 (0)	16 (0)	19 (0)	2 (0)	4 (1)	97 (1)	1.0
<i>Haemophilus</i>	34 (1)	11 (0)	—	—	1 (0)	46 (1)	2.2
<i>Pneumococcus</i>	17 (1)	8 (1)	9 (0)	—	8 (3)	42 (5)	12.0
Unknown						25 (0)	0
Totals						210 (7)	3.3

Blood cultures were positive in 40% of haemophilus, 16% of pneumococcal, but in only 5% of meningococcal cases, in spite of the fact that 44% of meningococcal infections had erythematous or petechial rashes.

Complete information regarding sequelae is known for the past 111 cases as detailed in Table II.

Subdural effusion was rare. It was suspected in five cases, but proved in only one due to haemophilus influenzae. All recovered.

TABLE II

SEQUELAE IN 111 CASES

Aetiology	Cases (no.)	Focal neurological signs developing during acute phase	Sequelae	Detailed sequelae
<i>Meningococcus</i>	48	11	2	A.B. foot drop; epilepsy; C.D.; mild partial deafness
<i>Haemophilus</i>	29		2	1 bilateral severe deafness; 1 mild unilateral deafness
<i>Pneumococcus</i>	12	3	1	1 hydrocephalus, deaf, blind, mental defective
Unknown	22	4	2	1 dysarthria; 1 cerebellar ataxia
Totals	111		7 (6.3%)	

DISCUSSION

All patients were followed up for a minimum of one year. Two of the patients with sequelae are worth describing in more detail.

A.B. MENINGOCOCCAL MENINGITIS AND SEPTICAEMIA A 17-year-old girl admitted on 2 November 1964 on the second day of illness with a diagnosis of food poisoning. On examination, deeply unconscious with extensive haemorrhages and marked neck stiffness, bilateral papilloedema, and stomach aspirate containing coffee grounds. Cerebrospinal fluid—22,990 polymorphs/c.mm,

protein 950 mg/100 ml. After 24 hours' routine therapy plus prednisolone she developed evidence of brain-stem oedema with irregular respirations and hyperpyrexia. Cooling with intravenous pethidine, chlorpromazine, and promethazine was started, which produced a satisfactory fall in temperature. Over the next three days, further deterioration included generalized convulsions, evidence of pyramidal tract damage, and anuria. On the fourth hospital day pharyngeal paralysis was evident with pooling of secretions, and spontaneous respiration became grossly irregular and inadequate. Intubation was followed by tracheostomy with intermittent positive pressure respiration, this being required for five days. After the return of spontaneous respiration it was a further four days before consciousness returned. The anuria responded to a modified Bull's regime with ultimate complete renal recovery. On discharge from hospital eight weeks after admission, the only abnormality was a left foot drop. However, this girl has had an occasional grand mal seizure since discharge, but these are easily controlled and she is back at work leading a normal life.

Emergency hypothermia in the treatment of meningococcal meningitis has since been reported by Robinson and Buckler (1965). Their patient also recovered.

C.D. MENINGOCOCCAL MENINGITIS AND SEPTICAEMIA A 15-year-old girl admitted to hospital on the third day of illness. On examination, semi-conscious, marked cerebral irritation, very toxic with an extensive rash. Suppurative arthritis left elbow and right wrist. As the CSF protein was 600 mg/100 ml. steroids were added to routine therapy. Consciousness returned on the the third hospital day and revealed a total aphasia. During the subsequent course of her illness this girl developed convulsions, cranial nerve palsies including a right 6th, left 3rd, bilateral lower motor neurone facial palsy, and bilateral deafness, radiculitis affecting the left foot, arthritis of left elbow, both knees and the right hip, and a severe pericarditis. On discharge 15 weeks after admission to hospital, the only residual neurological deficit was a moderate degree of bilateral hearing loss. Further improvement has occurred and for practical purposes hearing is normal. She leads an active life with a full-time office job.

Tracheostomy and intermittent positive pressure respiration was required in one other case in this series—a girl of 5 years with haemophilus influenza meningitis, who suffered respiratory arrest 48 hours after admission. Her subsequent course was uneventful and recovery complete.

The overall mortality was 3.3% (Table I) with a 12% mortality in pneumococcal cases. The better prognosis of this type of meningitis in the 5 to 20 age group appears in the Table and confirms previous reports. McKenzie, Love, Lawson, Pinkerton, Jamieson, and Stevenson (1967) had no deaths in

15 cases of pneumococcal meningitis treated with systemic and intrathecal cephaloridine but, as the authors state, a larger series is needed. However, the results are promising and justify further trials. A 12% mortality for pneumococcal meningitis is acceptable compared with 22% (Mathies *et al.*, 1965) or 36% from a national survey carried out by Bevan-Jones and Miller in 1967. The regular use of intrathecal penicillin for at least five days is believed to contribute to this and the intrathecal use of cephaloridine may well be partly responsible for the absence of deaths in the small series mentioned above. The treatment schedule used in the present series has the disadvantage of a multi-drug regime which varies with the type of meningitis being treated. In an attempt to simplify treatment, ampicillin has been widely used with satisfactory results, but this necessitates intravenous therapy because of the large doses required. Mathies *et al.* (1965), using a dosage of 150 mg/kg/day, reported an overall mortality of 8.3% (6.3% when patients dying within 12 hours of admission were excluded) in a series of 192 cases. The deaths according to aetiological agent were meningococcal 5.3%, haemophilus 6%, and pneumococcal 22% with no isolate, no deaths. Although there is a significance at the 5% level between a mortality of 8.3% and 3.6%, there is no statistical significance in the death rates of the three bacteriologically proved types between the present and the ampicillin-treated series.

Many factors affect survival in meningitis and it is not suggested that the regimes used here are superior to ampicillin. Indeed, Fleming, Murray, Fujiwara, Prichard, and McNaughton (1966) had only one 'inevitable' death in a series of 41 cases of meningitis in a children's hospital treated with 400 mg/kg ampicillin/day, the drug being given intravenously for a minimum of five days. Intrathecal ampicillin was not used in either of these series. Thrupp, Leedom, Ivler, Wehrle, Portnoy, and Mathies (1965) have shown that CSF levels of ampicillin are variable but tend to be highest in the first three days of treatment. In spite of the fact that the minimal bactericidal levels against haemophilus influenzae only approximated the *in vitro* minimal bactericidal level against the haemophilus influenzae isolated from the CSF, the mortality was low and the CSF ampicillin levels in the cases investigated bore no relationship to the final clinical outcome.

The random use of antibiotics outside hospital is rightly condemned, but in spite of the fact that their use in an undiagnosed meningitis makes a definitive diagnosis much more difficult, if not impossible, the absence of deaths in this group—present series 25 cases, Mathies *et al.* (1965) 29 cases—suggests

that this probably saved some lives. It does, however, prolong the patient's illness and often increases the need for investigations to exclude such conditions as intracranial abscess or tuberculous meningitis.

Theoretically, inhibition of growth by a bacteriostatic drug—sulphadiazine or chloramphenicol—lessens the effect of a bactericidal agent—for example, penicillin—which acts on the cell wall. In a discussion on the treatment of pyogenic meningitis Rose (1967) implied that such combinations should be avoided, but this is not confirmed by the results obtained in the present series.

Ampicillin is clearly a satisfactory treatment for meningitis, although no better than penicillin G for pneumococcal or meningococcal infections. There are obvious advantages in starting therapy in all cases with one drug which can be altered later in the light of bacteriological results. The main disadvantage of ampicillin is the need for intravenous therapy, which in our opinion is not otherwise required in the majority of patients suffering from pyogenic meningitis.

Cephaloridine is at present under trial in my department in pneumococcal cases, but treatment schedules for the other types remain unaltered. There will probably always be an inevitable mortality due to some cases arriving too late for therapy to be effective. The regimes described here have the merits of ease of administration and at least equal success with any other in current use.

SUMMARY

A series of 210 cases of the common varieties of pyogenic meningitis with a 3.3% mortality is reported. There were 97 meningococcal (one death), 42 haemophilus (one death), 42 pneumococcal (five deaths), and 25 of unknown aetiology (no deaths). Details of the antibiotics used are described.

The results compare satisfactorily with other series. The merits of ampicillin in the treatment of meningitis are discussed.

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The August 1968 Issue

THE AUGUST 1968 ISSUE CONTAINS THE FOLLOWING PAPERS

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Book Reviews

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BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, W.C.1, price 18s. 6d.

longing for the alien, aliens in space, humanoids in space (aliens envisaged by fantasy), belief in flying saucers and yearning for guardians, and Hamlet and Prospero. The approach is wide-ranging, even discursive, and the psychological insights tentative; it has not the overwhelming plausibility that Freud's excursions offered, and its lack of balance and of a continuous theme renders it scrappy—more suited to be offered in chunks in the columns of a 'quality weekly' than as a serious publication. There is an ingenious suggestion about the real-life model for Prospero.

THE PSYCHOLOGY OF ANXIETY By E. E. Levitt. (Pp. 259; illustrated. 36s.) Staples Press: London. 1968.

This book is easy to read and provides a pleasant account of the subject of anxiety, suitable for those in whom some psychological trappings are considered appropriate. It would be a pity, however, if it were to fall into the hands of a potential serious student of the subject; it devalues the attempts made to provide a physiological measure of anxiety, it is insufficiently critical of the questionnaire method on which it relies heavily, and ignores a whole range of recent important work—for instance, that by Lader and Wing in this journal 27, 210; 28, 78; 28, 414—that is proving of value in extending our knowledge of anxiety.

BASIC PSYCHIATRY By M. Sim and E. B. Gordon. (Pp. viii + 262. 25s.) Livingstone: Edinburgh. 1968.

A book which compresses much of the material of psychological medicine in the form of short, ready-made answers to a series of questions will probably be welcomed by many of the increasing number of examination candidates in psychiatry. At the same time students will appreciate that a summary presentation of this type cannot be achieved without omissions and distortions. Indeed, the authors not only acknowledge the need for a larger textbook in their preface, but go so far as to conclude their compendium with a pointed suggestion: 'Those who desire a more comprehensive text with adequate reference should consult *Guide to Psychiatry* by Myre Sim, also published by E. & S. Livingstone Limited.'

BOOKS RECEIVED

Books noticed here may also be reviewed later

FUNDAMENTALS OF NEUROLOGY By E. Gardner. (Pp. xiii + 367; 161 figures. 64s.) Saunders: Philadelphia, London, and Toronto. 1968.

THE PROBLEMS AND PROSPECTS OF LSD Edited by J. Thomas Ungerleider. (Pp. xv + 109; 1 figure. \$5.00). Thomas: Springfield, Illinois. 1968.

THE BIODYNAMIC ROOTS OF HUMAN BEHAVIOUR By Jules H. Masserman. (Pp. ix + 119. \$5.75). Thomas: Springfield, Illinois. 1968.

DAS NEUROLOGIE UND PSYCHISCHE DEFEKTSYNDROMBEI FRUHKINDLICHEM HIRNSCHADEN By G. Huffmann.

(Pp. viii + 118; 24 figures; 17 tables. DM 38.00). Thieme: Stuttgart. 1968.

BEAT TO BEAT HEMODYNAMIC EFFECTS OF LUNG INFLATION AND NORMAL RESPIRATION IN ANAESTHETIZED AND CONSCIOUS DOGS By André A. Charlier. (Pp. 112; illustrated.) Presses Académiques Européennes S.C.: Brussels. 1968.

EINFLUSS DER KARLSBADER MINERALWÄSSER AUF DIE BILDUNG UND DIE AUSSCHIEDUNG DER GALLE By Jaroslav Benda. (Pp. 229; illustrated.) Imperial Karlovy Vary: Prague. 1966.

STIMULUS AND RESPONSE. The Law of Initial Value. By J. Wilder. (Pp. viii + 352; 24 figures. 84s.) John Wright: Bristol. 1967.

INTERDISCIPLINARY TOPICS IN GERONTOLOGY. 2. Methodological Problems in Cross-National Studies in Aging. Edited by Ethel Shanas and J. Madge. (Pp. vi + 113; illustrated. 48s.) Karger: Basel and New York. 1968.

HANDBUCH DER NEUROCHIRURGIE Edited by H. Olivecrona and W. Tönnis. (Pp. x + 666; illustrated. DM 392; \$98.00.) Springer: Berlin and New York. 1968.

NOTICE

INTERNATIONAL SYMPOSIUM ON CLINICAL APPLICATIONS OF ISOTOPE CLEARANCE MEASUREMENT OF CEREBRAL BLOOD FLOW

An International Symposium on the Clinical Applications of Isotope Clearance Measurement of Cerebral Blood Flow will be held from 1 to 12 April 1969. Details may be obtained from Dr. med. M. Brock, 65-Mainz, Neurochirurgische Univ.-Klinik, Lanenbeckstrasse 1, Western Germany.

SOCIETY FOR RESEARCH INTO HYDROCEPHALUS AND SPINA BIFIDA

The thirteenth Annual Meeting of the Society will take place under the Presidency of Dr. J. L. Emery at the Institute of Psychiatry, DeCrespigny Park, Denmark Hill, London S.E.5, on 19, 20, and 21 June 1969. Further information from Dr. A. L. Woolf, Midland Centre for Neurosurgery and Neurology, Holly Lane, Smethwick, Warley, Worcestershire.

INTERNATIONAL CONGRESS ON CYBERNETICS

An International Congress on Cybernetics will be held in London from 1 to 5 September 1969. Further information may be obtained from Dr. J. Rose, College of Technology and Design, Blackburn, BB2 1LH, Lancashire, UK.

CORRECTION

We regret that, because of an error that occurred during the final printing of the paper by Dr. G. Donald W. McKendrick "The Treatment of Pyogenic Meningitis" (October 1968, p. 528), the paper was incorrectly attributed to G. Donald and W. McKendrick, and that the error was perpetuated in the 1968 index.