TREATMENT OF CEREBROSPINAL MENINGITIS

A REVIEW OF 103 CASES

BY

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AND

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Introduction

The limitations of serum in the treatment of cerebrospinal fever affecting the youngest age group of the population have been known for many years. In their classical work on cerebrospinal fever Worster-Drought and Kennedy (1919) give the mortality for cases under 2½ years as over 75 per cent., and the published statistics of other authors have in the main agreed with this figure. At Cork Street Hospital our case mortality in past years among this age group conformed to the accepted rates in spite of daily spinal drainage and intensive intrathecal serum therapy. A definite improvement followed the introduction of sulphanilamide, which since 1937 had been used as an adjuvant to intrathecal serum therapy, but still the general mortality rate for the cases was 57 per cent. Then last autumn came M & B 693. Its introduction to Ireland happened to synchronize with the assumption by one of us (W. J. R.) of duty as resident medical officer at the hospital. We began to use M & B 693 at the same time as we decided to abandon the orthodox intrathecal route for serum administration. The results obtained showed a dramatic improvement. Not only did ten out of eleven consecutive cases recover (five of these patients being under 1 year of age, and all, except one, being infants or young children), but the clinical improvement in the individual cases was considerably speeded up and none of the successful cases developed any permanent disability. The case mortality in the under 1 year group was actually reduced from 78.26 per cent. among a series of forty-six cases treated by the old methods to 16.66 per cent. in a series of six cases treated by the new. A remarkable feature was the complete absence of hydrocephalus, which hitherto had been a very frequent occurrence in recovered cases of posterior basic meningitis.

The one death in the series occurred quite suddenly from respiratory failure when the child seemed to be responding to treatment. This phenomenon of sudden respiratory failure during the acute stage of the disease is well attested. Worster-Drought and Kennedy (1919), quoting Fairley and Stewart, mention that it occurred no fewer than nineteen times in one series of cases. It is obvious that no method of treatment, however efficacious, can be expected to eliminate the risk of this chance happening.

It has to be admitted that the series here reported as treated by the "new method" is very small as compared with the large number of cases treated by intrathecal serum. For this the time interval since the introduction of M & B 693 is alone responsible. In the seven months which have elapsed since that drug became available in Ireland all cases admitted to Cork Street Hospital have been treated with it and the intrathecal route of serum avoided (the "new method"). For nearly two years

before October, 1938, all our cases received prontosil album and/or soluseptasine, with intrathecal serum following daily spinal drainage (the "intermediate method"). For the two years previous to that (1935 and 1936) the treatment was the same as the "intermediate" without the addition of sulphanilamide in any form (the "old method"). No element of selection was observed at any stage: all the cases of confirmed cerebrospinal meningitis treated in the hospital since January 1, 1935, are included in this survey. One of us (W. J. R.) was personally responsible for the detailed treatment of all the cases in which the "new method" was used.

As to whether the same improvement in results would have been obtained by using M & B 693 alone, without serum given extrathetically, we are not in a position to say, but it seemed to us reasonable to endeavour to neutralize the toxæmia, which is part of the clinical picture in meningococcal meningitis, by the intravenous and intraperitoneal administration of specific antibodies while relying on chemotherapy to produce the antibacterial effects. The drainage of the canal for a few days seemed also indicated to lessen pressure symptoms, and, at the very least, it afforded a means of assessing the progress of the case by physical, cellular, and bacteriological examination of the cerebrospinal fluid withdrawn.

Review of Cases

The object of this paper is to describe and compare results of the different modes of treatment of cerebrospinal meningitis employed in Cork Street Hospital from the beginning of 1935 up to the present time. The review concerns 103 cases and covers a period of four and a quarter years. Broadly speaking, the methods of treatment employed during the period under review were:

Old Method: 1935-6.—Daily spinal drainage followed by intrathecal and intramuscular serum therapy until the cerebrospinal fluid was clear and sterile.

Age of Patient	Cases	Recovered	Deaths	Case Mortality per cent.
0-1 year	17	1	16	94.11
1-5 years	7	3	4	57.14
5-15 "	4	1	3	75.00
15-25 "	5	2	3	60.00
Over 25 years ..	3	2	1	33.33
Total	36	9	27	75.00

Intermediate Method: 1937 to September, 1938.—The treatment was the same as in 1935-6, with the addition of prontosil album orally and/or soluseptasine intramuscularly.

Age of Patient	Cases	Recovered	Deaths	Case Mortality per cent.
0-1 year	29	9	20	68.96
1-5 years	13	7	6	46.15
5-15 "	9	5	4	44.44
15-25 "	3	1	2	66.66
Over 25 years ..	2	2	0	—
Total	56	24	32	57.14

New Method: October, 1938, to April, 1939.—(1) M & B 693 orally; (2) avoidance of intrathecal therapy;

(3) intravenous and intraperitoneal serum therapy; (4) daily spinal drainage until cerebrospinal fluid was clear and sterile.

Age of Patient	Cases	Recovered	Deaths	Case Mortality per cent.
0-1 year	6	5	1	16.66
1-5 years.. ..	3	3	0	—
5-15 „	1	1	0	—
15-25 „	—	—	—	—
Over 25 years ..	1	1	0	—
Total	11	10	1	9.09

The above tables show the results analysed according to age.

Details of Cases treated by New Method

As shown, these numbered eleven; six were under 1 year of age, and in this group the only death in the series occurred. The following is a brief résumé of all the cases treated.

Case I

A male aged 7 months was admitted from St. Ultan's Hospital on October 20, 1938, as a case of meningitis—eleven days ill before admission: clinically a meningitis. Lumbar puncture, performed at St. Ultan's, had yielded a turbid fluid which contained meningococci. Lumbar puncture on each of four succeeding days yielded successively 16 c.cm., 30 c.cm., 16 c.cm., and 15 c.cm. of cerebrospinal fluid. Meningococci were present in the first two. The fourth specimen was normal.

Treatment.—Twenty c.cm. of A.M.S.* was given intramuscularly on the day of admission and on the next day. On the third and fourth days 20 c.cm. of M.A.T.† were administered intraperitoneally. M & B 693, 0.25 gramme four-hourly, was given for five days, and also soluseptasine, 2 c.cm. morning and evening. (The strength of soluseptasine was 10 per cent. in each case in which it was given in this series.) Response was immediate and marked. The notes on October 25, 1938 (sixth day in hospital) were as follows: “Child much better; no head retraction or rigidity, expression bright, taking nourishment well. Child able to sit up.—W. J. R.”

The subsequent course of the case was uneventful—the child made a complete recovery, and was discharged on the twenty-sixth day of the disease (sixteen days after admission to Cork Street Hospital) apparently perfectly normal.

Case II

A female child aged 4 months, admitted from the National Children's Hospital on October 28, 1938, the fourth day of the disease. Signs of meningitis well marked. Baby in very emaciated condition. Purpuric rash all over body. Temperature on admission 102° F.; pulse 160. Patient gravely ill. Salines were given by the subcutaneous and continuous rectal drip methods. Eighteen c.cm. of what appeared to be pure pus was obtained by lumbar puncture, and on examination was found to contain meningococci in considerable numbers. Four subsequent lumbar punctures were done. In three of these specimens meningococci were present. The last specimen was clear and contained no meningococci.

Treatment.—Large doses of meningococcal serum were given by the intravenous, intramuscular, and intraperitoneal routes—in all 200 c.cm. of serum, in divided doses. M & B 693, 0.25 gramme, was given four-hourly, as well as soluseptasine in doses of 2 c.cm. morning and evening, until the fluid was clear. Although the child was very ill for several days, the following note was made on November 3 (sixth day

after admission): “Condition very satisfactory. Colour improved. No head retraction; able to move head from side to side. Baby looks quite intelligent. Taking feeds well. An urticarial serum rash present.”

The subsequent course of the case was uneventful. There was a slight pyrexia lasting about two days associated with an urticarial serum rash, but recovery proceeded rapidly, and on the twenty-second day of the disease (two and a half weeks after admission) the child was able to be discharged, and appeared to be normal both physically and mentally.

Case III

A man aged 55 was admitted from St. Michael's Hospital, Dunlaoghaire, on November 14, 1938, the fifth day of the disease. The case was clinically a meningitis, with neck rigidity and some head retraction. Spinal puncture yielded 14 c.cm. of very turbid fluid under marked tension; it contained meningococci, with excess in polynuclears and no sugar. Twenty c.cm. of A.M.S. was given intramuscularly on admission, followed some four hours after by 30 c.cm. of M.A.T. intravenously with 40 c.cm. of glucose. On the following day (the sixth of the disease) the patient was drowsy, had slight head retraction, and still showed the classical signs of meningitis. Thirty c.cm. of M.A.T. intravenously and 10 c.cm. of soluseptasine were given twice a day, as well as 1 gramme of M & B 693 four-hourly. A lumbar puncture yielded 50 c.cm. of turbid fluid under tension; the fluid still showed meningococci and excess of polynuclears. On this night 30 c.cm. of M.A.T. was repeated intravenously, with 40 c.cm. of glucose. On the third day (the seventh of disease) the patient's general condition was fairly good. He was not so drowsy, his pupils were equal and reacted briskly to light. On this day he received 30 c.cm. of M.A.T. intravenously and the same amount of A.M.S. intramuscularly in the evening. Ten c.cm. of soluseptasine was still given morning and evening, and also 0.5 gramme of M & B 693 four-hourly. Lumbar puncture yielded 15 c.cm. of turbid fluid under less tension. This fluid for the first time showed no meningococci. The patient did not subsequently undergo spinal puncture, but on the following two days (the eighth and ninth days of disease) received 30 c.cm. of M.A.T. intravenously as well as 0.5 gramme of M & B 693 four-hourly.

The subsequent course of the case was uneventful: the patient made an uninterrupted recovery, his temperature never rising after the second day, even though a serum rash developed about ten days after his admission to hospital. He was discharged on December 6 (just three weeks after admission) physically and mentally normal. He was the first adult patient serum-treated in Cork Street Hospital for meningococcal meningitis by completely extrathecal routes.

Case IV

A female child aged 2, admitted from the Adelaide Hospital on November 24, 1938, the seventh day of illness. On admission the case was clinically one of meningitis, but the patient suffered concurrently from scarlet fever and aural diphtheria. She was gravely ill when admitted, and her life was despaired of during the first week. A lumbar puncture was done on six successive days. She drained badly on the second and the fourth punctures. Meningococci, present in the cerebrospinal fluid on the first occasion, were not found subsequently.

Treatment.—In all, 240 c.cm. of meningococcal serum was given by intravenous, intraperitoneal, and intramuscular routes. M & B 693, 0.5 gramme four-hourly, was given for five days, as well as 2 c.cm. of soluseptasine morning and evening over the same period. Recovery was slowly effected because of a troublesome serum rash of an urticarial and morbilliform type which appeared at different periods. Facial paralysis developed on the ninth day; this eventually cleared up. Internal strabismus also developed; this was most pronounced at first, but gradually improved, and was very slight when the child left the hospital on January 7, 1939. The ear discharge remained positive for *Corynebacterium diphtheriae* for several weeks, and necessitated the prolonged stay in hospital.

* A.M.S. = Polyvalent anti-meningococcus serum (Mulford).

† M.A.T. = Meningococcal antitoxin (P. D. and Co.).

Case V

A boy aged 7 years was admitted from the Children's Hospital, Temple Street, on January 5, 1939, the fifth day of the disease. He had been taken to Temple Street on that day, and turbid cerebrospinal fluid was obtained by lumbar puncture there. A lumbar puncture was done at Cork Street on five successive days. Only the first two specimens contained meningococci.

Treatment.—Thirty c.cm. of A.M.S. was given intramuscularly on admission, followed by a daily intravenous injection of 30 c.cm. of M.A.T. for four days. M & B 693, 0.5 gramme four-hourly, was given for five days. He was discharged on February 13 (five weeks after admission). This boy's protracted stay in hospital was due to deafness, which eventually cleared up.

Case VI

A boy aged 5 years, admitted on February 7, 1939, the fifth day of illness. The cerebrospinal fluid was very purulent, containing meningococci in considerable numbers. This was a sharp case. A lumbar puncture was performed on five successive days (15 c.cm., 38 c.cm., 8 c.cm., 30 c.cm., and 48 c.cm. of cerebrospinal fluid were obtained respectively). Meningococci were absent after the first two punctures.

Treatment.—Eighty c.cm. of M.A.T. intravenously and 100 c.cm. of M.A.T. intraperitoneally were given in divided doses during the first four days. M & B 693, 0.5 gramme four-hourly, was administered on the first day, being increased to 1 gramme four-hourly on the second day; but as it was taken reluctantly 5 c.cm. of soluseptasine was given twice daily for four days.

The boy was discharged perfectly well on March 10, after four weeks in hospital.

Case VII

A female child aged 11½ months was admitted from St. Ultan's Hospital on February 17, 1939, the third day of the disease. A lumbar puncture performed at St. Ultan's had revealed meningococci in the cerebrospinal fluid. The baby was in a wasted and dehydrated condition on admission. The clinical signs of meningitis were present, and there was marked head retraction and arching of the back. The pupils were dilated and reacted sluggishly to light. Diarrhoea and vomiting were present; respirations were 44, bronchopneumonia was well marked. Salines were given subcutaneously and by continuous rectal drip. Lumbar puncture after admission yielded 20 c.cm. of very turbid cerebrospinal fluid; on February 18 punctures were done morning and evening, but yielded only a few c.cm. of very turbid fluid. On the 19th 10 c.cm. of cerebrospinal fluid, withdrawn by lumbar puncture, showed a clearer fluid, and on the 21st 30 c.cm. withdrawn proved to be absolutely clear.

Treatment.—Thirty c.cm. of A.M.S. was given intramuscularly on admission (February 17, 1939); on February 18 50 c.cm. of M.A.T. intraperitoneally, and also 4½ oz. of glucose saline (5 per cent.) into the peritoneal cavity at the same time; and M & B 693, 0.5 gramme four-hourly, daily until February 21, when the dose was halved. On the 23rd M & B 693 was discontinued. All signs and symptoms of meningitis had disappeared at this stage. The baby was discharged on April 8, looking normal in every way.

The prolonged stay in hospital (seven weeks) was not associated with the meningitis. We had a good deal of trouble with the baby's feeding before we got her back to normal weight.

Case VIII

A male child aged 4½ months, admitted from St. Ultan's Hospital on February 25, 1939. Two days ill before admission. Signs of meningitis well marked. Anterior fontanelle tense; diarrhoea and vomiting present. Seven lumbar punctures were done before the cerebrospinal fluid was free of meningococci.

Treatment.—Twenty c.cm. of A.M.S. was given intramuscularly on admission, and an intraperitoneal injection of M.A.T. on three successive mornings (30 c.cm., 40 c.cm., and 30 c.cm. respectively). M & B 693, 0.5 gramme, was given four-hourly on the first day and 0.25 gramme four-hourly every day until the fluid was clear. This baby did not take M & B 693 well in the beginning on account of the constant vomiting, and this may account for the delay in getting the cerebrospinal fluid sterile. (Saline was given by subcutaneous and continuous rectal drip for the first three days.)

The baby was discharged on March 20 (a little over three weeks after admission) normal in every way and considerably increased in weight.

Case IX

A boy aged 3 years 3 months was admitted on March 11, 1939, as a case of meningitis. He was very rigid, with marked arching of the back. Lumbar puncture after admission revealed a very turbid cerebrospinal fluid with large flakes of pus which came away with difficulty; 40 c.cm. of what looked like pure pus was withdrawn. Meningococci were present in large numbers. A puncture was performed on the three succeeding days and again after an interval of one day—five punctures in all. The cerebrospinal fluid on the last occasion was clear and sterile.

Treatment.—Forty c.cm. of M.A.T. intraperitoneally was given on admission, followed next morning by 20 c.cm. of M.A.T. intravenously. A rather severe rigor occurred after intravenous injection. On each of the next two mornings 30 c.cm. M.A.T. was given intraperitoneally. Recovery was uneventful, except for serum rashes, and the child was allowed up two weeks after admission. He was marked for discharge at the end of another week, but unfortunately got an attack of tonsillitis, which delayed his departure from hospital until April 13. In all he was thirty-four days in hospital. This child received 0.5 gramme of M & B 693 every four hours for the five days immediately following admission.

Case X

A male child aged 1 year was on March 22, 1939, admitted from the Children's Hospital, Temple Street, where he had been taken that day. He had been sick for about ten days, according to the mother. A lumbar puncture had been performed at Temple Street, and as a result of the findings the baby was sent on to us. The classical signs of meningitis were present. We withdrew 12 c.cm. of very turbid cerebrospinal fluid that evening.

Treatment.—Twenty c.cm. of A.M.S. was given intramuscularly and 0.25 gramme of M & B 693 four-hourly. The following note was made next morning: "Rigidity less marked—colour poor—face very pale—heart rapid and tone soft—general condition rather poor. Prognosis not good." A spinal puncture was done, but only a few c.cm. of fluid which looked like pure pus were obtained. It came through the largest needle with the greatest difficulty, and contained meningococci. Fifty c.cm. of M.A.T. was given intraperitoneally and 10 c.cm. of M.A.T. intramuscularly, with 0.5 gramme of M & B 693 four-hourly. Coramine was also given. One of us (W. J. R.) saw the baby at 11.45 o'clock that night. He looked better and had taken his feeds well during the day. There was no vomiting. He died quite suddenly with symptoms of respiratory paralysis at 5 o'clock the next morning.

Post-mortem Findings in Brain Specimen.—On incising the dura the meninges bulged. Pus was present under the meninges, with marked basal distribution, and the basal exudate appeared to be organizing in places. The meningeal vessels were somewhat congested. No haemorrhages were found, nor was there any observable focal suppuration. The brain tissues were unaffected.

Case XI

A female child aged 1 year. This case, the eleventh and last of this series, was the best so far as response to treatment is concerned. When admitted on April 6, 1939, the fourth

day of illness, well-marked signs of meningitis were present. Lumbar puncture on four successive days yielded respectively 30 c.cm., 33 c.cm., 30 c.cm., and 35 c.cm. of cerebrospinal fluid. The first two specimens were turbid and contained meningococci. The last specimen was clear, and the cell count was normal.

Treatment.—On the day of admission 80 c.cm. of M.A.T. was given intraperitoneally, and on the following morning 30 c.cm. of M.A.T. intravenously. M & B 693 0.5 gramme was given four-hourly for the first three days, followed by 0.25 gramme four-hourly for one day. On April 12 she was sitting up playing with her toys. She was discharged, looking perfectly normal, on the twelfth day of her stay in hospital.

Chart showing the case mortality for the last four periods October to March.

The graph (kindly drawn for us by Dr. J. G. Tynan, one of our medical officers) compares the case mortality among the age groups 0-1 year and 1-5 years during each successive period October to March, beginning October, 1935, to March, 1936, and ending October, 1938, to March, 1939. It may be assumed that the virulence of the prevailing organism in each of the periods was more or less uniform.

As a control there were two cases (not included in the foregoing) which had received intrathecal serum before admission to Cork Street Hospital, but which were treated by the new method after admission to hospital. Both these patients died, although the details of their treatment differed in no way from those of the patients who recovered.

We are kindly permitted by Dr. W. R. F. Collis (physician, National Children's Hospital, Dublin) to say that following our line of treatment at Cork Street Hospital he has had four recoveries among five cases treated, aged respectively 5 months, 8 months, 2 years, and 3 years. His fatal case was that of a patient aged 3 months, and was of the fulminating type. Dr. Collis's method was similar to that employed in Cork Street Hospital, except that he did not drain the spinal canal so frequently and gave rather less serum.

Summary

Eleven consecutive cases of fully authenticated meningococcal meningitis treated with M & B 693, extrathecal serum, and spinal drainage are reported with one death, a case mortality of 9.09 per cent.

Six of the patients were under 1 year of age, and of these five recovered—a case mortality of 16.66 per cent. for this age group, as compared with 78.26 per cent. in a series of forty-six cases under 1 year of age treated by the older method of intrathecal serum. None of the cases treated by the new method developed hydrocephalus or other disability.

In the one fatal case of the series death occurred suddenly from respiratory failure during the acute stage of the disease.

Generally speaking, within three or four days of the beginning of treatment a striking clinical improvement was noticed, as contrasted with a much more delayed reaction in the cases successfully treated by the older methods.

The good results of this line of treatment were confirmed by a smaller series of cases treated along similar lines—that is, M & B 693 plus extrathecal serum—by Dr. W. R. F. Collis.

We take this opportunity of thanking Dr. W. P. O'Callaghan, the hospital bacteriologist, for his thorough and careful examinations of nearly fifty specimens of cerebrospinal fluid submitted to him from the cases treated with M & B 693, as well as for his necropsy on the one fatal case in the series.

REFERENCE

Worster-Drought, C., and Kennedy, A. Mills (1919). *Cerebrospinal Fever*, A. and C. Black, London.

** Since this article was submitted for publication three further bacteriologically confirmed cases have been treated successfully by the above method. The patients were aged 4 months, 9 months, and 19 years respectively. The latter, a military case, was covered in a petechial rash on admission, all three patients being desperately ill. These cases bring the figures in this series to fourteen consecutive cases with thirteen recoveries, a case mortality of 7.14 per cent. Eight of the patients were under 1 year of age and seven recovered, giving a mortality rate of 12.5 per cent. for that age group.

THREE CASES OF CEREBROSPINAL FEVER TREATED BY M & B 693

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Three cases of cerebrospinal fever were recently admitted to the hospital under the care of Dr. L. G. Mackey. They were each treated by the administration of M & B 693 and by daily lumbar punctures. In view of the fact that such treatment is a recent innovation the details are briefly recorded.

Case I

A man aged 49 was admitted at 7 p.m. on February 1, 1939, having complained four days before of general malaise beginning with a rigor, and having suffered from headache, vomiting, and severe abdominal pain for the last two days. On admission his temperature was 100.4° F., his pulse rate 100, and his respiration rate 29. His mental condition was stuporous, but he could be aroused without difficulty. He had considerable neck rigidity and a bilateral positive Kernig sign and a positive Brudzinski sign. Several small petechiae were present on the arms, trunk, and legs. Lumbar puncture disclosed turbid cerebrospinal fluid under a pressure of over 300 mm. Direct films of the cerebrospinal fluid showed many polymorphonuclear cells and a number of intracellular and extracellular Gram-negative kidney-shaped diplococci. Culture yielded a Gram-negative diplococcus which agglutinated Group I meningococcal serum almost to titre. The biochemical findings were: chlorides, 658 mg.; sugar, 12 mg.; and protein, 440 mg. per 100 c.cm.

M & B 693 was given by mouth in the doses shown below. Daily lumbar puncture was performed until the fluid was at normal pressure on two successive days. The temperature and pulse became normal by the following morning, and by the third day there was a great improvement in the patient's