Clinical and other Notes.

SIX CASES OF CEREBROSPINAL MENINGITIS TREATED WITH M & B 693, MILITARY ISOLATION HOSPITAL, ALDERSHOT.

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In the spring of last year, during my short tenure of office at the Military Isolation Hospital, Aldershot, six cases of cerebrospinal meningitis were admitted. Of these, four were bacteriologically proved to be of meningococcal origin. In each case the diplococcus _N. meningitidis_ (Group I) was grown from the cerebrospinal fluid. Two cases were diagnosed clinically, but the diagnosis was not bacteriologically supported. The reason for this was that the first specimens of cerebrospinal fluid were sterile, and subsequent puncture was not indicated for the patients’ greater good.

All cases had a lumbar puncture performed on them for diagnostic purposes. After that, lumbar puncture was only performed when indicated for the relief of symptoms.

All cases were treated with M & B 693 in varying doses. Three were young soldiers, one an infant girl of 7 months, one a boy of 16, and one a man of 38.

In the treatment of the first of these cases, the importance of heavy initial dosage was not fully appreciated. The small dose given, however, did not retard recovery. This was probably due to the fact that he was diagnosed and got under treatment quickly. In subsequent cases this was rectified, and a heavy initial dose given.

Concentrated antimeningococcal serum was used, chiefly from a disinclination to reject precipitately that which had in the past been found of value. Or, in other words, a desire to give the patient every chance. There was, however, also a feeling that whereas the M & B 693 would kill the organism, the serum would neutralize any toxin already in the system. Serum was not given to any great extent, usually only when lumbar puncture was performed; except in the case of the one patient who was admitted quite unconscious. In three cases, where some of the M & B 693 was vomited, or where unconsciousness made oral administration impossible, soluseptasine was given intravenously and intramuscularly until such time as oral administration of M & B 693 and adequate retention of the drug was possible.

All six cases recovered completely, and comparatively rapidly. The majority of them were inquiring plaintively why they were not getting twice as much breakfast by the second or third morning. In fact a voracious appetite was a marked feature of all cases early in convalescence.
As far as was possible with such a small number of cases, a "routine treatment" was worked out. It was: On admission, lumbar puncture, with replacement by antimeningococcal serum intrathecally, the dose depending upon the amount of cerebrospinal fluid withdrawn. Four tablets of M & B 693 (30 grains) were given by mouth immediately, and repeated in four hours. Thereafter 2 tablets (15 grains) were given every four hours until the more critical period had passed, and then two tablets three times a day until all symptoms had completely disappeared. Lumbar puncture was only repeated when indicated for the relief of symptoms.

Case 1.—This patient, a boy aged 16, was admitted to the hospital suffering from a mild attack of rubella, which ran a normal course until the day he was due for discharge. He then had a rigor, and his temperature rose to 106°F. He complained of severe frontal headache and a pain in the neck. He was ejecting a copious brown vomit, was very pale, with rigid neck, and retraction of the head. Kernig's sign was doubtful, but was positive next morning. His pulse was fast, strong, and of good volume. Temperature had fallen to 104.8°F. by evening. Lumbar puncture was performed, and 25 c.c. of fluid of a slight but definite turbidity were drawn off, and 20 c.c. of concentrated antimeningococcal serum introduced intrathecally. The laboratory report showed a great increase of leucocytes—mainly polymorphs; globulin was increased, and sugar not decreased. The centrifuged deposit showed about 90 per cent polymorphs. No Gram-negative diplococci were seen or grown.

He had been given 7½ grains M & B 693, to be repeated four-hourly, but this was almost immediately increased to 15 grains three times a day.

By the evening of the second day his temperature was 98.6°F., and it never rose above 99°F. again, except over a period of one day, when he developed a severe serum rash.

By the evening of the third day all symptoms had disappeared, and apart from the serum sickness he made an uninterrupted recovery and was discharged on leave on the fifty-fourth day.

M & B 693 was discontinued on the sixth day.

Case 2.—An infant girl, aged 7 months, was admitted as a transfer from the Louise Margaret Hospital, Aldershot, on April 16, 1939. She had been found to be unwell when taken from her pram the day before. She cried and refused food all night. She was taken to the Louise Margaret Hospital. There she was reported as having her knees drawn up and spastic, her arms flexed and quivering, and pupils fixed. There was neck rigidity, and reflexes were elicited with difficulty. Lumbar puncture was performed, and N. meningitidis Group I was cultured from the fluid. Cells were predominantly polymorphs, globulin was increased, and sugar absent. There were a few epithelial cells. Gram-negative diplococci were seen in direct smear.

On admission to the Isolation Hospital she was flushed, her neck was very
rigid, and her head drawn back. Kernig's sign was positive. Her thighs were flexed upon the abdomen, and she gave the characteristic meningeal cry. Temperature was 102.2° F., and pulse 130.

She was given an intramuscular injection of concentrated antimeningococcal serum, 1 c.c. and 15 grains of M & B 693, in the twenty-four hours. The tablets were powdered and given in four doses. She was much better next morning, having slept most of the night, but resented very much being touched. Temperature had fallen to 101° F. M & B 693 was continued as for the previous day. On the third day M & B 693 was reduced by approximately 4 grains in the day, and was continued for ten days, when it was discontinued. The child improved very slightly during the next five days, and on the sixth day of her illness she had a relapse. Her temperature rose to 102.8° F., and all symptoms were intensified. Lumbar puncture was performed that day and the next, and on each occasion 1 c.c. of concentrated antimeningococcal serum was introduced through the lumbar puncture needle.

On the eighth day temperature had fallen to 100° F., and head retraction, Kernig's positive sign, and neck rigidity had disappeared. On the ninth day all symptoms and signs had gone. Her temperature during the remainder of her stay in hospital was a little irregular at times, and once rose to 102° F., but this was due to teething and the "normal abnormalities" of childhood. She was discharged, fit and well, on May 25, the fiftieth day of her illness.

Case 3.—This patient, a man aged 20, reported sick on the morning of April 21, 1939, complaining of abdominal pain and vomiting. He was sent to the Cambridge Hospital, Aldershot, as a query acute abdomen. He was detained, and as cerebrospinal meningitis was suspected, he had a lumbar puncture performed the same morning. A turbid fluid under pressure was obtained. It contained many pus cells, and small yellow clots of pus. N. meningitidis was seen in direct smear, and the Group I organism was grown from it.

He was admitted to the Military Isolation Hospital the same day, early in the afternoon. His pulse was 83 and his temperature 101° F. He had severe frontal headache, with pain and rigidity in the neck. There was intense photophobia and vomiting. Kernig's sign was positive, and there was a typical rash on the body and limbs. Patient was semi-conscious, muttering, and very ill indeed. Lumbar puncture was carried out, and 10 c.c. of turbid fluid withdrawn and replaced by 10 c.c. of concentrated antimeningococcal serum. He was also given 20 c.c. of serum intramuscularly. He was given 30 grains of M & B 693, and this was repeated in four hours, and thereafter he was given 15 grains three times a day.

He was vomiting so much on the night of admission that two intramuscular injections of soluseptasine were given, 5 c.c. on each occasion. Vomiting ceased after the second injection, and thereafter M & B 693 was retained by mouth.
On April 23 all symptoms and signs had disappeared, except the rash, which persisted until the following day. His temperature never rose above 98.6° again. M & B 693 was continued for several days after the disappearance of symptoms. Patient was discharged on June 1, the forty-second day after admission.

Case 4.—This young soldier, aged 19, was seen by the Orderly Medical Officer, the Cambridge Hospital, Aldershot, on the night of June 11, 1939, and admitted to the Military Isolation Hospital. He was complaining of a severe headache and photophobia. He had a temperature of 102.2° F. and a pulse of 100. There was a pink macular eruption on the back of the wrists and legs. There was some rigidity of the neck, reflexes were sluggish, and Kernig's sign was negative. He had a cough and a sore throat. The Orderly Medical Officer did a lumbar puncture on admission. The fluid was clear and not under pressure. That night he was very restless and comatose at times. Headache was very intense, and he vomited copiously at times. A lumbar puncture was done the next morning, the fluid was turbid, and under pressure 15 c.c. were removed and 10 c.c. of antimeningooccal serum introduced intrathecally. There was a large number of pus cells in the fluid, Gram-negative diplococci were seen on direct smear and a growth of *N. meningitidis* was obtained on culture. The organism was Group I.

He was given 30 grains of M & B 693, and this was repeated in four hours, and he was then put on 15 grains three times a day. That morning the rash had faded, Kernig's sign was positive, and the headache was intense. He had a pain in his back and his neck was rigid.

During the night of the 12th-13th he slept for long periods and was rational when he awoke, all symptoms were greatly reduced in intensity, and vomiting had ceased. On the 14th the only symptoms remaining were a slight headache and slight stiffness of the neck.

On the night of the 15th he complained of a slight pain in his right knee-cap. He developed a pronounced and painful synovitis of that knee, which continued until June 21, when it began to subside. This was accompanied by a slight fever at times, but there was no pronounced rise after the second day.

On the tenth day M & B 693 was reduced to 7½ grains three times a day, and on the thirteenth day to twice a day. It was discontinued on the seventeenth day.

He was discharged on leave on the forty-ninth day after admission, having made a complete recovery.

Case 5.—On June 18, 1939, a N.C.O. aged 38 reported to the Cambridge Hospital, Aldershot, complaining of vomiting and severe headache. He was stated to have been in hospital three months previously as a case of malaria (relapse).

A blood-film was examined that day for malaria parasites. None was seen. There was, however, an 80 per cent polymorphonuclear leucocytosis.
During the next three days the temperature was intermittent. On June 20 another blood-film was examined with similar result.

In the early morning of June 21 he was found to be unconscious. There was slight head retraction, no rash, pupils were equal, but contracted and not reacting to light. Kernig's sign was positive. Lumbar puncture was carried out, and a turbid fluid under pressure was drawn off. Pus cells were present in enormous numbers, and Gram-negative diplococci, extra- and intracellular, resembling meningococci, were seen. On culture a pure growth of *N. meningitidis* Group I was seen.

He was admitted to the Isolation Hospital at 10.30 a.m. on June 21. He was unconscious, with a poor colour and a slow variable pulse. Lumbar puncture was carried out, 15 c.c. of fluid removed, and 10 c.c. of concentrated antimeningococcal serum introduced. Soluseptasine, 5 c.c., was given intravenously, and 5 c.c. intramuscularly. He was given 1 c.c. of camphor in oil at 1 p.m. The laboratory report on the fluid confirmed the earlier report.

At 2.15 p.m. he had another lumbar puncture, and 30 c.c. of serum were introduced. Soluseptasine, 5 c.c., was given intravenously. At 6 p.m. he was given 10 c.c. soluseptasine intravenously, and 40 c.c. of serum intramuscularly. Coramine was ordered to be given every two hours if necessary.

At 10 p.m. lumbar puncture was again performed, and 10 c.c. of serum introduced. Soluseptasine, 5 c.c., was given intravenously. He was incontinent.

The next day (22nd) his condition was unchanged. Lumbar puncture was performed twice, and a total of 60 c.c. of serum was given intrathecally and 30 c.c. soluseptasine intravenously. With the help of a dropper he was given a few minims of brandy. He developed a large crop of herpes round his mouth, which was successfully treated with iodex. He was markedly more sensitive to touch.

On the 23rd the patient showed the first signs of returning consciousness, whilst having lumbar puncture performed in the morning. The sign took the form of an abusive epithet hurled at the operator, and was received with considerable joy by that officer and the nursing staff. He was semi-conscious that day, and slept well that night. He had lumbar puncture performed twice, 30 c.c. of fluid being withdrawn. He had 30 c.c. of serum intrathecally, and 30 c.c. intramuscularly, and 30 c.c. of soluseptasine intravenously. He took fluids well, and had tea and glucose, and brandy. His temperature fell, and his pulse was of good volume.

M & B 693 was first given at 6 a.m. the following day, the 24th. He swallowed it as a powder with considerable difficulty, and from that time was given 15 grains every four hours. Lumbar puncture was not performed that day but was, for the last time, on the 25th, when 20 c.c. of fluid were withdrawn. The fluid was clear. No further serum was given.

On July 8 M & B 693 was reduced to 1 tablet three times a day, the drug being discontinued on July 11.
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He remained incontinent until June 27, and all symptoms had cleared up by July 4. The last to go were the incontinence and stiffness of the neck, which persisted long after all pain had gone.

At one period there was considerable anxiety about his mental condition. For many days he rambled, thinking he was in India, and though able to answer simple questions, was defeated by anything involving thought. For example, although he knew his wife by her Christian name, he did not know who was meant by "Your wife," and asserted that, although M—— had been to see him every day, his wife had never been. But his mental condition gradually improved, and he is now as mentally fit as ever.

He was transferred to the Cambridge Hospital, Aldershot, on August 8 for general massage and electrical treatment to hasten his returning strength. This was the forty-ninth day after admission. A blood test was done on June 29, to ascertain if the M & B 693 was doing any damage. It was not. On the contrary, there was a moderate leucocytosis.

Case 6.—A young soldier, aged 26, was admitted on June 27, 1939, complaining of severe headache, with pain and stiffness of his neck. Pupils were equal, contracted, and sluggish in reaction to light. Reflexes, generally, were sluggish. There was a positive Kernig's sign. His temperature was 101·4°F.

Lumbar puncture was performed, and the fluid was found to be clear, but under pressure. The laboratory reported the fluid as being normal. Concentrated antimeningococcal serum was introduced intrathecally—(15 c.c.), and M & B 693, 30 grains, was given. The M & B 693 was repeated in four hours, and then he was given 15 grains every four hours. During the first twenty-four hours a certain amount of the drug was vomited.

Blood showed a marked polymorphonuclear leucocytosis, the total leucocyte count being 25,600 per c.c.

On the second day, the 28th, he again had a lumbar puncture carried out. The fluid was turbid and under pressure. Serum, 15 c.c., was given. He was also given, intravenously, 15 c.c. of soluseptasine. His temperature fell to normal that day, and did not again rise.

On the third day, the 29th, his condition was very much improved; all symptoms were subsiding. M & B 693 was reduced to 15 grains three times a day. During the next two days there was a little improvement.

On July 2 he was very much better, headache and neckache had gone, and he was much brighter. M & B 693 was discontinued on July 4.

That night he had a very bad attack of serum sickness which was, however, afebrile. On the 5th the urticarial rash had faded, and he was much better.

From this time he made a rapid and uninterrupted recovery, and was discharged on leave on August 2, thirty-seven days after admission.

I would like to draw attention to four points of interest:

(1) In these cases lumbar puncture during the first twenty-four hours
may produce a normal, clear, cerebrospinal fluid. If serum is then given intrathecally the fluid will certainly be turbid the next day. The question then arises whether it would be better to withhold serum and to carry out lumbar puncture again within twelve hours.

(2) There may be an intermittent fever during the acute stage. In Case 5 this served to cloud the diagnosis, in combination with the old history of malaria.

(3) The complication of synovitis in Case 4 is worthy of note. This complication is mentioned in the literature, but is not common.

(4) Case 5 received very large doses of serum. He had 210 c.c. of concentrated serum in three days. In spite of this he never had serum sickness. This patient was so gravely ill on admission, and so very weak when he at last became semiconscious, that one cannot avoid the opinion that had it not been for M & B 693 there would have been another and more rapid termination to his illness.

In cases such as these the new soluble form of M & B 693 will be greatly welcomed.

I would like to say how very grateful I am to the Medical Specialist, Cambridge Hospital, and to the Assistant Director of Pathology and the staff of the Leishman Laboratory for all their help and advice, without which I would not have been able to achieve what was, in effect, a happy ending.

INTENSIVE TREATMENT OF GONORRHOEA WITH M & B 693.

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A REPORT on M & B 693 in the treatment of gonorrhoea by Bowie, Anderson, Dawson and Mackay, of Aberdeen, was published in the British Medical Journal of April 8, 1939.

It concluded with a record of a notable experiment in intensive treatment on 23 cases by what they termed the "8.4.2 treatment."

A supply of M & B 693 was received for use in the venereal division of the Military Hospital, Gibraltar, in August, and it was decided to experiment with "8.4.2," as local garrison conditions appeared particularly appropriate for the purpose.

The results to date have so exceeded expectations that it is felt that a preliminary report is justified to direct attention to the "8.4.2 treatment" as one which appears to have definite military importance, and therefore deserves more extensive trial. Should fuller experience confirm that these results are dependable, the treatment of gonorrhoea in the Services, both in peace and in the field, will assume an entirely new aspect.