with a positive Wassermann reaction we have endeavoured to improve the condition by intravenous injection of small doses of novarsenobillon. It would appear that there is some improvement possible, but unfortunately the Wassermann reaction persists in spite of this treatment. It is too early for us to state definitely whether we shall be inclined, as the result of this treatment, to alter the very unfavourable prognosis that we are inclined to form in aortitis.

REFERENCES.

- ¹ Allbutt, *Diseases of the Arteries, including Angina Pectoris*.
² A Collective Investigation of Ten Thousand Recruits with Doubtful Heart Conditions. *BRITISH MEDICAL JOURNAL*, May 18th, 1918, p. 556; September 7th, 1918, p. 248; April 26th, 1919, p. 510; May 3rd, 1919, p. 544.

TREATMENT OF CEREBRO-SPINAL FEVER BY MONOTYPICAL SERUM.

BY

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I VENTURE to bring to notice a digest of twelve consecutive cases of cerebro-spinal fever which have come to my notice, and to point out in particular that no case has died where it was possible to treat by monotypical serum.

The work of Dr. M. H. Gordon, C.M.G., who was in charge of the Central Cerebro-spinal Fever Laboratory, has demonstrated that 98 per cent. of cases of cerebro-spinal meningitis serologically fall into one of four types.

Those of us who were engaged in the work at out stations were supplied with agglutinating serums to the four types. It was a relatively easy matter to determine the type.

A growth on tryptagar was obtained from the cerebro-spinal fluid, emulsified, heated to 65° C. to destroy the autolysin, and tested against the four types of agglutinating serums in dilutions of 1 in 50, 1 in 100, and 1 in 200; 0.5 c.cm. serum was mixed with 0.5 c.cm. emulsion of cocci, and the final dilutions then were 1 in 100, 1 in 200, and 1 in 400. Clear and absolute agglutination could usually be readily seen at the end of eighteen hours, and thus the case was typed. For treatment pooled serum containing 50 per cent. of antibodies to Type 1, and 50 per cent. of antibodies to Type 2 was issued, and in addition monotypical serum to be used after the type was determined.

It might be argued that pooled serum ought to contain antibodies to all the types, but typing of the cases as they came showed something like 40 per cent. to be Type 1, 42 per cent. to be Type 2, 16 per cent. to be Type 3, and 2 per cent. to be Type 4.

It will be at once seen that to add antibodies of Type 3 and Type 4 to such a pooled serum would reduce its value by 50 per cent. to 82 per cent. of the total cases. These serums were prepared under the direction of Dr. Gordon, and were tested both as regards their antimicrobial potency and their anti-endotoxic values.

Of the 12 cases which came to my notice, 8 recovered, and 4 died. The deaths all occurred in soldiers; two of them were dead before they were seen by me, and the other two comatose.

On July 11th, 1918, I was called to a military hospital to see a man who had been newly admitted. I saw him at once, but he had just died. The striking feature was a deep plum-coloured rash over the thighs, legs, arms, neck, cheeks, and even to the tip of the nose. The deep mottled colour and confluent nature of this rash marked it out for special notice. Lumbar puncture after death yielded a turbid fluid full of polymorphs and Gram-negative diplococci, and most of the diplococci were extracellular. The growth which was obtained proved to be Type 2.

The second case seen after death was from the same unit. A medical officer who came to see me later on the same day said that a man had been admitted to the same military hospital at 4 p.m. the day before, and had died at 4 o'clock that morning. I saw the body in the mortuary at 11.30 a.m. There was here, too, a deep plum-coloured rash, and puncture seven and a half hours after death yielded a growth which proved to be meningococcus Type 2. The fluid was turbid and full of polymorphs, and contained many Gram-negative diplococci, mainly extracellular.

I was not able to get any good histories of the illnesses of these two unfortunate cases. They were no doubt missed as cerebro-spinal fever cases owing to the number of men being dealt with in the July epidemic of influenza.

One of them had been ill from July 2nd to 5th with influenza, and one returning from leave had made a long railway journey on July 7th. These two men were

stationed at a brigade training school. There were 56 other men there, and 6 of them were found to have meningococci in the posterior nasopharynx. With the two fatal cases this gives a carrier rate of 14 per cent. (8 out of 58). All the carriers proved to be Type 2.

The third death occurred in a man sent a thirty mile motor journey to a military hospital as "mental." He was seen just before death, when there was a deep mottled rash over arms and legs. Lumbar puncture at noon yielded a very turbid fluid full of polymorphs and Gram-negative diplococci. Pooled serum was given at the puncture, but he never rallied, and died a few hours later.

The fourth case was similar. He died three hours after being first seen. Both of these cases yielded Type 2 growths.

The feature common to them all was a deep mottled rash, and indeed I had begun to look on these rashes as being Type 2 cases, and I risked the type in the last case and gave Type 2 serum on the first and only puncture, and not a pooled serum. The second feature was the very great number of extracellular diplococci in the fluid.

In Case III no contacts were examined by me, and in Case IV, among 24 contacts 4 were positive, so that with the case there were 5 carriers among 25 men, giving the carrier rate of 20 per cent. Necropsies were not obtained.

Reviewing those cases, all were Type 2. Two were dead before any specific treatment was asked for, the second two were moribund when first seen, and died within four hours of lumbar puncture—that is, they were dead before the type could be determined. The age of three of the cases was 18 years, and one (Case III) was 37 years of age.

All the cases showed the usual signs and symptoms of the disease. There were eight recoveries. One was a woman aged 49, and one a boy aged 11. The others were soldiers, four of whom were 18 or 19 years of age, one was 24 years, and the last, a discharged soldier, 34 years of age. In all the cerebro-spinal fluid was turbid, with polymorphs and Gram-negative diplococci, mainly intracellular, but in one patient, whose condition was very critical for some days, the fluid showed many extracellular diplococci.

Seven of the cases showed slight rashes, mainly petechial, and only at points of pressure. Five of the cases gave growths which proved to be Type 1, two proved to be Type 2, one of these showed many extracellular organisms, and one case (the boy) was Type 3.

Causation.

Of the eight patients that recovered, three had suffered from influenza and were recovering when they took ill. Three had had long railway journeys before becoming ill. Of these, one left Aldershot on March 6th, 1919, and became ill on March 8th, 1919; a second, who left Portsmouth on February 12th, 1919, became ill February 15th, 1919; a third left France May 11th, 1919, and became ill three days after reaching home. This is to be compared with Case II among the deaths, who left his home, London district, July 7th, 1918, and became ill on July 10th, 1918.

No depressing factors such as T.A.B. inoculation or vaccination could be traced as having any connexion with the onset of the illness. Four only of the cases had less than six months' service and two of these were the two deaths first recorded. There was no overcrowding.

Examination of Contacts.

In two of the cases no contacts were examined by me. In the case of the woman who recovered, all the contacts examined proved negative with one exception. The patient was Type 1, and the contact was Type 2, but it was subsequently ascertained that this carrier had nursed a patient of Type 2 who died at Ipswich.

This patient could have hardly infected others, as she occupied a room to herself in a good-sized house, but it is noteworthy that a pure growth of Type 1 coccus was obtained from her nasopharynx. Of the five remaining cases, one slept in a six-roomed empty house with thirty other men. There were six carriers besides himself, all Type 1, a carrier rate of 23 per cent. A second, who occupied a billet with two other men, showed one carrier, that is, two out of three men were carriers. No others were found in the company. In the case of the third, the patient who took ill after coming from Aldershot, two out of the sixteen men examined were carriers, but they were Type 1 and the case was Type 2. This man could scarcely have infected the unit in two days; and the two carriers were accidental discoveries. The fourth case lived in barracks with thirty other men; four carriers were found, three of whom corresponded in type with the patient's coccus, therefore there were four serologically similar types

among thirty-one men, a carrier rate of 13 per cent. In the fifth case twenty-nine contacts showed five carriers, and with the positive cases gives 20 per cent. carrier rate, all Type 1.

Treatment.

As soon as a likely case of meningitis was seen a lumbar puncture was made, and if the fluid was turbid and middle-ear disease excluded, pooled serum equal to two-thirds of the volume of cerebro-spinal fluid withdrawn was given intrathecally. The serum was given at body temperature and allowed to run in by gravitation, thus ensuring a slow and even flow. Generally 60 to 70 c.cm. of turbid fluid was withdrawn, and 40 to 50 c.cm. of pooled serum allowed to run in.

The fluid was at once examined for diplococci, and plated on at least four tryptic agar plates. By next morning there was always sufficient growth to enable one to determine the type. It is a matter of urgent importance to determine the type with the least possible delay in the manner described above. Agglutination is more rapid at 55° C. than at 37° C.; Tulloch has shown that this is due to the more rapid convection currents. Browning¹ in his work on the agglutination of the enterica group, points out that agglutination can be hastened by alternate heating and cooling. After the rack has been in the incubator at 55° C. it should be removed and left at room temperature for ten minutes and then returned. He shows that agglutination will sometimes occur suddenly in the cold. This principle applies to the meningococcus. A long narrow tube which exposes a greater surface to variations of temperature gives more rapid convection currents.

I always set up my agglutinations in a Wassermann tray. I use a hot-air incubator at 55° C. and remove the tray at the end of thirty minutes, allow it to stand for five minutes in the cold, and then return it. I can generally see agglutination beginning in three hours, and it is thus quite possible to give the patient his own type serum on the second day. I see the patient on the morning of the second day, and if he does not seem too distressed I wait for the type, and do the second lumbar puncture on the afternoon of the second day.

In the eight recoveries this procedure was adopted. Five of the cases were Type 1. One required fourteen injections of Type 1 serum before he finally recovered. A second required four injections; and the three others had each three injections of monotypical serum.

The first patient, who required fourteen injections, had to all appearance recovered after two monotypical injections, but relapsed three days later; he finally recovered with the use of serum and an autogenous vaccine. The injections were given daily, and every Type 1 case made a long stride towards recovery after the first injection of monotypical serum. Two cases of Type 2 were punctured morning and evening, one for three days and the other for five days. A monograph issued by Major Hine, of the Central Cerebro-spinal Fever Laboratory, pointed out that Type 2 serum was not so rich in anti-endotoxin as Type 1 serum, and he suggested puncture twice a day, a procedure which was followed here with excellent result.

The only case of Type 3 was the boy of 11 years. He had been ill for five days before he was seen. He only showed any change after the type was determined, and he was given Type 3 serum. He recovered after four injections. He was the only case to show any permanent defect as a result of the disease. He was deaf, and this nerve deafness was probably present before treatment was begun. As above mentioned, the one case that relapsed was also treated with an autogenous vaccine. If a vaccine is to be of any use it must be combined with lumbar puncture. In the ordinary case the intracerebral pressure is high, and until this pressure is reduced by puncture no antibodies can reach the seat of infection. The use of vaccine does raise the resistance, and combined with lumbar puncture the immunizing response can be carried to the centres of infection.

Since this paper was prepared for publication a thirteenth case came to my notice. The patient, a girl aged 14 years, was treated by Dr. W. F. Corfield, Medical Officer of Health, Colchester, at Myland Infectious Hospital. I ascertained that the infection was Type 3; she recovered after four daily injections of Type 3 serum. This case was complicated by unilateral iridocyclitis, no doubt of meningococcal origin. She had been ill for four days before admission, and the right iris was then seen to be fixed in semi-dilatation; the cornea was dull, and there was pericorneal injection. The eye was treated energetically with atropin ointment and hot fomentations; undoubted optic neuritis is present, and there is some injection which is regressive; the patient can see and count fingers. It

seemed at one time that panophthalmitis would develop. This complication is not uncommon,² and is stated to have been present in 3 to 6 per cent. in a Paris epidemic. It is worthy of note that the only two cases to have after-effects belonged to Type 3; I would not attribute any special virulence to Type 3, but believe that the complications were due to the cases coming under treatment late. In this connexion the constant warning of military medical officers to be on guard for any possible case of meningitis allowed of an early diagnosis. The boy of 11 years with deafness first received treatment on the fifth day of his illness, and this last case on the fourth day.

Summary.

1. Early treatment affords every prospect of success.
2. Type 2 is the most virulent.
3. A deep confluent rash is of grave significance, and many extracellular diplococci mean a severe case.
4. To ascertain the type early, and then use monotypical serum, affords the best chance of recovery.
5. Of ten cases that had serum eight recovered.
6. No case that lived long enough for the type to be determined died.
7. Vaccine treatment may help in a relapse when improvement is slow.

Nine of the ten cases who had serum were treated at Myland Infectious Hospital, Colchester. To the staff there, for careful nursing, and to my laboratory assistant, Miss Carder, grateful thanks are due.

REFERENCES.

- ¹ Browning: *Applied Bacteriology*, pp. 26 and 27. ² Foster and Gaskell: *Cerebro-spinal Fever*, pp. 104 and 24.

THE ASSOCIATION OF LETHARGY WITH THE INFLUENZA BACILLUS.

BY

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In a paper published in the *BRITISH MEDICAL JOURNAL* for March 1st, 1919, I gave my reasons for considering that *B. influenzae* was the cause of influenza. They may be briefly recapitulated:

1. The bacillus can be isolated from the large majority of cases of influenza, 80 to 90 per cent.; between the epidemics from only an occasional case that must be considered a carrier.
2. A pure influenza antigen protects when used prophylactically. It is interesting to note the close correspondence of my figures using a pure antigen with Sir W. Leishman's figures for the army using a mixed antigen, approximately an 86 per cent. protection in both cases.
3. A pure influenza antigen rapidly aborts the disease in uncomplicated cases.
4. A pure influenza antigen during a reaction can produce transitory typical symptoms of the disease.
5. The serum of influenza patients agglutinates the influenza bacillus sometimes in a dilution as high as 1 in 1,000.

It is, in my opinion, a great pity that pure antigens are not being used for prophylactic purposes on a large scale. No conclusion can be come to by the use of mixed antigens.

If the connexion of influenza with the influenza bacillus is not generally accepted, still less is the connexion of it with encephalitis lethargica. This disease is vaguely thought to have some epidemiological connexion with the influenza epidemic. The following brief accounts of four patients treated with pure influenza antigen may encourage others to try the method and help to clear up the etiology of a dangerous condition.

CASE I.

A medical student had had for some days a temperature ranging from 100° to 102° before taking to his bed. He complained of seeing double. He became increasingly sleepy, was delirious, and had hallucinations; when spoken to he could be roused up, and talk fairly sensibly. His conjunctivae were congested; he was badly constipated, and passed urine under him. He had, in fact, symptoms suggestive of lethargic encephalitis. On the chance that the infection might be caused by the influenza bacillus (the case occurred during the epidemic) I gave him subcutaneously 2½ million pure influenza antigen. The improvement was marked at the end of twelve hours. Thirty-six hours later I gave him 5 million, and forty-eight hours later 7½ million. After this he had complete control of his functions and he was no longer lethargic, although his memory was still defective. He still had difficulty in reading, and his temperature was not quite normal—99° F. I then gave him 10 million in the morning, forty-eight hours after the last dose; that evening his lethargic symptoms returned in full