

H. INFLUENZAE MENINGITIS IN RELATION TO TREATMENT

A CLINICAL STUDY OF FOUR CASES

BY

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The increase in recovery rate of *H. influenzae* meningitis in recent years, due to chemotherapeutic and antibiotic therapy, has led to a greater interest in the condition. *H. influenzae* type b rabbit serum has also been used with success in America (Alexander, 1943, 1944), but supplies so far have not been available in this country for an adequate test.

It would seem that *H. influenzae* meningitis is by no means a rarity. Out of the 29 cases of meningitis of all types admitted to this department between May 1, 1946, and Feb. 1, 1947, four were of the *H. influenzae* group, including one of mixed flora; and McIntosh and Drysdale (1945), working in the same area, have reported a further two cases. In view of the not infrequent occurrence of the condition it is important that early diagnosis be made and adequate therapy instituted.

It has been our more recent practice here to suspect *H. influenzae* meningitis in all cases in which, on initial lumbar puncture and direct smear examination, other organisms could not be implicated, and to begin treatment as for *H. influenzae* meningitis. The advent of pure (i.e., white) penicillin in economic supply has diminished the undesirability of large doses of intrathecal penicillin by reducing the incidence and severity of reactions. Prior to this we used a Seitz-filtered watery solution of the yellow sodium salt, which, when given in large doses intrathecally, produced severe cerebral reactions. Penicillin-sensitivity tests and cerebrospinal fluid penicillin concentrations were obtained in all our cases except Case 2, but we found that they bore little relation to the clinical response. Possibly more recent methods of estimation will show greater clinical correlation and be of more value in estimating the therapeutic needs.

Three of four cases treated here have made complete recoveries, the fourth patient dying of intercurrent measles, with bronchopneumonia as a further complication. While it is realized that the series is too small for generalization, when taken in conjunction with the recently published series by Zinnemann (1946) a fairly reliable method of treatment may be formulated, together with suggestions for variation to meet resistance to routine treatment.

Case 1

M.R., aged 11 months, was admitted on May 19, 1946, following pneumonia three weeks previously. The complaints were drowsiness, irritability, slight vomiting, and squint. Examination showed slightly raised temperature, slight neck rigidity, and a left otitis media. Lumbar puncture produced a turbid fluid which on culture yielded *H. influenzae*, sensitive to penicillin and slightly sensitive to sulphamezathine, sulphathiazole, and sulphadiazine.

Treatment.—(1) Sulphamezathine, 4.5 g. on the first day and 3 g. daily thereafter for 8 days. Total, 28.5 g. (2) Intrathecal

penicillin. Administration was very irregular. So far as was possible lumbar puncture was alternated with cisternal puncture. For the first 5 days 30,000 units were given daily, then stopped for 4 days; there followed 30,000 units for 2 days,

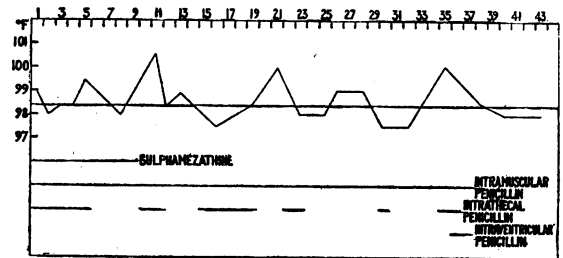


FIG. 1.—Chart of Case 1.

stopped for 3 days; 50,000 units for 5 days, stopped for 2 days; 50,000 units for 2 days, stopped for 6 days; 50,000 units for 1 day, stopped for 4 days, and finally 25,000 units for 2 days. Total, 660,000 units. (3) Intramuscular penicillin averaged 90,000 units daily in doses of 15,000 units four-hourly. Total, 3,330,000 units.

The temperature had fallen by the seventh day after admission, but never really settled. The cerebrospinal fluid, which had been clear on the second day, became turbid again on the 15th day, though cultures were sterile from the 13th day. On the 20th day the temperature rose, and continued to swing intermittently in spite of treatment till the 38th day. It had by then become apparent that there was resistance to treatment, possibly by a blockage in the cerebrospinal fluid circulation cutting off penicillin from a nidus of infection. With a view to overcoming this, ventricular punctures were performed through the anterior fontanelle on the 36th and 37th days. Blood-stained fluid was obtained, and 25,000 units of penicillin were injected into a lateral ventricle on each occasion. Subsequent to this the temperature settled satisfactorily, and the child was discharged on the 62nd day fully recovered, and has remained well since. The patient's clinical condition had closely followed the rise and fall of temperature.

Case 2

J.F., aged 10 weeks, was admitted on June 10, 1946, with a history of being off colour for one day, with some vomiting. Examination showed a flushed, sweating child with some respiratory distress. Slight neck rigidity was present. Lumbar puncture produced a blood-stained fluid which on culture yielded: (a) *Staph. aureus*; (b) *Str. viridans* or possibly pneumococcus; (c) *Str. anhaemolyticus*; (d) *H. influenzae* (this was not typed). These organisms were all sensitive in some degree to sulphathiazole and to a less extent to sulphamezathine. No growth was obtained in the subsequent culture. Sensitivity to penicillin was not investigated. Brain abscess or middle-ear disease was suspected, but no evidence of either was discovered then or later.

Treatment.—(1) Intrathecal penicillin, 25,000 units, was given daily for 9 days. Total, 225,000 units. (2) Sulphamezathine, 4.5 g. on the first day and 3 g. thereafter. On receipt of the sensitivity results on the fourth day sulphathiazole was substituted in 3 g. doses daily until the 12th day from admission. Total, 37.5 g. (3) Intramuscular penicillin, 10,000 units four-hourly for 13 days. Total, 780,000 units.

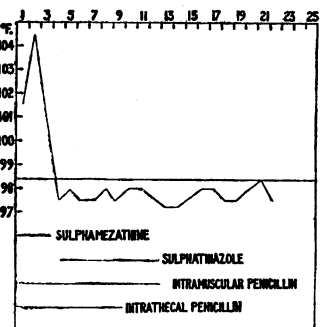


FIG. 2.—Chart of Case 2.

The cerebrospinal fluid was sterile on the eighth day. The temperature fell on the third day and remained settled till discharge on the 22nd day. After discharge there was some suspicion of hydrocephalus, but this proved unfounded. The child has continued well since.

Case 3

J. B., aged 7 months, was admitted on Aug. 22, 1946, with four days' history of vomiting and restlessness. Examination showed neck rigidity and a bulging fontanelle. Lumbar puncture produced a turbid fluid which yielded *H. influenzae* on culture. The strain isolated was of the smooth capsulated variety, but did not agglutinate with the six known antisera for types a to f. The classification of this strain is still under investigation.* The organism was slightly sensitive to penicillin and sulphathiazole.

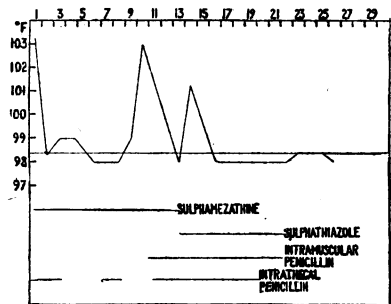


FIG. 3.—Chart of Case 3.

was given daily in doses of 15,000 units from the 11th to the 21st day of admission. Total, 990,000 units. (3) Sulphamezathine, 7 g. on the first day, and 3 g. daily till the 12th day, when the sensitivity results were obtained, and sulphathiazole, 3 g. daily, was substituted till the 21st day. Totals: sulphamezathine, 40 g.; sulphathiazole, 27 g.

The temperature settled and the fluid became clear on the sixth day, when culture was sterile. On the 10th day a relapse occurred, the fluid becoming turbid and the temperature rising. *H. influenzae* was again cultured from the cerebrospinal fluid. On the 16th day the temperature settled, the fluid became clear and sterile, and the child made an uninterrupted recovery. She has remained well since.

During treatment severe reactions followed many of the intrathecal penicillin injections of 45,000 and 50,000 units. These consisted of twitchings of the limbs and body, sometimes tremors, turning up of the eyes, and an embarrassed respiration leading occasionally to cyanosis. These occurred one to four hours after injection, and lasted up to three hours. Chloral hydrate partially controlled them, and it became a routine practice to give large doses prior to puncture, which had the effect of lessening the reactions. The cause of these delayed reactions is obscure.

Case 4

J. L., aged 13 months, was admitted on Jan. 20, 1946, with a two-day history of drowsiness, irritability, and slight neck stiffness. Examination revealed neck rigidity and Kernig's sign. Lumbar puncture produced a turbid fluid giving *H. influenzae* type b on culture. This was relatively resistant to all sulphonamides and slightly sensitive to penicillin.

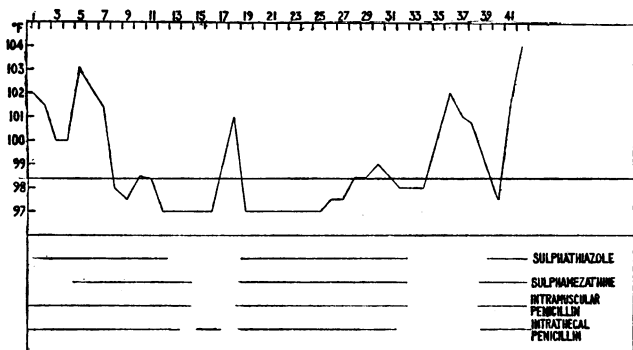


FIG. 4.—Chart of Case 4.

* As we go to press we are informed by Drs. M. Pittman and K. Zinnemann that this organism is of type a (A).

Treatment.—(1) Intrathecal penicillin, 50,000 units daily by alternate cisternal and lumbar puncture. Pure penicillin was used in this case, and it was found that the reactions were less frequent and less severe. For 13 days 50,000 units were administered daily, then stopped for 2 days; 50,000 units for 1 day, stopped for 2 days; 50,000 units for a further 13 days, stopped for 8 days, and finally administered for 4 days. Total, 1,550,000 units. (2) Intramuscular penicillin, 125,000 units daily. This was given as an oil-wax suspension in one dose daily for 5 days. Total, 750,000 units. (3) Sulphathiazole, 4.5 g. daily, given in three-hourly doses by mouth for 11 days. Total, 49.5 g.; also from the 19th to 32nd day. Total, 63 g.; and from the 40th to the 42nd day. Total, 13.5 g. Combined total, 126 g.

The temperature remained raised, and on the fifth day the oil-wax suspension of penicillin was replaced by an aqueous solution, 20,000 units four-hourly for 9 days. Total, 1,080,000 units. From the 19th to 32nd day 1,680,000 units of penicillin in aqueous solution were given, and from the 39th to 42nd day 480,000 units—a combined total of 3,240,000 units of aqueous solution of penicillin.

Sulphamezathine 0.5 g., total 27 g., was given every four hours for 9 days in addition to the sulphathiazole, on the principle expounded by Frisk *et al.* (1947). Sulphamezathine, 0.5 g. four-hourly, was also given from the 19th to 32nd day (total, 42 g.) and from the 39th to 42nd day (total, 12 g.), making a combined total of 81 g.

The temperature promptly fell and was normal on the eighth day, and the spinal fluid became clear and sterile. Intrathecal penicillin was stopped on the 13th day and the rest of the treatment on the 14th day. On the 17th day the temperature rose, the cerebrospinal fluid became turbid and produced *H. influenzae* type b on culture. Treatment was recommenced as before. On the 20th day the symptoms subsided, and two days later the fluid was sterile. On the 30th day the temperature rose to 99° F. (37.2° C.). No meningitic symptoms appeared; the cerebrospinal fluid was clear and on culture was sterile. Measles was suspected. In case this was another relapse, 50,000 units of penicillin and 6 ml. of air were administered. The temperature subsided on the 32nd day and all treatment was stopped.

On the 36th day the temperature was 102° F. (38.9° C.) with no symptoms of meningitis, and the chest was normal. Measles was again suspected; and on the 38th day a morbilliform rash appeared on the body. Photophobia was present, but no Koplik's spots were seen. Measles was diagnosed. No serum to account for a serum rash had been given. Next day (39th) meningitic symptoms were again evident, and lumbar puncture proved the occurrence of another relapse. The cerebrospinal fluid was very thick and the needle was practically blocked. At this point the technique of washing out the spinal canal was adopted together with injection into the canal of heparin and air (Alexander, 1944). The procedure was as follows: Three ml. of normal saline was injected by cisternal route and drained by lumbar route. This was repeated several times until about 30 ml. of cerebrospinal fluid in addition to the saline had been drained away. This allowed as much purulent cerebrospinal fluid to be removed in as short a space of time as possible, and prevented pockets of purulent material forming in the canal. Nikethamide, 1 ml., was given intramuscularly before and after; 0.2 ml. heparin (10 mg., or 1,000 Toronto units) and 10 ml. air (i.e., one-third the quantity of cerebrospinal fluid removed) were then injected. The object of this was to separate existing adhesions and prevent further adhesions forming, also to allow better diffusion of the penicillin, 50,000 units of which was injected intrathecally at the same time. Intramuscular penicillin, 20,000 units in aqueous solution, was then given four-hourly, and sulphamezathine therapy was started again.

On the 40th day, cisternal puncture being unsuccessful, normal saline was injected and withdrawn by lumbar puncture after preliminary withdrawal of cerebrospinal fluid. Ten ml. of saline was used each time—a total of 60 ml. The fluid was purulent at first, but merely turbid at the end of the irrigation. 50,000 units of penicillin, 0.2 ml. of heparin, and 2 ml. of air were given intrathecally.

Unfortunately, the child developed bronchopneumonia on the 39th day. Sulphathiazole was administered as well as sulphamezathine. Since the 38th day the child had been listless, with distressed respiration, and the chief difficulty encountered was that of keeping respiration going after lumbar or cisternal puncture. He collapsed several times, and it became increasingly difficult to resuscitate him.

On the 42nd day his condition appeared to improve and the cerebrospinal fluid was only slightly purulent, but the bronchopneumonia persisted and the child died.

Extract from Post-mortem Report (Dr. J. H. Prain).—“Intense purulent meningitis with greenish muco-gelatinous exudate, covering mainly the base of the brain, but with spread to lateral and superior surfaces. Similar material extends down the spinal column surrounding the cord for the whole length of the canal. There was no evidence of developing hydrocephalus.”

Discussion

Zinnemann (1946) emphasizes the need for continuing treatment until culture of the C.S.F. has been sterile for seven days. This has been our experience. In all our cases, except Case 2 when treatment was continued until the temperature had remained normal for six days, relapse occurred owing to insufficient treatment. The relationship between temperature and C.S.F. sterility is not definitely apparent, the culture frequently becoming sterile before the fall in temperature. In view of the delay in obtaining culture reports under many circumstances, we feel that treatment may safely be related to the temperature chart and will be adequate if intrathecal penicillin is continued until the temperature has been normal for seven days.

A high dosage of intrathecal penicillin was found necessary, 50,000 units daily being satisfactory, preferably preceded by chloral hydrate. We prefer the single injection daily, as the cumulative trauma of repeated lumbar puncture is considerable, and with pure penicillin the reaction risk is decreased. We further attempted to decrease the trauma by alternating lumbar and cisternal puncture.

It is important to ascertain the sensitivity of the infecting organism to various sulphonamides, as this appears to vary. A new chemotherapeutic principle, involving the use of two or more sulphonamides simultaneously, expounded by Frisk *et al.* (1947), has opened the way to increased doses of sulphonamides without unduly increasing the risk, and is worthy of a trial in resistant cases.

In the majority of conditions requiring intramuscular penicillin we have found the oil-wax suspension satisfactory. However, in a listless child absorption may well be delayed, and four-hourly injections of a watery solution until the child becomes more mobile probably give a better absorption rate.

In Cases 1 and 4 there was some apparent hold-up of penicillin circulation in the C.S.F. To overcome this, the method of injecting air and heparin intrathecally was adopted in Case 4. In cases where the fontanelle is still patent, ventricular puncture seemed a practical and possibly more certain alternative, and this was tried with apparent success in Case 1. One of us (J.T.) has had a resistant case of pneumococcal meningitis that responded to ventricular injection of penicillin. Case 4 appeared to be doing well until a febrile period of several days followed by morbilliform rash and photophobia developed. This was almost certainly measles, as cases had occurred in the ward. After this pneumonia developed, and the child died in spite of improving cerebrospinal fluid.

Conclusion

H. influenzae meningitis must be treated early and adequately to ensure maximum success in treatment.

50,000 units of pure penicillin should be given intrathecally daily, preceded by chloral hydrate by mouth or intramuscularly, until the temperature has remained normal for seven days. Full doses of a sulphonamide, the choice depending on sensitivity tests, should be given also in conjunction with intrathecal penicillin. The initial sulphonamide doses should be given intramuscularly. Until sensitivity has been ascertained, sulphamezathine, sulphadiazine, or sulphathiazole, or two of them together, should be given. Intramuscular penicillin is also given, starting with the watery solution four-hourly, and as recovery occurs replacing it with the oil-wax suspension.

It is of the utmost importance to persist with intrathecal injections of penicillin until the temperature has been normal for at least seven days, despite apparently normal cerebrospinal fluid in the interval.

Resistance to treatment can be met by using more than one sulphonamide, each in full dose, and if practicable by ventricular injections of penicillin.

American reports of type b rabbit serum are encouraging. It would appear to be of value only, however, in cases caused by *H. influenzae* type b.

Summary

Four cases of *H. influenzae* meningitis are described. In the period reviewed the incidence of *H. influenzae* meningitis was 13.8% of all meningitis in this department.

The importance of treating all unclassified cases of purulent meningitis fully and promptly with intrathecal and intramuscular penicillin and sulphonamides is discussed.

The use of two sulphonamides, each in full dose simultaneously, was adopted, and is considered to have been helpful.

Treatment should be continued for seven days after the temperature has become normal. The return of normal cerebrospinal fluid is definitely not an indication for ceasing treatment at once.

As cultures of cerebrospinal fluid may be sterile before the temperature becomes normal, the temperature is at least as important as the culture findings in deciding when to cease treatment.

The value of intraventricular injections of penicillin in resistant cases is mentioned, also experience in using intrathecal wash-outs and the use of intrathecal air and heparin injections.

Cerebral reactions following intrathecal injections of 50,000 units of penicillin are described. Their varying severity and unpredictable time of onset are mentioned.

Dilution of the penicillin with 10 ml. of cerebrospinal fluid at the time of injection did not prevent these reactions; but chloral hydrate was useful in diminishing them.

Acknowledgment is due to Dr. Jean G. Bryson, who was associated with Cases 1 and 2; to Dr. May I. Milne, who was associated with Case 4; to Sisters Meekison and Crichton, for their interest and help; to Prof. Tulloch and his staff, for their patience with our many demands on their time; and to Dr. K. Zinnemann for additional information regarding typing of *H. influenzae* strains.

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Speaking on the role of voluntary workers in the National Health Service, Mr. John Edwards, Parliamentary Secretary to the Ministry of Health, told hospital nurses and contributors at the Royal Buckinghamshire Hospital, Aylesbury, recently that it was vital that the supply of voluntary work should be kept alive. There was an unlimited amount of work to be done in improving the hospitals; only a small proportion of this could be achieved solely by voluntary effort, but with the help of the Chancellor of the Exchequer the apparently impracticable vision of those who had the hospitals at heart could be made a reality.