PNEUMOCOCCAL MENINGITIS OF REFRACTORY TYPE TREATED BY REPLACEMENT OF C.S.F. WITH PENICILLIN

BY

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Does the pneumococcus develop resistance to penicillin? It would seem from a study of the following case that it does, although such resistance has not, so far as I know, hitherto been noted.

Case Report

The patient, a female child aged 13 months, was admitted to hospital as a typical case of bronchopneumonia, which responded in three days to a combined course of sulphamezathine and penicillin. She then appeared to be well for a fortnight, but at the end of this time the pneumonia recurred and did not respond to treatment.

Twenty-four days after the beginning of the illness slight neck stiffness was noted and was thought to be due to meningism. Nevertheless, a lumbar puncture was performed and C.S.F. under normal pressure was withdrawn. Contamination with blood precluded its immediate examination, but a typical culture of encapsulated lanceolate diplococci was obtained, giving a diagnosis of pneumococcal meningitis. Later examination of the C.S.F. confirmed this. The organisms were tested against penicillin and were found to be moderately sensitive. (The test used was a modification of the filter-paper method which was in vogue at that time. On this occasion the strain was inhibited by a concentration of 5-10 units of penicillin per ml.) Lumbar puncture was immedi-

penicillin *in vitro* was now found to be slight (growth inhibited by 10-20 units per ml.). Accordingly the dosage was increased, 10,000 units being given intrathecally twice daily. The results were dramatic, for in less than 72 hours the C.S.F. was quite clear. The sugar had returned to normal, but there was still some neck stiffness. Improvement continued until the 18th day, when the C.S.F. again became cloudy, with an increased cell count. It was decided that, as penicillin given by lumbar puncture was unlikely to inhibit organisms in the exudate at the base of the brain, the drug should also be given into the ventricles so that it could penetrate with the C.S.F. every part of the circulation. This was done, with some improvement.

It was felt, however, that it was possible that once the penicillin in the C.S.F. had been brought to a high level it could be maintained by heavy intramuscular doses. That this was probably correct is shown by the fact that improvement was maintained for some days by intramuscular dosage alone, until unfortunately, by a mischance, the intramuscular penicillin was stopped one evening. Next morning the meningitis had recurred in a severe form with tooth-grinding and neck stiffness. The C.S.F. was turbid and teeming with encapsulated pneumococci, which were now said to be completely resistant *in vitro* up to 25 units of penicillin per ml. (24th day).

However, as the Queckenstedt test was normal and as indigo carmine injected into the ventricle appeared at lumbar puncture next day, thus demonstrating patency of the system, it was decided to resume intensive treatment (24th day). This produced some improvement, but on the 28th day, in view of the sharp drop in the sugar, it was decided that the only hope lay in more drastic treatment.

Both clinically and *in vitro* the resistance of the organism had appeared to rise, necessitating repeated increase in the dosage of penicillin. As strong solutions of penicillin are irritant it was decided that the only practicable thing to do was to replace the infected C.S.F. with penicillin solution of a safe concentration. It was thus hoped to spread the penicillin as evenly as possible over the whole system.

ately repeated, turbid fluid under increased pressure was withdrawn, and intrathecal penicillin therapy was begun, details of which are given in the Chart. (The days are numbered from the beginning of treatment for meningitis.) On the fifth day neck stiffness had almost disappeared and the C.S.F. was found to be nearly normal, as judged by the glucose level, which experience showed to be the most sensitive index to the state of the infection, and the first figure to be affected by either an increase or a decrease in its severity.

On the sixth and seventh days, however, relapse occurred in spite of treatment. Neck stiffness became pronounced and the fluid again became turbid. Sensitivity of the organism to

Consequently, on the 32nd day simultaneous puncture of the right ventricle and the lumbar region was performed. Indigo carmine (3 ml.; 1%) was injected by the lumbar needle to serve as a marker, and it was followed by 45 ml. of penicillin solution (1,000 units per ml.). The dye appeared through the ventricular needle and both needles were then withdrawn. There were no ill effects from the operation and great improvement in the C.S.F., the sugar rising sharply in spite of the dilution by saline. The cells increased greatly (see Table), but as all were old and degenerate it was almost certainly due to the "stirring up of the mud" all the way up the cord and the base of the brain.

Table Showing Cell and Sugar Content of C.S.F.

Day	Cells per c.mm.	Sugar mg./100 ml.	Day	Cells per c.mm.	Sugar mg./100 ml.
2	1,700	39	33	2,200	75
5	610	66	35	160	78
6	280	31	37	130	70
7	1,800	33	39	280	51
9	360	92	43	65	66
12	28	65	44	290	59
18	800	59	46	140	47
24	—	25	47	20	61
27	4,000	54	50	14,560	57
28	1,000	29	52	210	65
31	100	63	53	20,000	17

Paracolon bacilli were found on days 50, 51, 52, and 53.

During the next few days the patient improved, but intensive penicillin therapy was continued in order to keep up the concentration in the C.S.F. By the 37th day the cerebral cry had quite disappeared, as had the neck stiffness. During the succeeding days, although the condition of the meningitis fluctuated, the child improved greatly. She began to resist treatment forcibly, to eat well, and to play with her toys. Up to the 47th day honours were divided between the penicillin and the organisms, although the Queckenstedt test remained normal. Repeated examination of the nose and ear by an E.N.T. surgeon again revealed no source of reinfection.

On the 53rd day, however, there was a disastrous relapse. The neck became retracted and the C.S.F. purulent and under increased pressure. Paracolon bacilli (first noted in a culture four days before) were seen in large numbers in a smear, although no pneumococci were present. In spite of double cleaning with iodine, these bacilli had presumably been introduced from the skin by the needle. The "cerebral cry" returned, and in spite of intensive intravenous sulphonamides the patient became collapsed and comatose. Convulsions developed at 8 p.m. and death came three and a half hours later. Unfortunately it was impossible to perform a post-mortem examination, invaluable as this would have been.

Discussion

The infecting organism rapidly developed an apparent resistance to penicillin *in vitro* (at least according to the tests used at that time), but it was still possible to kill it *in vivo* by means of large doses. It appeared likely that the case would ultimately have become chronic in the same way as do some cases of tuberculous meningitis treated with streptomycin, relapse occurring as soon as the drug is withdrawn. Because large doses of intrathecal penicillin were known to be dangerous, this case was at first treated too conservatively. The initial doses should have been bigger and given twice daily. If this had been done the organism might have been destroyed before it became resistant. In a case of meningitis of this severity large doses are worth the risk. The child seemed to suffer no ill effects from the use of huge intrathecal doses. It seems that it is local concentration, not dosage, which is dangerous, but it is dosage or general concentration which is important therapeutically. C.S.F. lavage and replacement with penicillin offer a reasonable method of achieving this general concentration safely, and a technique has been developed and found to be satisfactory. C.S.F. replacement had no ill effects. It is also possible, while doing this, to demonstrate with dye the patency of the foramina of Magendie and Luschka. This is important in prognosis.

Finally, it is known that penicillin is poorly excreted into the C.S.F., but it has been demonstrated clinically that large intramuscular doses can keep up the concentration once this has been achieved by intrathecal administration.

The case demonstrates the necessity for a bold approach and decision in the treatment of pneumococcal meningitis. Intensive treatment, with close observation and frequent

laboratory examinations, is essential if the disease is not to become chronic, and if a final cure is to be achieved.

Summary

A case of pneumococcal meningitis is described in detail. Apparent growth of resistance to penicillin on the part of the organisms is demonstrated, and the necessity for maintaining a high concentration of the drug in the C.S.F. is shown. C.S.F. replacement therapy and its results are described, and it is shown that penicillin concentration in the C.S.F. can be maintained by intramuscular dosage. A technique for demonstrating patency of the foramina in the roof of the fourth ventricle is given.

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Medical Memoranda

Chloramphenicol in Typhoid Fever

In view of preliminary reports of cases of typhoid fever treated by chloramphenicol (chloromycetin) (Bradley, 1949; Murgatroyd, 1949), it is considered that publication of the following case may be of interest.

CASE REPORT

A Service patient aged 20 was admitted to hospital on June 4, 1949, with a provisional diagnosis of typhoid fever. Preventive inoculation with T.A.B. was reported to have been given in February, 1949.

He had sailed from Port Said on May 21 and first felt unwell on May 26, complaining of headache, vomiting, and sore throat. He disembarked at Southampton on May 31 and travelled by train to his home in Nottinghamshire. He still complained of frontal headache, had several rigors, and also complained of marked generalized weakness. On June 2 he had epistaxis, and on the following day was admitted to the medical ward of a general hospital for P.U.O. A few papules were noticed on the abdomen on June 4, and he was transferred to an isolation hospital. There was no history of constipation or diarrhoea.

On admission his temperature was 104° F. (40° C.), pulse 138, and respirations 26. He was mentally confused, answered questions slowly, and had difficulty in pronouncing words. There were a dozen rose-coloured spots on the front of his abdomen, which was distended but resonant. The spleen was not palpable. There were no other physical signs except a coarse bilateral nystagmus which was congenital. His condition deteriorated until on June 6 he was comatose and could not be roused. The eyes were sunken, the tongue was covered with a brown fur, and there was muttering delirium with purposeless picking at the bedclothes. The rash was heavy on the chest and buttocks, and there was retention of urine. Constipation was marked, and it continued throughout the illness. The white cell count was 6,000 (polymorphs 78%, lymphocytes 19%, eosinophils 2%, and monocytes 1%). No abnormal red or white cells were found, and films showed no malaria parasites. The urine was sterile, but a non-lactose-fermenter was grown on blood culture.

On June 8 the pulse was irregular and he showed signs of hypostatic pneumonia. At this stage a supply of chloramphenicol was obtained and an initial dose of 16 capsules (4 g.) was given by nasal tube. This was followed by six capsules (1.5 g.) with glucose twice daily for four days. Two days after treatment was started there was such a remarkable improvement in his condition that he was able to swallow capsules and fluids normally and to answer questions, although his speech was slurred and indistinct. On the following day (June 12) temperature, pulse, and respirations had returned to normal (see Chart) and he asked for food and permission to