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same way as do some cases of tuberculous meningitis treated with streptomycin, relapse occurring as soon as the drug is withdrawn.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.

Acknowledgments are due to Dr. C. Adamson, of Durham County Hospital, for permission to publish the case, and to Mr. P. O. D. Hopps for his invaluable work in the laboratory.

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

walk round his bed. Chloramphenicol was continued with a dosage of three capsules twice daily for a further week, making a total dosage of 33½ g. He made an uninterrupted recovery except for slight hoarseness of voice lasting two days, and when seen in August he was feeling very well and had regained his usual weight.

Bacteriological Results.—June 4:—Supplementary report from Salmonella Reference Laboratory: Blood culture organism has the following antigenic structure: O = IX, XII (Vi); H=d. Therefore it is *Salmonella typhi*. Dr. Felix, Central Enteric Laboratory, reported that the culture belonged to an untypable Vi strain (degraded). June 8: Faeces positive for *Salmonella typhi*. The patient's serum gave a positive agglutination with this organism to a titre of 1/250. June 14:—Blood Widal test: *Typhosus*, H —, O 1/250; *paratyphosus A*, H —, O 1/500; *paratyphosus B*, H —, O 1/250.

Three subsequent specimens of faeces and urine showed no pathogens, and he was discharged from hospital in excellent health on July 7. A subsequent examination of faeces on August 11 was negative for organisms of the enteric group.

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Staphylococcal Portal Pyaemia

This condition has a grave prognosis, and before the introduction of penicillin was nearly always fatal. In the following case a severe infection of several weeks' duration was cured by combined penicillin and sulphonamide therapy.

CASE REPORT

The patient, a fitter aged 31, was referred to hospital with a diagnosis of infective hepatitis. His illness had apparently commenced three weeks previously with complete loss of appetite followed by severe upper abdominal pain, constipation, and vomiting. A few days before admission he noticed his urine was dark and his faeces pale. Before this illness the patient had been troubled with recurring carbuncles of the skin, but had not received any chemotherapy. The last one occurred on the buttock and had healed two weeks before his present symptoms began. He had served in the Middle East during the war and gave a history of several attacks of malaria, but none of dysentery.

On examination he was pale and thin. Icterus was observed in the conjunctivae but not in the skin. The temperature was 100.4° F. (38° C.). There was epigastric tenderness, but no enlargement of the liver or spleen, and no ascites. The urine showed a trace of bile.

The patient's temperature rose the following day to 102° F. (38.9° C.), and thereafter exhibited a daily swing from 99 to 103° F. (37.2–39.4° C.). Blood count showed: haemoglobin 83%; white cells 31,800 per c.mm. (polymorphs 91%, lymphocytes 7%, monocytes 2%). The clinical picture was unlike that of infective hepatitis, which view was supported by the results of liver function tests (thymol turbidity, 1 unit; thymol flocculation, 0; alkaline phosphatase (Jenner and Kay) 19.2 units). His condition deteriorated rapidly. The jaundice became deeper, and was apparent in the skin as well as the conjunctivae; the liver became tender and enlarged to four finger-breadths below the right costal margin. The abdominal pain was almost constant and became very severe. The haemoglobin fell to 66% and the white cells increased to 41,000 per c.mm. The patient was now dehydrated, thin, and desperately ill. He vomited on several occasions and had severe anorexia.

One week after admission he complained of pain in both shoulders, and these joints became swollen, hot, and painful to move. The diagnosis of pyaemia with multiple liver abscesses and suppurative arthritis of the shoulder joints then became apparent, and was confirmed by a blood culture. The organism was a penicillin-sensitive *Staphylococcus aureus*. A few days previously a needle biopsy of the liver (performed by Dr. H. A. Dewar) showed infiltration of the portal tracts with polymorphs. A fluoroscopic examination did not show any elevation or restricted movement of the diaphragm.

Penicillin, one million units daily, was started on the tenth day after admission. After three days the evening temperature was still 102° F. (38.9° C.). The next day sulphamezathine was added; the temperature fell rapidly to normal and the patient's condition improved dramatically. His appetite returned, the jaundice faded, and the liver diminished in size and lost its tenderness. He began to put on weight and became lively and cheerful. The penicillin was continued for ten days and the sulphamezathine to a total dosage of 40 g. The swelling and pain in the left shoulder joint subsided, but the right shoulder remained painful and stiff. There was no radiographic bone or joint change. The affected joint was treated by immobilization in a sling for three weeks, followed by exercises and heat. During this time the patient showed a steady improvement and the temperature did not rise above normal. He was discharged after a month in hospital.

Six weeks later he was feeling well and was free of symptoms, apart from some residual stiffness in the right shoulder.

COMMENT

The diagnosis of pyaemic abscesses of the liver was assisted in this case by the development of metastatic arthritis in the shoulder joints. Both lesions were complications of a systemic pyaemia which appeared to follow a carbuncle. The suddenness of the hepatic enlargement was a striking feature, and was similar to that observed by Wyndham (1945) in each of his three cases. The appearance of jaundice may be taken as an indication of the severity of the infection, for it is regarded by several authors (Rothenberg and Linder, 1934; Ochsner *et al.*, 1938; Smith, 1944) as a late and infrequent sign of ominous significance occurring only when the abscesses are multiple and widespread throughout the organ.

I wish to express my thanks to Dr. A. G. Ogilvie for permission to record this case.

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