H. INFLUENZAE MENINGITIS

BY

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The treatment of influenzal meningitis, particularly in a young child, was usually unsuccessful before the introduction of the sulphonamides, serum, and antibiotics. These agents have altered the prognosis, but the choice of one or more of them is not easy, nor is the success attending each invariably predictable. This uncertainty of therapeutic response is much greater in cases which are diagnosed late or have received inadequate treatment. Alexander (1947) says that the sulphonamides, serum, and streptomycin, used singly, are all effective agents in certain circumstances. She concludes, however, that except in special institutions all of them are indicated simultaneously in a severe case, particularly as residual cerebral damage may be less after such combined treatment.

Alexander found that sulphonamide and antiserum were equally effective in protecting mice, but that together they exerted a pronounced synergistic action; she also found sulphadiazine, sulphathiazole, and sulphamerazine of approximately equal efficacy, although she employed mainly the first. Streptomycin was found to be the most potent agent against *H. influenzae*, though not adequate alone in the most severe infections; its use is limited by its toxicity and by the readiness with which the organism becomes drug-fast (*Lancet*, 1948). She found penicillin relatively ineffective at concentrations usually attained. It is not totally ineffective, however, and the supply of streptomycin and antiserum is so precarious in this country that penicillin is usually employed here. Gordon and Zinnemann (1945) pointed out that many strains of *H. influenzae* are relatively sensitive to large doses of penicillin. Successful results have been obtained by this means by Forgacs et al. (1945) in one out of two cases, McIntosh and Drysdale (1945), Drysdale et al. (1946), and Gerrard (1947) in single cases, and by Gottlieb and Forsyth (1947) in three out of four cases. Thomson et al. (1947) used sulphonamides with penicillin intramuscularly and intrathecally with three cures out of four. Unlike Alexander, they found no close relationship between the clinical response to a drug and the *in vitro* sensitivity of the organism to that drug.

The case here reported ran a long course, and was treated with every available drug, with ultimate success. We believe that in this case the administration of anti-influenzal rabbit serum was the deciding factor in bringing about recovery. The findings in the cerebrospinal fluid showed a remarkable difference after the antiserum, which fortifies our belief that recovery thereafter was not coincidental.

Case Report

M.S., aged sixteen months, had a normal infancy with no illnesses, and was well until Oct. 29, 1947, when he looked cold and vomited his breakfast. He was feverish and refused further food. The following morning he had a temperature of 103° F. and was given 0.5 g. of sulphathiazole, with 0.25 g. four-hourly afterwards. This dosage was maintained for five days and his temperature settled to 100° F. Throughout this period he took fluids well but little food. On Nov. 5 he vomited for the second time, and next day he was admitted to another hospital, where the diagnosis of influenzal meningitis was made and an intrathecal injection of 5,000 units of penicillin was given. This was repeated on Nov. 7 before his transfer to this hospital for streptomycin treatment.

On admission he was a very ill, feverish, flushed child of 21 lb. weight, rather apathetic during examination. No local lesion apart from the nervous system was discovered. The fontanelle was closed, and there was some neck stiffness but no head retraction. Kernig's sign was positive only on the left, there was no photophobia or squint, and the fundi were normal. All reflexes were present, including the abdominals, and the plantars were flexor.

Blood culture gave a growth of *H. influenzae*, Pittman type B.

Lumbar puncture yielded very turbid fluid, and streptomycin was injected intrathecally. At the same time intramuscular streptomycin was started. The cerebrospinal fluid formed a number of clots on standing, and was xanthochromic after centrifuging. There were 20,560 cells per c.mm., mainly polymorphs, protein was 640 mg. and the chlorides 670 mg., while the sugar was only 8 mg. per 100 ml. Smears showed many pleomorphic Gram-negative bacilli, identified culturally as *H. influenzae*, type B.

If Alexander's criterion that the cerebrospinal fluid sugar level is the best indication of the severity of a case, then this case was very severe.

Streptomycin treatment was intentionally given alone, but after forty-eight hours the expected sterilization of the cerebrospinal fluid had not been obtained, although the dosage had been 0.12 g. six-hourly intramuscularly and 0.1 g. intrathecally daily. Sulphadiazine was therefore given in full doses in addition, but still without clinical or pathological response. Heparin, 5 mg., was also given daily intrathecally at this time, with no observable effect. On Nov. 10 and 11 additional streptomycin was given, into the ventricle and cisterna magna respectively, but without the fluid becoming sterilized. The patient's clinical condition remained grave, so intramuscular penicillin was started on Nov. 13 and streptomycin stopped on Nov. 14. The only effect of the streptomycin was that the resistance of the organism to the drug had multiplied fifty-fold in a week.

The illness was still out of control, and on Nov. 18 intrathecal penicillin was started and sulphamezathine added to the sulphadiazine. In accordance with the policy of Thomson et al. (1947), chloral was given before intrathecal penicillin on all occasions to reduce reaction. On Nov. 18, 50,000 units of crystalline penicillin, well diluted, were given. An hour later a severe reaction occurred, with collapse, vomiting, bradycardia, twitching, and coma; recovery was complete after five hours. To avoid further reactions subsequent dosage was more moderate and stepped up slowly.

By the use of penicillin and sulphonamides the condition was controlled; cerebrospinal fluid findings improved, and the boy's clinical response was good. On Nov. 24 the sulphonamides were stopped because of a rash, and a slight fever on the following day was also attributed to sulphonamide sensitivity.

The illness was punctuated by three relapses after this first period of control of the infection. Each time intrathecal penicillin was continued for a period after the last positive culture and then omitted if the clinical condition and appearance of the cerebrospinal fluid seemed to warrant it. The period of intrathecal treatment after the cerebrospinal fluid became clear was seven days before the first relapse, and this period was lengthened with each recrudescence to over two weeks in the last period.

FIRST RELAPSE. The first relapse occurred clinically on Nov. 28, immediately after intrathecal penicillin was withdrawn three days after completion of the sulphonamide course. Sulphamezathine was restarted and the dose of intramuscular penicillin was augmented, since in vitro tests had shown immense resistance to streptomycin, moderate resistance to sulphonamides, and relative sensitivity to penicillin. The patient was therefore given 600,000 units of penicillin per day in divided intramuscular doses and the intrathecal doses were

stepped up to 25,000 units per day. The sulpha drug was discontinued on Dec. 3, but the clinical condition remained poor and the cerebrospinal fluid cell count rose slightly. On Dec. 13 sulphatriad was started. This is a mixture of the three sulphonamides found by Alexander (1947) to be most active, and it was given at first in the large doses of 7.5 g. per day. The fever continued, but after the cerebrospinal fluid had been sterile for eight days the intrathecal penicillin was stopped in case this was in fact the cause of the pyrexia.

SECOND RELAPSE. The second relapse occurred immediately when intrathecal penicillin was omitted on Dec. 15, and was clinical as well as bacteriological. (On the three previous days positive cultures had been obtained, but as they consisted of single colonies and demanded further identification the results were not available.) Control was re-established with intrathecal penicillin and large sulphonamide dosage, and this was maintained until Dec. 27, when intrathecal administration was reduced to alternate days without immediate ill effects. When the cerebrospinal fluid on Dec. 30 was found to be clear, intramuscular penicillin was stopped.

THIRD RELAPSE. The third relapse took place as soon as intrathecal penicillin was not given daily, and was seen bacteriologically on Dec. 30, 1947, and clinically on Jan. 2, 1948. The position was reviewed, and it seemed that no combination of the agents so far tried would be permanently effective. It appeared further that intrathecal penicillin with high doses of sulphonamide was the most effective treatment. Intramuscular penicillin seemed to be useless.

At this stage, therefore, haemophilus rabbit antiserum was given by slow intravenous drip, in a dosage of 50 mg. of antibody nitrogen. It must be mentioned here that in the week following the injection of the antibody no excess of it was demonstrable in the blood. The sulphatriad dosage was stepped up again to 6 g. per day, and daily intrathecal penicillin was resumed, although after the first three days the amount was less than had previously failed to produce permanent sterilization of the cerebrospinal fluid.

Prompt clinical response occurred, and the cerebrospinal fluid became, and remained, sterile. Improvement was maintained and the patient was discharged on Feb. 8, 1948. He weighed 23 lb., and seemed normal for his age. There were no neurological sequelae, and he appeared mentally normal.

PATHOLOGICAL FINDINGS

Only the cell count and polymorph percentage are represented in the graph. The protein curve follows roughly the cell curve, with which the sugar and chloride curves vary inversely.

It will be seen that the percentage of polymorphs

in the cerebrospinal fluid fell after the first period of infection, and although rising transiently with each relapse the rise was not maintained, the polymorphs being rapidly replaced by lymphocytes. It was not until the antiserum was given that a polymorph predominance, such as is usually seen in influenzal meningitis, was achieved and maintained. After the antiserum also, the total count, which between the relapses had fallen to a very low figure, remained at a higher level.

The initial sensitivity of the *H. influenzae* to streptomycin was 2 units per ml. on Fildes' medium by the cup method. By the tube method in Levinthal broth, however, its sensitivity was 20 units per ml. This latter method approximates far more to in vivo conditions than does the plate method, and in the present case at least appears to give a more reliable indication of the response to therapy. Cultures obtained on the fourth day of streptomycin treatment had become resistant to 1,000 units per ml. by plate and tube methods.

Streptomycin blood levels fell from 64 units one hour after to 8 units six hours after the intramuscular injections, while levels of 16 to 32 units per ml. of cerebrospinal fluid were regularly found twenty-four hours after intrathecal injection.

The penicillin sensitivity of the organism by both plate and tube methods was 1 unit per ml. Of all the sulphonamide drugs available, none inhibited growth at concentrations less than 25 mg. per 100 ml. Neither of these two sensitivities had changed in the last positive culture.

In spite of nearly 300 g. of sulpha drugs, at no time did the blood leucocyte count fall below 6,000 per c.mm., there was never a threat of agranulocytosis, and sulphonamide crystals were never seen in the urine.

Comment

Streptomycin in this case was a total failure. It was foredoomed because the organism was naturally too resistant, apart from its resistance being enhanced by treatment. Natural streptomycin resistance seems to be rare in America, but in three out of five cases of influenzal meningitis seen this winter the organism isolated has had the same order of streptomycin resistance as that in the case under discussion.

The antiserum used was made and purified here by the methods of Alexander (1939) and Alexander and Heidelberger (1940). The reluctance to use it before other agents had been fully tried was in proportion to the time and labour necessary to stimulate adequate antibody production in rabbits. The failure to demonstrate excess antibody in the blood was probably due to the small dose given relative to the severity of the case as judged by Alexander's criteria, and this again was influenced

by the amount of antiserum available. Alexander et al. (1942) mention the presence of antibody to *H. influenzae* in a case recovering without antiserum treatment. Zinnemann (1946) also refers to three cases which developed antibody, of which two recovered and one died. In seven cases successfully treated here without antiserum, in no instance was antibody to be found in the blood. We feel, therefore, that the failure to demonstrate it in the case presented here does not mean that the antiserum played no part. Indeed we feel that the response, both clinically and cytologically, following its administration can only be attributed to the antibody given. This change in the cerebrospinal fluid cells from lymphocytes to polymorphs has not to our knowledge been previously reported.

It is obviously undesirable to create more drug-fast strains of organisms than can be possibly avoided. It is clear, too, from a perusal of the literature as well as in our own experience, that strains of *H. influenzae* differ widely in their sensitivity to the various therapeutic agents available. Thus, the treatment of a given case should depend upon the sensitivities of the organism concerned. The determination of these sensitivities may take up to three days in the laboratory, during which time some form of treatment must be started. We feel that during this period adequate doses of a sulphonamide, preferably sulphadiazine, and intrathecal penicillin should be given. This therapy gives a reasonable chance of cure, and even in the present refractory case achieved a measure of control. A precise regimen of treatment can be evolved only when laboratory investigations are completed.

Summary

A case of *H. influenzae* meningitis is presented in detail.

Treatment with streptomycin was a total failure, and the disease was only partly controlled by penicillin and sulphonamides. After three relapses the case was cured by the addition of *H. influenzae* rabbit antiserum to these drugs.

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