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RECENT DEVELOPMENTS IN SOME CHILDHOOD INFECTIONS.

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- DISCUSSION -

Seventeen cases of meningitis due to the Haemophilus influenzae (Pittman type b) have been treated in the three years 1944-1946, in 16 infants with 15 cures. There were two deaths, but one child was apparently cured twice.

SULPHADIAZINE.

The main factor in these good results is considered to be the use of sulphadiazine in full dosage for the first two weeks, and the continuation of the drug for at least a further two weeks in a reduced dosage. The course of this drug varied a little in detail from case to case, but was never less than a month in duration. The dosage was sometimes reduced after the first week from 1.0 gramme to 0.5 gramme six-hourly, if the condition of the child was sufficiently encouraging, but no child received less than a total of 60 grammes, and one child received 99 grammes.

Routine white blood counts and microscopic examinations of the urine were carried out every other day after the first week, but no case of haematuria attributable to the sulphadiazine occurred, and no toxic blood effects were encountered to force us to discontinue sulpha-therapy. The W.B.C. count in one case fell to 4,800 / c.mm. on the thirteenth day of treatment, but the sulphadiazine was continued in spite of this. The W.B.C. rose next day to 5,300 and then to 7,600 four days later, without any untoward incidents.

ANTI-SERUM.

The second line of attack with the specific Haemophilus influenzae anti-serum (prepared in rabbits) is also considered to be of definite value, particularly in babies who were shown by Fothergill and Wright (13) to have no natural immune bodies against this organism between the ages of two months and three years. It was used in 12 cases, and was also given intramuscularly. Although some workers favour giving some or all of the dose intravenously, I have been quite satisfied with the thigh injection, and was sometimes glad the veins had been saved for blood transfusions which occasionally became necessary.

North, Wilson, and Anderson (14) in their analysis published from the Commonwealth Serum Laboratories, seemed to favour the intramuscular route also, although this conclusion is possibly based on figures that include some of our cases as we supplied reports on our use of the serum to them in our earlier cases. It was always administered over the first two or three days after diagnosis, in a dosage of from 60-120 c.cs. except in the one case alreadymentioned in which there was a clinical relapse and the organisms re-appeared in the cerebrospinal fluid on the twenty-first day, necessitating a further dose of 60 c.cs. of anti-serum; and also one other who received a further injection of 30 c.cs. on the eleventh day. The usual procedure was to give 30 or 60 c.cs. as an initial dose, either immediately if gram-negative bacilli were seen on a direct smear of the centrifuged cerebrospinal fluid depôsit, or the next day when the culture result was known; and to repeat this over the next two days to a maximum of 120 c.cs. if the clinical condition did not show a definite improvement, or if the pus cells and organisms did not disappear promptly from the cerebrospinal fluid. It was not unusual for the cerebrospinal fluid to change from a grossly turbid to a macroscopically clear appearance in a few days (e.g. case 15: 25/11/46, 30,800 pus cells /c.mm. cerebrospinal fluid; 30/11/46, 210 pus cells /c.mm. cerebrospinal fluid).

In the last three cases the sugar content in the cerebrospinal fluid was estimated by the method of Alexander (5), and the serum dosage varied accordingly. If the sugar content of the cerebrospinal fluid is less than 15 mgms. per centum, 120 c.cs. of serum is given; if the sugar content is from 18-25 mgms. per centum, 90 c.cs. is given; if between 25-40 mgms. per centum, 60 c.cs. is given, and if over 40 mgms. per centum, 30 c.cs. is given. Urticarial reactions were infrequent and never alarming.

PENICILLIN.

As already mentioned, after we had discovered a penicillin-sensitive strain of the Haemophilus influenzae this possibility received confirmation in a published report elsewhere. Our use of

penicillin in treatment subsequently received further support in the laboratory report of Gordon and Zinnemann (15), and in a case report by McIntosh and Drysdale (16). Penicillin sensitivity tests were carried out as a routine on the strains of Haemophilus influenzae isolated in the last seven cases, and growth of the organism was found to be completely inhibited by one drop of a solution containing 5 units per ml in 4 cases, 10 units in two cases and 25 units in one case. These results, like those of North et al (17), suggest that penicillin could not be regarded as a complete substitute for other therapy.

The usual intrathecal dose varied from 15,000- 45,000 units in 3-5 c.c. of physiological saline. This was given at least twice in the first two days of treatment, and usually several further injections were given during the first week or so when lumbar punctures were repeated to follow the response to treatment. Unfortunately the case records do not adequately record the number of such further intrathecal injections. The first injection was done as a routine through the original lumbar puncture when turbid fluid was found. It has been shown by Cairns, Duthie, Lewis, and Smith (18) (in a study on pneumococcal meningitis) that penicillin diffuses along the cerebrospinal pathways with great facility, often reaching the lateral ventricles from the lumbar region, and only in one forlorn case did we consider it necessary to attempt ventricular puncture.

Intrathecal penicillin has been shown to maintain a high concentration in the cerebrospinal fluid for 12 or more hours, and in view of the proven sensitivity of the organism in this series of cases, its use is considered justifiable. Although penicillin was also given intramuscularly in these seven cases, this is possibly not so necessary. It has always been accepted that penicillin does not normally pass into the cerebrospinal fluid through the healthy meninges in any great concentration, but some authorities have stated that in meningitis some penicillin injected intramuscularly did find its way through the choroidal plexus. This view has been challenged by Kinsman and

d'Alonzo (19) whose work in cerebrospinal fever suggests that after the initial septicaemic stage is past, penicillin by intrathecal administration might be adequate by itself. They failed to find any considerable concentration of the drug in the cerebrospinal fluid from intramuscular injection at all. This is in agreement with Smith, Duthie, and Cairns (20) who, in a further paper on pneumococcal meningitis, stressed the importance of intrathecal penicillin and the doubtful spinal fluid concentrations of the drug obtained by intramuscular injections. Nevertheless, even with the purer preparations of penicillin that were available in 1946, these workers still discouraged using a dose higher than 20,000 units intrathecally at any one time.

These views, however, are at variance with the attitude of Erickson, Masten, and Suckle (21) who adhere apparently to an American Army wartime directive in advocating considerable caution in administering penicillin intrathecally in the treatment of any meningitis for fear of adhesions, transverse myelopathies, etc., with the conclusion that intraspinal injections should be avoided as much as possible. With this we cannot agree.

We have exceeded 45,000 units in a single dose intrathecally in one case only (during the relapse in Case 13), and this child admittedly developed a urinary retention that required catheterization for three days. This was the only immediate ill effect seen in the whole series, and no late sequelae attributable to the intrathecal penicillin injections have been observed. Perhaps the purer penicillin now available (some of it is from 1,400 to 1,500 units per mgm.), and our adherence to physiological saline as the diluent, have been factors in this, although it must be confessed that the tonicity of various strengths of penicillin solutions is somewhat obscure, and will obviously vary with the impurities present as well. Asepsis, of course, is also rigidly observed.

Heparin (5,000 units) was injected intrathecally in four cases to minimise adhesion formation, but has been abandoned. Occasionally 5-10 c.cs. of air were injected intrathecally with the same intention. This, at least, is safe, although its effect is

doubtful.

We realize that when three substances are used to treat a disease, it is difficult to apportion the credit for the cure that is obtained. This may be unscientific, but in fighting influenzal meningitis in infants we intend to continue with any agent which has a reasonable justification and is found to be of use.

Zinneman (22), in a review of twenty cases from various English hospitals (from whom he had been sent specimens of cerebrospinal fluid) strongly supported the combined use of sulphadiazine, penicillin, and specific antiserum. The English experience with the antiserum, however, appears to have been somewhat limited up to that time.

We have not yet used streptomycin in the treatment of influenzal meningitis. This newer antibiotic apparently is useful, but it has yet to be shown that it will improve on the results obtained in this series. Alexander, Leidy, Rake, and Donovick (23), in reviewing a series of 25 cases treated by streptomycin, concluded that the value of this drug is limited in severe cases, and suggest the use of all three agents - rabbit anti-serum, sulphadiazine, and streptomycin.

SUMMARY.

(1) Seventeen cases of purulent meningitis due to Haemophilus influenzae were treated at the Adelaide Children's Hospital in the three years 1944-46.

(2) Two of these cases were in the one child who had a second attack (or a recrudescence) eleven months after an apparently complete recovery.

(3) In these 17 cases (in 16 children) 15 recoveries were obtained and two deaths occurred.

(4) The two infants who died (aged 2 months and 13 months) had been severely ill for two weeks and two months respectively before specific treatment was instituted, and it is doubtful whether our therapy should be judged in these two cases.

(5) Of the 15 recoveries, two were attributable to sulphadiazine alone; in five cases sulphadiazine was combined with the use of specific anti-serum; in one case sulphadiazine and penicillin were employed; and seven patients were treated with sulphadiazine, specific anti-serum, and penicillin. Thirteen of these cases were under the age of 2 years.

(6) One other case believed to be influenzal meningitis, and treated by these three agents recovered, but is not included in the figures because the organism was not isolated.

(7) The frequency of the disease in infants, and the importance of prolonging the administration of sulphadiazine for a period of approximately one month to minimize the risks of relapse, is stressed.

SUMMARIES OF CEREBROSPINAL FLUID FINDINGS AND TREATMENT.

CASE 1.

F.O'M., aged 4 years. Admitted 7/1/44 after treatment elsewhere with 8 grammes sulphapyridine and 24 grammes sulphathiazole. Sulphathiazole continued in Adelaide Children's Hospital until 24/1/44 when changed to sulphadiazine 4 grammes daily because of haematuria. Continued until 15/2/44. Total sulphadiazine dosage, 80 grammes.

c.s.f. (11/1/44): 51 cells /c.mm. (all pmns.). Protein, 35 mgms./100 c.cs. Sugar present (not estimated). Sterile.

(14/1/44): 2,000 cells/c.mm. (all pmns.) Protein, 60 mgms. No sugar detected. Sterile on culture.

(16/1/44): 110 cells/c.mm. No sugar detected. Sterile on culture.

(21/1/44): 1,700 cells/c.mm. (all pmns.) Protein, 95 mgms. /100 c.c. No sugar detected. Haemophilus influenzae on culture.

(9/2/44): 135 cells/c.mm. (65 per cent lymphocytes). Sugar present. Protein normal. Sterile.
Discharged well on 22/2/44.