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MENINGITIS DUE TO PITTMAN AND NON-PITTMAN STRAINS OF *H. INFLUENZAE*

BY

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For the last few years treatment with sulphonamides has been extensively applied to cases of meningitis due to *H. influenzae*. In this country several cases treated successfully in this way have been recorded: Jones (1937), Teggart (1938), Roberts (1939), Sakula (1940), Harold (1941), Jacoby (1941), Archer and Singer (1943), Birch (1943), and Matthews (1943). None of these reports give any clue as to the serological type of the *H. influenzae* strains isolated. Two reports have been published in this country about unsuccessful treatment with sulphonamides of meningitis due to *H. influenzae*—Mackenzie, Page, and Ward (1940) and Jones and Sudds (1942). The latter paper is the only one in which a serological examination of the organism responsible was carried out; the culture was of the b type (Pittman, 1931).

A third group of papers give accounts of both successes and failures in *H. influenzae* meningitis (serological types not given) using the sulphonamides for treatment: Mutch (1941), Davies (1943), and Moir (1943). Davies and Moir, however, emphasize the importance of using large doses of these drugs at an early stage. Moir also stresses their continued use after meningeal symptoms have disappeared, in order to avoid relapses. Mutch has suggested that strains isolated in this country should be examined not only culturally but also serologically. Mutch and Davies are not very favourably impressed by the curative value of these drugs in this condition, particularly with infants.

American Views on Treatment

American publications on this subject are more numerous, and several reviews have been published: Bigler and Haralambie (1939), Aléman (1940), Neal, Appelbaum, and Jackson (1940), Lindsay, Rice, and Selinger (1940), Alexander (1941), Mitchell (1941), Neter (1942), Alexander, Ellis, and Leidy (1942), and Knouf, Mitchell, and Hamilton (1942). The general tone of the reviews is that sulphapyridine is more useful than sulphanilamide in the treatment of these cases, and some authors claim that the combination of an antiserum to *H. influenzae* and sulphapyridine provides the best form of treatment available at present. Neal, Appelbaum, and Jackson (1940) reported on 29 patients, 20 of whom were treated with this combination, 9 being given sulphapyridine alone. Of the 29 patients 14 recovered. The mortality rate was therefore 52%. Of the

14 patients recovered 5 had received the drug alone. Lindsay, Rice, and Selinger (1940), in reviewing 108 cases, showed that treatment with antisera reduced the mortality from 97% to 83%: by adding sulphanilamide and sulphapyridine the mortality for 13 cases was further reduced to 54%. Knouf, Mitchell, and Hamilton (1942) report altogether on four comparable series of 63 patients treated during the last 10 years. Group 1 consisted of 19 patients treated only symptomatically. In this group all patients died. Group 2 also had 19 patients. These were treated with anti-influenza serum. All died. In Group 3, which consisted of 13 sulphanilamide-treated patients, there was one survivor. Group 4 was made up of 12 patients, with 9 survivors, or a mortality of 25%. The patients in this group were treated with sulphapyridine.

Strains of *H. influenzae*

Pittman (1931) had shown that the majority of *H. influenzae* strains isolated from meningitis cases in the United States belonged to a special group of this organism, which is characterized by possessing a capsule consisting of carbohydrates. This capsule has antigenic properties. Six different types of capsular antigens can be differentiated, and the American meningitis strains belong mostly to Type b. According to Pittman capsulated strains have a smooth appearance, but the colonies are rough when the strains lose their capsules, whereas the strains usually isolated from the respiratory tract are non-type-specific and have a rough appearance when first isolated. Fothergill and Chandler (1936), on the strength of virulence and agglutination experiments on dissociated smooth strains, regarded all rough strains as avirulent variants of *H. influenzae*. Pittman (1939) could protect mice easily with sulphapyridine against infection with *H. influenzae* (non-type-specific). Pittman (1942), using *H. influenzae* (Type b) and confirming the findings of Povitzky (1937) with meningeal strains, showed that in experimental infections of mice the combination of antiserum and sulphapyridine gave a higher percentage of cures than either of these substances alone. Pittman (1942) also found sulphanilamide not very effective as compared with sulphapyridine, sulphathiazole, and sulphadiazine; furthermore, that several strains of *H. influenzae* (Type b) showed different sensitivity to the drugs. There are two fatal meningitis cases on record (Pittman, 1933; Mulder, 1939) in which rough strains (non-type-specific) were isolated from the cerebrospinal fluid. Neither of these two cases was treated with sulphanilamide or any of its compounds. Pittman (1931) has shown that rough strains, and Allison, Gordon, and Zinnemann (1943) have shown that respiratory strains not belonging to the Pittman types, are virulent for white mice, although this virulence is lower than that of strains of the Pittman types. In view, therefore, of the small number of cases reported as being due to non-capsulated strains of *H. influenzae*, and their theoretical importance, we are recording the following cases of meningitis, which responded very well to sulphapyridine and which could be shown not to belong to any of the Pittman types.

Non-Pittman Type of Meningitis treated with Sulphapyridine

Case 1.—G. R., aged 7. Fell from tricycle Aug. 14, 1942. Persistent headache and vomiting since. On admission, Aug. 21, T. 97.6°, P. 92, R. 20; appeared fairly well; quiet. Pupils equal, reacted briskly. Some neck rigidity. Abdominal reflexes equal and active. Knee-jerks—R. normal, L. almost absent. Triceps jerks equal. No Kernig, no Brudzinski, no Babinski. Tone of limbs normal. Swelling size of a walnut L. occipital region. Lumbar puncture: 10 c.cm. fluid removed; no increase of pressure; fluid slightly turbid. Aug. 22: Mentally very bright; no pain; neck rigidity marked; Brudzinski positive; Kernig negative, but test causes obvious pain; knee-jerks not obtained; T. 100°, P. 114, R. 22. Aug. 23: Neck rigidity less; T. normal, and never raised again. Aug. 24: Cyanosis (from sulphapyridine). Aug. 25: Neck rigidity almost gone. Aug. 27: No neck rigidity; no knee-jerks, otherwise appeared normal. Sept. 5: Discharged quite well. *Treatment.*—Aug. 21: Sulphapyridine 2 g. (4 tablets) stat.; 1.5 g. four-hourly for 24 hours; alkaline mixture (pot. cit. gr. 40, sod. bic. gr. 20) given four-hourly, along with sulphapyridine. Aug. 22: Sulphapyridine 1 g. four-hourly. Aug. 24: Sulphapyridine 0.5 g. four-hourly. Aug. 26: Sulphapyridine discontinued. Total dose of sulphapyridine, 26 g.

Case 2.—T. S., aged 5. Admitted March 3, 1943. Since March 1 had had headache and vomiting. On admission did not seem ill;

T. 102.4°—after that it was never above normal. The only abnormal signs were head retraction, neck rigidity, and positive Kernig. A lumbar puncture was performed on admission, and 25 c.cm. of turbid fluid removed under pressure. He was given sulphapyridine 2 g. on admission, and over a period of 7 days a total of 21 g. On March 5 he appeared much brighter and the neck rigidity was less marked. On March 9 he seemed quite well.

The colonies of the strains of *H. influenzae* isolated from Cases 1 and 2 had serrated edges when first isolated, and were in no way found to differ from the strains which we regularly isolated from cases of bronchiectasis. Strain 1 (G. R.) gave a negative and Strain 2 (T. S.) a positive indole reaction.

Agglutinations were carried out with the technique described by Allison, Gordon, and Zinnemann (1943). Neither strain gave a specific agglutination with the agglutinating *H. influenzae* sera a to f when incubation was carried out at 37° C. An agglutinating serum, prepared by immunizing a rabbit with the strain isolated from Case 1, did not agglutinate the Pittman strains a to f at 37° C., nor did the serum agglutinate the strain from Case 2, but it gave a good agglutination with its own strain. Agglutinations were also carried out at 56° C. to exclude the possibility of the strains' being rough variants of any of the Pittman types. According to Pittman (1931) and Mulder (1939), agglutinations at higher temperatures are not due to type-specific but to species-specific antibodies.

Strain 1 gave a marked agglutination at 56° C. with the serum prepared from this same strain, whereas Strain 2 did not give a specific agglutination with this serum. None of the Pittman strains a to f gave a specific agglutination with the serum produced with Strain 1. Neither Strain 1 nor Strain 2 gave a specific agglutination with any of the Pittman agglutinating sera a to f at 56° C. We therefore believe that the strains of *H. influenzae* isolated from these two cases of meningitis are not different from strains commonly isolated from respiratory conditions.

Although such strains have a lower virulence than capsulated *H. influenzae* strains, they are by no means avirulent. The virulence of these two strains was tested by injecting 0.5 and 1 c.cm. of 24-hours Levinthal broth cultures intraperitoneally into 6 mice—3 mice for each dose. The mice injected with 1 c.cm. of culture died within 5 days and a culture of *H. influenzae* was recovered from the heart blood. Of the mice injected with 0.5 c.cm. of culture, none of those injected with Strain 1 died, and only one out of the three injected with Strain 2 died. This is in contrast to the virulence of the meningial type Pittman b, which is much more virulent to mice, and of which 0.5 c.cm. injected intraperitoneally kills constantly within three days all the mice injected.

H. influenzae strains possessing the characteristics of respiratory strains are therefore apparently able to cause meningitic conditions in man.

As is evident from the literature quoted in the early part of this paper, very few cases of *H. influenzae* meningitis have been typed serologically in this country. We are therefore giving an account of the following three cases which occurred recently after the second case described. The strains isolated from these cases were of the Pittman type b.

Pittman Type b Cases

Case 3.—H. D., aged 5. This boy was admitted to the Brotherton Wing of the General Infirmary at Leeds under the care of Dr. Wilfred C. Vining, to whom we are indebted for the clinical notes of this case. On May 26, 1943, the child complained of headache and loss of appetite, and became irritable and restless. He was first seen on May 29. The condition was then semicomatose. There were stiffness of the neck and incontinence, and the knee-jerks were absent. He was admitted the same afternoon. Sulphathiazole was administered—4 g. to be given in the first 24 hours; and intramuscular sulphapyridine 1 g. immediately. Lumbar puncture. Fluid was under considerable pressure and grossly turbid. Cells: 655 polymorphs per c.mm. The patient died within a few hours of admission, his illness lasting only about 3 days. The film from the centrifuged deposit of the c.s.f. showed masses of pleomorphic Gram-negative bacilli and numerous pus cells. On culturing, a profuse growth of *H. influenzae* was obtained. The colonies had a moist opaque appearance on chocolate agar, characteristic of the capsulated Pittman types, and on agglutination with the various type antisera gave a marked specific agglutination with Type b antiserum. Wet

preparations from the agglutinated culture stained with methylene blue showed swelling of the capsules.

Case 4.—I. A., aged 2. A portion of brain from this girl was received from an inquest, at which it was stated that the child had not been ill except on the day before death. At the necropsy an acute endocarditis and a meningitis with only a small exudate were found. A pure culture of *H. influenzae* was obtained from the meningeal exudate. The colonies were opaque and of a smooth mucoid appearance. The strain gave a marked agglutination with Type b antiserum. Swelling of the capsules could be seen in wet preparations.

As these two cases had such a fulminating and fatal course, and as treatment was begun only a few hours before death occurred in the one case and no treatment at all was administered in the other, they cannot be compared from the point of view of therapy with the other two cases. The third case in this series was the following:

Case 5.—V. S., aged 5. This girl was admitted on Nov. 1, 1943, to the Brotherton Wing of the General Infirmary at Leeds under the care of Dr. J. R. H. Towers, to whom we should like to express our thanks for the clinical notes of the case. She had started three days previously with general malaise and pyrexia followed by vomiting. Apparently the evidence of an intracranial lesion appeared at the end of the second day, with severe headache, some neck retraction, and confusion. These were followed by gradually deepening stupor. At the time of admission marked head retraction and Kernig's sign were present, with a temperature of 102°. Lumbar puncture revealed turbid cerebrospinal fluid, which contained 2,880 polymorph leucocytes per c.mm. and Gram-negative filamentous rods, which on subculture proved to be *H. influenzae*. This strain gave a characteristic agglutination with the *H. influenzae* Type b antiserum, and swelling of the capsules was seen in wet preparations. Treatment was with sulphapyridine, 2 g. being given first intramuscularly, then 1 g. four-hourly by mouth, and later 0.5 g. four-hourly. There were three recurrences of temperature, each accompanied by headache and each one following the cessation of sulphapyridine therapy. The cerebrospinal fluid withdrawn after the first recurrence (Nov. 6) contained about 16 cells per c.mm., and on culture gave a scanty growth of *H. influenzae*, serologically of Type b. The cell content on the second recurrence (Nov. 18) rose to 164 per c.mm. The total amount of sulphapyridine given was 46.25 g. The patient was discharged on Dec. 9, symptom-free, and has remained well since.

This fifth case responded to sulphapyridine treatment, though not as easily as Cases 1 and 2, and illustrates the advisability of continuing treatment in cases of *H. influenzae* (Type b) meningitis for some time after the temperature has returned to normal and bacteriological examination of the cerebrospinal fluid has established the absence of *H. influenzae*.

There does not seem to be much known at present regarding the relative response of non-type-specific and type-specific strains of *H. influenzae* to sulphapyridine or any other sulphonamide. We think, therefore, that it would be advisable, wherever possible, to type all strains of *H. influenzae* from cases of meningitis with a view ultimately to determining any differences in prognosis and treatment of these cases.

Summary

Two cases of meningitis caused by *H. influenzae*, and their successful treatment with sulphapyridine, are described.

According to agglutination reactions, the strains isolated from these cases do not belong to any of the six Pittman *H. influenzae* types; apparently they are not different from the strains commonly isolated from respiratory conditions. Previously only two cases caused by such strains have been described.

Two fulminant and fatal cases which were found to be due to *H. influenzae* Type b are recorded. Hardly any treatment could be given in one case and no treatment at all in the other; these cases therefore cannot be compared with the other two cases from the point of view of therapy.

A clinically severe case of meningitis due to *H. influenzae* Type b is described, which responded well to sulphapyridine treatment. The three recurrences of meningitic symptoms after cessation of sulphapyridine suggest a continuation of therapy for a time after the return of the temperature to normal and after the cerebrospinal fluid has proved to be free of *H. influenzae*.

It would be advisable, in our opinion, to type as many strains as possible from cases of meningitis due to *H. influenzae*

with a view to determining any possible differences in prognosis and treatment.

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SULPHONAMIDE ALLERGY

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Sensitization to sulphonamide drugs may arise after internal or external administration. In the latter case the reaction is an eczematous dermatitis, and in the former a syndrome consisting of drug fever, skin eruption, leucocytosis, and—more uncommonly—joint effusions, conjunctivitis, jaundice, agranulocytosis, or other features.

When a patient develops any of these types of allergy, oral administration of the drug causes sharp reactions which render future sulphonamide therapy unpleasant or dangerous. In these cases the question which naturally arises is whether such reactions will occur if other drugs of the sulphonamide series are given. This is a point which has received little attention up till now. Moeschlin (1942) reported six cases sensitized to sulphathiazole, of which two reacted to other sulphonamides. Haviland and Long (1940) exposed two sulphathiazole-sensitive patients to sulphapyridine and obtained reactions. Cases of both single and multiple sensitivities have been described by Erskine (1938), Goodman and Arthur (1941), Bloom (1942), Costello (1943), and Swartz and Lever (1943).

All these cases followed internal administration. That the eczematous form of allergy can also exist to single or multiple sulphonamides was shown in a previous report (Park and Platts, 1942). The investigation reported here was undertaken to determine the frequency of these two types of allergy.

Methods Used

Forty cases of both internal and eczematous allergy have been investigated by skin tests and oral medication with various sulphonamides and the related compounds, sulphanilic acid and procaine.

For oral testing, a mixture was used which disguised the slightly bitter taste of the sulphonamide and in which different drugs could be given without the patient being aware of any change. The first dose was usually 0.5 g., and was worked up in the absence of a reaction to 1 g. four-hourly for 48 hours. Reactions in the eczematous cases consisted of a local flare-up plus a general

dermatitis, starting in about six hours, and, in the internal cases, of pyrexia starting in about two hours.

Skin tests were used in the eczematous cases only. Since ordinary patch tests are unreliable in sulphonamide eczema, a modified scratch technique was used, with 50% pastes of powdered sulphonamides in hydrous lanolin and a 2% lanolin paste of procaine. These were either rubbed repeatedly into the scratch or applied over it as a patch. The final method evolved was to apply four different test materials to one long scratch on pieces of cloth about an inch apart, and cover with adhesive for 48 hours. The positive reaction was seen on that part of the scratch in contact with the offending substance only.

Results

The results of the tests are shown in the following table:

[illegible]

Discussion

All drugs of the sulphonamide series consist chemically of the para-amino-phenyl-sulphonic radical ($\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_2-$), linked to various side chains, thus:

In the case of sulphanilamide the side chain is NH_2 , and in the case of sulphanilic acid is OH .

Of these 40 cases 24 reacted only to the individual drug by which they were initially sensitized, thus being allergic to the sulphonamide group plus all or part of the side chain. The last case (see table) shows how highly specific this allergy can be, being insensitive to sulphadiazine but sensitive to the same compound with two methyl groups added (sulphamezathine).

Allergy to Multiple Sulphonamides.—It was found that no case was allergic to more than one of the series without being allergic to them all and to sulphanilic acid. The group common to all