other 2 strains showed marked inhibition. Even with 0.5 unit per c.cm. of medium the growths of 3 strains were completely inhibited and those of 6 markedly so. One of the strains (Morris) varied in its sensitivity to penicillin, as in earlier experiments it showed inhibited growths even up to 5 units of penicillin per c.cm. of medium.

Discussion

These experiments establish the fact that *H. influenzae* strains are not insensitive to penicillin, though the sensitivity is very much lower than that of staphylococcal and streptococcal strains. This finding supports the results obtained by Hobby (1944). She investigated the action of penicillin on a number of Gram-negative organisms previously considered to be insensitive to penicillin. *H. influenzae* was not included in her experiments. She states that "it is apparent that penicillin exerts an antibacterial action against Gram-negative as well as Gram-positive organisms."

The practical application of these observations is restricted to cases of *H. influenzae* meningitis at the present time, since the role of *H. influenzae* as a pathogen in the respiratory tract is still under discussion. The mortality in cases of *H. influenzae* meningitis, treated non-specifically, is about 97% (Lindsay, Rice, and Selinger, 1940). Treatment with sulphonamides appears to have reduced this mortality, and, in combination with specific rabbit antiserum therapy, has lowered it further to 26% of 75 cases quoted (Alexander, 1943). Unfortunately type-specific rabbit antiserum is not available in this country, and penicillin as an additional means of treating *H. influenzae* meningitis appears to be worthy of trial. Penicillin, however, does not seem to penetrate the meninges readily, Fleming (1943) having shown that after intramuscular administration the concentration of penicillin in the cerebrospinal fluid is only one-quarter to one-half of that in the serum. For the most effective treatment of meningitis due to *H. influenzae* it would be necessary, therefore, to administer penicillin intrathecally in addition to the usual intramuscular or intravenous methods. A concentration of at least 2.5 units per c.cm. in the cerebrospinal fluid should be reached at the outset. Later, more exact determination of the penicillin sensitivity of the particular *H. influenzae* strain isolated and assay of the penicillin content of the cerebrospinal fluid should serve as a guide to the further dosage to be given.

Summary

Fifteen *H. influenzae* strains from the nasopharynx and 28 *H. influenzae* strains from bronchial secretions were examined for their penicillin sensitivity. The growths of 31 of these respiratory strains were completely inhibited by 2.5 units of penicillin per c.cm. of medium. Only 7 strains showed growths on media containing 5 units of penicillin per c.cm., with evidence of marked inhibition.

The growths of 18 *H. influenzae* strains, 16 of which were of Pittman's Type b and all of which were isolated from the cerebrospinal fluid, were completely inhibited on medium containing 5 units of penicillin per c.cm. The growths of 16 strains were completely inhibited with 2.5 units of penicillin, the growths of 12 strains completely inhibited with 1 unit of penicillin, and only 3 strains completely inhibited with 0.5 unit of penicillin per c.cm. of medium.

It is suggested that penicillin therapy is worthy of trial in cases of *H. influenzae* meningitis.

Our thanks are due to Prof. J. W. McLeod for the supply of penicillin made available to him for experimental purposes by the M.R.C., and to Prof. W. J. Tulloch and Drs. J. M. Croll, J. S. Faulds, F. W. Gunz, A. I. Messer, G. McIntosh, K. Rogers, and C. J. Young for some of the meningeal strains of *H. influenzae* used.

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MENINGITIS DUE TO A PENICILLIN- AND SULPHONAMIDE-SENSITIVE PITTMAN b STRAIN OF H. INFLUENZAE: RECOVERY

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The following case appears to be of interest by reason of (1) the occurrence of *H. infllenzae* meningitis during convalescence from meningococcal meningitis; (2) the isolation of a Pittman b type of organism which was sensitive to penicillin and sulphonamides (sulphamezathine and sulphathiazole); (3) complete recovery following treatment with penicillin and sulphamezathine.

Case Report

A female child aged 2½ years became suddenly ill on June 18 with vomiting and difficulty in walking. She was admitted next day to Dundee Royal Infirmary, where lumbar puncture revealed purulent fluid under increased pressure from which a pure culture of meningococci was obtained. In the course of three days while in the Infirmary she had been given 58,000 units of penicillin intrathecally and 10.5 g. of sulphadiazine by mouth, and was transferred to King's Cross (Infectious Diseases) Hospital, Dundee, on June 21.

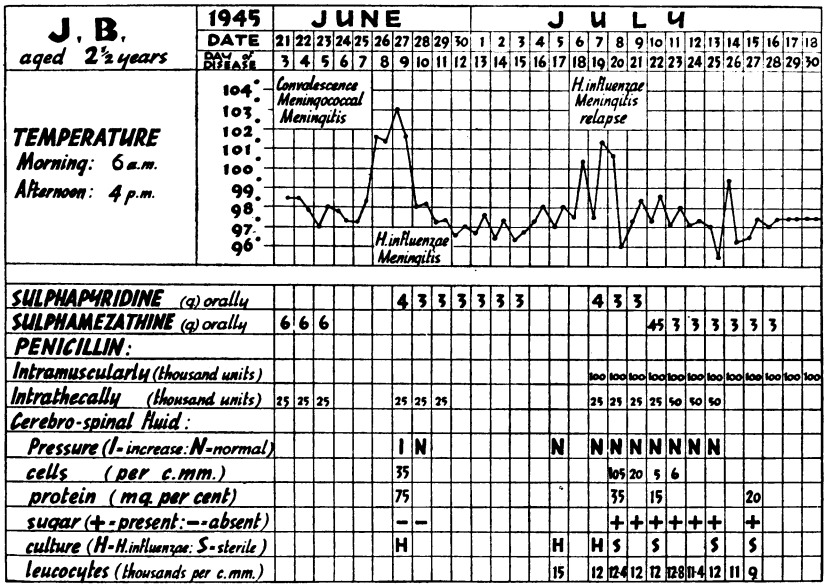
On admission she was semicomatose and irritable. Pupils were equal and reacted to light (the left sluggishly). Kernig's sign was present; abdominal reflexes were absent. Temperature, pulse, and respirations were respectively 98.4° F., 144, and 32. Lumbar puncture revealed slightly turbid fluid under normal pressure. During June 21, 22, and 23 she received 18 g. of sulphamezathine by mouth and 75,000 units of penicillin intrathecally, and on June 23 lumbar puncture produced clear fluid under normal pressure; sugar was present. On June 24 the child's clinical condition appeared to be normal. It will be noted that for the meningococcal infection she had been given 133,000 units of penicillin intrathecally and 28.5 g. of sulphonamide (sulphadiazine 10.5 g., and sulphamezathine 18 g.) by mouth. On June 25 the evening temperature rose at 8 p.m. to 101° F. and the child became flushed and irritable, showing signs of upper respiratory catarrh—cough, injected conjunctivae, excessive lacrimation, congested buccal mucous membrane—suggestive of the invasive stage of measles, but Koplik's spots were not seen.

By June 27 marked neck rigidity had developed, Kernig's sign was present, muscular twitchings of the face and hands were observed, and lumbar puncture produced turbid fluid under increased pressure containing 35 cells per c.mm. and 75 mg. of protein per 100 c.cm. Sugar was absent. Numerous Gram-negative bacilli were demonstrated microscopically and a pure growth of *H. influenzae* (filamentous form) was reported by Prof. Tulloch. During the 7 days June 27 to July 3 the patient was given 75,000 units of Seitz-filtered penicillin intrathecally and 22 g. of sulphapyridine by mouth. On June 28 muscular twitchings were much less frequent, and next day had ceased. Improvement continued on July 1, 2, and 3, and on July 5 lumbar puncture revealed clear fluid under normal pressure; sugar was present. The evening temperature rose to 100.4° F. on July 6 and to 101.6° F. on the following evening, and a culture of *H. influenzae* was reported from the fluid obtained on July 5 and 7. During July 7, 8, and 9, 10 g. of sulphapyridine by mouth, 75,000 units of penicillin intrathecally, and 300,000 units of penicillin intramuscularly (12,500 units three-hourly) were given. On July 9 Prof. Tulloch reported that the organism was sensitive to penicillin (not so marked as standard staphylococcus), sulphamezathine, and sulphathiazole, but insensitive to sulphapyridine. Dr. Gordon, of Leeds, very kindly examined the culture, and reported that the organism possessed the characteristic colonial and serological features of a Pittman Type b.

In view of the bacteriological report sulphamezathine was substituted for sulphapyridine and during the 7 days July 10 to 16 22.5 g. were given by mouth. During the 9 days July 10 to 18, 175,000 units of penicillin were given intrathecally and 900,000 units intramuscularly (3-hourly injection). Apart from listlessness and the presence of intention tremors of the hands and forearms when picking up her toys, the child remained free from symptoms and her temperature became normal on July 8, on which day lumbar puncture revealed less turbid fluid, under normal pressure, containing 105 cells per c.mm. and 35 mg. of protein per 100 c.cm.: sugar was present: culture was sterile. On July 9 turbidity of fluid was less and cells numbered 20 per c.mm. Next day the fluid was clear, with sugar present and cells 5 per c.mm.: culture was sterile.

Cultures repeated on July 13, 15, and 23 were also sterile. Since treatment was restarted on July 7, 32.5 g. of sulphonamide by mouth (10 g. sulphapyridine, 22.5 g. sulphamezathine), 250,000 units of penicillin intrathecally, and 1,200,000 units of penicillin intramuscularly were administered. Details of daily dosages and of leucocyte counts are shown in the Chart, from which it will be seen that the standard intrathecal dose of 25,000 units of penicillin was increased to 50,000 units on July 11, 12, and 13. The injection on the last date gave rise immediately to the following symptoms:

As soon as the injection had been completed the child lay on her side with knees drawn up and uttering agonized cries continuously. Five minutes after the injection myoclonic movements of the face, arms, and lower limbs occurred, lasting about one minute. Five minutes later pallor, sweating, and vomiting occurred: the pulse rate was 125 per minute and the temperature 95.4° F. Gradual recovery took place over the course of 6 hours: 8 hours after the injection the temperature was 101° F. Next day the condition was normal, and recovery proceeded without interruption. The patient was discharged fully recovered on Aug. 16.



Discussion

An excellent review of the results obtained during the last five years in the treatment of meningitis due to *H. influenzae* has been given by Mutch (1941) and by Gordon, Woodcock, and Zinnemann (1944). In all but one (Jones and Sudds, 1942) of the references cited by the last-named authors serological examination of the causal organism had not been carried out. Gordon, Woodcock, and Zinnemann, following the suggestion of Mutch (1941), have examined serologically the organisms isolated from five cases. From two patients, aged 7 and 5 years, non-Pittman strains were isolated: both recovered after treatment with sulphapyridine (26 g. in 6 days and 21 g. in 7 days respectively). The other three cases were due to Pittman b strains. One of the patients, aged 5 years, recovered after three relapses, following the administration of 46.25 g. sulphapyridine. The remaining two were fatal: one of these patients, aged 5 years, died shortly after admission and before an adequate dosage of sulphathiazole could be given; the other, aged 2, died suddenly without specific treatment having been given, and the organism was obtained from a post-mortem specimen. Forgacs, Hutchinson, and Rewell (1945) described 2 cases, from both of which they recovered a penicillin- and sulphadiazine-sensitive Pittman b strain of *H. influenzae*. In their first case, aged 2½ years, striking improvement followed the intramuscular injection of 30.000 units of penicillin alone, and complete recovery resulted after giving about 210.000 units of penicillin intramuscularly and 36 g. of sulphadiazine within 7 days. The second patient, aged 1 year, died 10 hours after admission, having received approximately 12,000 units of penicillin and 2 g. of sulphamezathine. The prompt response observed in the present case after administration of penicillin and sulphapyridine was almost certainly due to the former, as the organism was found to be insensitive to the latter, although rapidly acquired drug resistance cannot be excluded, since sensitivity tests were not conducted until after relapse had occurred. The tendency for *H. influenzae* meningitis cases to relapse has been a feature of this infection. Archer and Singer (1943) reported the case of a child 5½ years of age who relapsed two days after receiving 30 g. of sulphapyridine in 10 days. Complete recovery followed the administration of 32 g. of sulphathiazole in 7 days. Birch (1943) treated a child of 3 years with 23.75 g. of sulphapyridine in 8½ days: 6 days after clinical recovery relapse took place. Permanent recovery followed the administration of 10 g. of sulphapyridine in 3½ days. One of the cases described by Gordon, Woodcock, and Zinnemann (1944), referred to above, relapsed on each of three occasions when sulphapyridine was withdrawn. Complete recovery ultimately ensued after 46.25 g. of the drug had been given. In the present case relapse occurred three days after cessation of treatment with sulphapyridine (22 g. in 7 days) and penicillin (75,000 units intrathecally in 3 days), followed by complete recovery after administration of 22.5 g. of sulphamezathine in 7 days, 1,200,000 units of penicillin (intramuscularly in 12 days. and 250,000 units of penicillin (intrathecally) in 7 days. This case endorses the recommendation of Forgacs, Hutchinson, and Rewell that cases of *H. influenzae* meningitis should be treated without delay with a combination of penicillin and a sulphonamide. In view of the high incidence of bacteriaemia (Mutch, 1941) combined systemic and intrathecal administration of penicillin is indicated. While sulphamezathine, sulphadiazine, or sulphathiazole is suitable for the beginning of treatment, sensitivity tests should be carried out with a series of sulphonamides in order that the most potent may be used, or another be held in reserve should relapse or drug sensitivity occur.

Summary

A case of *H. influenzae* meningitis which occurred during convalescence from meningococcal meningitis is described.

The organism belonged to the Pittman b type and was sensitive to penicillin, sulphamezathine, and sulphathiazole, but insensitive to sulphapyridine. Complete recovery followed treatment with penicillin and sulphamezathine in combination.

We desire to acknowledge our thanks to Prof. W. J. Tulloch for helpful advice; to Dr. J. Brodie, Lecturer in Bacteriology, University of St. Andrews, who carried out the bacteriological work; and to Dr. J. Gordon, Senior Lecturer in Bacteriology, University of Leeds, who typed the organism and to whom our notes of the case have been given for inclusion in his group of Pittman b type cases.

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The report of the joint committee on the training and qualification of hospital administrators has been published as a pamphlet of sixteen pages by the Institute of Hospital Administrators, 12, Grosvenor Crescent, London, S.W.1. A representative conference held under the chairmanship of Sir William Goodenough in June. 1943, expressed the opinion that this branch of work is of such importance as to call for special training, leading to a recognized qualification, and that a standard qualifying examination should be established. The joint committee comprised representatives of Government Departments, the Association of Municipal Corporations, the British Hospitals Association, the County Councils Association, the Mental Hospitals Association, the L.C.C., and other interested bodies. The report includes among main recommendations that a standard examination in hospital administration common to all sections of the hospital service should be established; that it should be divided into two parts—intermediate and final; and that entry to the final examination should be restricted to persons with a minimum of two years' service on the administrative staff of a hospital.