A SURVEY OF THE OUTCOME OF 20 CASES OF *H. INFLUENZAE* MENINGITIS RELATED TO BACTERIAL TYPE

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Considerable progress in the treatment of *H. influenzae* meningitis has been made since Margaret Pittman (1931) showed that most strains isolated from this condition belong to the serological type b—one of six types all characterized by possessing capsules composed of polysaccharides. Early efforts at specific treatment were directed towards producing an effective type-specific *H. influenzae* antiserum (Pittman, 1933; Wilkes-Weiss and Huntington, 1936; Fothergill, 1937). These succeeded in reducing the fatality rate only from 97% without specific treatment (Lindsay, Rice, and Selinger, 1940) to 80–84%. The sera used by Pittman and others were prepared by immunizing horses. In 1936 Horsfall, Goodner, and MacLeod showed that in the case of type-specific pneumococcus serum the therapeutic qualities of rabbit sera are superior to those of horse sera. They explained this finding as most probably due to the smaller size of the antibody molecule in rabbit serum, which diffuses more readily into infected foci and so combines more effectively with the antigen. Excess of horse serum also causes a prozone effect which is not obtained with rabbit serum. These inferior combining qualities of horse antiserum may be responsible for the poor therapeutic results of Pittman, of Wilkes-Weiss and Huntington, and of Fothergill, since there are close analogies in the antigenic structures of pneumococci and *H. influenzae* (Pittman, 1931; Alexander, 1943a).

The introduction of sulphonamide therapy made an effective antibacterial treatment a practical possibility for the first time. The results were reviewed in this country by Mutch (1941) and by J. Gordon, Woodcock, and Zinnemann (1944). In a series of papers Alexander, Heidelberger, and collaborators (1939, 1940, 1942, 1943a, 1943b, 1944), in *in vitro* and mouse experiments as well as in clinical trials, laid the foundations for a rational therapy based on a combination of the most effective sulphonamide—i.e., sulphadiazine—with rabbit anti-*H. influenzae* type b serum. Alexander (1944) thus succeeded in reducing the mortality rate to 22% in a total of 87 patients all treated within 7 years. In a report which was only seen when this survey was going to press Smith, Wilson and Hodes (1946) give an account of 28 cases of *H. influenzae* meningitis treated with the combination of sulphonamides and *H. influenzae* type b rabbit antiserum. The recovery rate was 85.7%.

Experience of this condition is comparatively slight in this country, as cases occur only sporadically over a wide area. From a number of case reports it seemed as if sulphonamide therapy alone might be sufficient (J. Gordon, Woodcock, and Zinnemann, 1944). As reports of more cases accumulated it became evident, however, that this therapy was proving disappointing in many instances. Recently Alexander (1944) pointed out "that the capacity of the sulphonamides to effect complete recovery from type b *H. influenzae* infection is influenced by two factors. First, the infection must be relatively mild. Secondly, the drug must be started early in the course of the infection. It is believed that only under such conditions will sufficient time be afforded to the patient to produce through his own powers sufficient antibody to overcome the disease."

The Emergency Public Health Laboratory Service has now secured a small stock of *H. influenzae* type b specific rabbit antiserum. Thus it is possible to make practical use of the typing of *H. influenzae* strains isolated from meningitis—a pro-

cedure advocated recently in this country (Mutch, 1941; J. Gordon, Woodcock, and Zinnemann, 1944). An outline of the main points of Alexander's (1943b, 1944) routine treatment may therefore be useful.

All material necessary for the isolation of the causative organism and for typing should be collected before starting specific treatment. The capsule-swelling technique carried out on the organisms in the C.S.F. is the quickest way of establishing the type of *H. influenzae*. To confirm the result typing by agglutination on a slide and/or in tubes should be carried out with the isolated strain. Using the agglutination tests alone will delay the result for 24 to 48 hours.

1. The first dose of sulphonamide—sulphadiazine or sulphamezathine—is given intravenously.

2. A continuous intravenous saline drip is established for 24 hours. The remainder of the daily dose of sulphonamide—i.e., 0.1 g. per kg. body weight in all—should be added to the drip. After the first 24 hours sulphonamide therapy is continued by mouth. The daily dose is 0.1 g. per kg. body weight, and is continued until 7 days after the C.S.F. is first shown to be sterile. Earlier cessation of sulphonamide treatment carries the risk of relapse.

3. The dose of specific serum to be administered is roughly determined by the glucose content of the C.S.F. Alexander (1943b) describes a simple adaptation of Benedict's qualitative method for quick determination of the sugar content of C.S.F. The specific antibody present in the therapeutic serum is given in milligrams of antibody nitrogen. The accompanying Table is a guide to the dosage of antiserum.

Table showing Dosage of *H. Influenzae* type b Rabbit antiserum based on Glucose Content of C.S.F.

Glucose in C.S.F. (mg. per 100 ml.)	Indicated Dose of Antibody Nitrogen (mg.)
< 15	100
15–25	75
25–40	50
> 40	25

4. The patient's progress is judged to a large extent by the changes in the C.S.F., which is examined daily. If within 24 hours sugar and chlorides have risen, no organisms are seen in direct smears, and the patient's serum causes capsular swelling when diluted 1 in 10 no further serum is required provided the C.S.F. continues to become normal; cultures become and remain sterile; and free antibody as shown by the capsular swelling test persists in the serum in adequate excess. If progress is not satisfactory at the end of 48 hours from the initiation of serum therapy a further dose equivalent to 25 mg. of antibody nitrogen should be given intrathecally.

5. Alexander's last clinical report (1944) is mainly concerned with protracted cases and cases belatedly subjected to specific treatment, which she terms "chronic *H. influenzae* meningitis," though in our view subchronic or subacute *H. influenzae* meningitis would seem to describe the condition more adequately, since the expectation of life can be measured in weeks or months and not in years. In Alexander's report two histories are given in which a striking improvement followed intrathecal introduction of air together with antiserum. She suggests that adhesions blocking the flow of fluid in the cerebrospinal canal are loosened, and she also advocates the injection of heparin intrathecally to prevent clotting.

Observations on Penicillin and Streptomycin Sensitivity

It was emphasized repeatedly in the early investigations of the antibiotic properties of penicillin that *H. influenzae* is an

outstanding example of an organism resistant to this substance. When supplies of penicillin became more ample higher concentrations could be employed and strains of *H. influenzae* were found to be sensitive to these. Straker (1945) reported two such strains, and she thought that smooth strains were more sensitive than respiratory ones. Private communications (K. B. Rogers, J. M. Croll, F. W. Gunz, and C. J. Young) supported the impression that penicillin had its uses in *H. influenzae* meningitis. M. Gordon and Zinnemann (1945), in a survey of the penicillin-sensitivity of a large collection of *H. influenzae* strains, established that this was not an occasional phenomenon; 43 respiratory and 18 meningeal strains were all found to be sensitive to penicillin, most of them in concentrations which allowed a rational use of the drug in conditions due to this organism. Three case reports of successful penicillin treatment, in combination with sulphonamides, of *H. influenzae* meningitis have been published hitherto (Forgacs, Hutchinson, and Rewell, 1945; McIntosh and Drysdale, 1945; Drysdale, McIntosh, and Brodie, 1946).

Quite recently, use of the new antibiotic streptomycin, mostly in combination with sulphonamides, has been reported in 6 cases of *H. influenzae* meningitis (Anderson and Jewell, 1945; Herrell and Nichols, 1945; Cairns, Duthie, and Smith, 1946). So far as can be judged, fairly large doses of streptomycin are required. Hewitt and Pittman (1946) find that cultures of *H. influenzae* show a decreasing sensitivity to antibiotics in the following order: streptomycin, penicillin X, and penicillin. Mouse experiments confirm the *in vitro* findings. The results of further clinical trials have to be awaited before their respective merits can be judged. Hewitt and Pittman's experiments suggest also that a synergistic action may take place when these antibiotic substances are combined with sulphonamides or specific rabbit antiserum.

Below are presented reports of 20 cases of *H. influenzae* meningitis treated in various ways. The survey is the result of inquiries made at a number of laboratories and hospitals from which strains of *H. influenzae* were received in this department for typing. The clinical details are those kindly given to me by the physicians under whose care the patients were placed and the pathologists concerned. These circumstances account for the diverse methods of treatment and dosage used.

Cases treated with Sulphonamides Only

Case 1.—J. M., a boy aged 1 year 5 months. (Under the care of Prof. J. C. Spence, Royal Victoria Infirmary, Newcastle-upon-Tyne.) Onset of symptoms 5/1/45. No special treatment at home. On admission on 24/1/45 signs of meningitis. C.S.F. turbid—cell count 13,000 per c.mm., no sugar present; *H. influenzae* type b isolated. Medication started with 2 g. sulphathiazole intravenously; subsequently 0.25–0.5 g. sulphathiazole by mouth 4-hourly for 13 days. Total amount given, 34 g. A clinical relapse was experienced on 31/1/45, when the dose of sulphathiazole was reduced from 3 g. to 1.5 g. per day. The cell count in the C.S.F. rose from 500 per c.mm. to 1,500 per c.mm. during the relapse. After discontinuation of sulphathiazole on 6/2/45 the cell count was still 800 per c.mm. Sulphadiazine therapy was therefore started on 12/2/45 with 0.5 g. 4-hourly for 18 days, and 0.25 g. 4-hourly for another 26 days. The sugar content of C.S.F. was normal from 12/2/45 onwards. After an initial rise to 1,200 on 15/2/45 the cell count in the C.S.F. declined slowly until it reached the figure of 30 cells per c.mm. on 9/3/45, at which level it remained with slow but steady clinical improvement until the child was discharged in normal physical and mental condition on 9/4/45. The total dosage of sulphadiazine given was 97 g.

Case 2.—M. S., a girl aged 3 years. (Under the care of Dr. M. L. Bery, Lincoln.) On 5/11/44 headache; a squint was noticed on the same day. Admitted on 8/11/44 with symptoms of meningitis. T. 101° F. (38.3° C.). Lumbar puncture: C.S.F. under pressure and milky in appearance. Treatment started with 1.5 g. sulphathiazole, then 0.5 g. 4-hourly for 3 days. When 9 g. had been administered the temperature had returned to normal although the pulse remained rapid. Therapy was discontinued and the temperature rose again to 104° F. (40° C.). *H. influenzae* type b isolated 15/11/44. A second course of sulphathiazole was started on 16/11/44, but was discontinued owing to vomiting. The total of sulphathiazole given in the two courses was 13.5 g. From then onwards the child's condition deteriorated slowly. A 3-day course of sulphanilamide amounting to a total of 10.5 g. was given from 27/11/44 to 30/11/44 with no effect. Death occurred on 1/1/45.

Case 3.—P. E., a girl aged 1 year 10 months. (Under the care of Dr. T. M. Pole, Grantham Hospital.) On 25/5/44 she fell ill

suddenly with violent vomiting of increasing severity. She was given 8 g. sulphanilamide before admission on 26/5/44, when she was stuporous but without neck rigidity, and Kernig ?+. T. 97° F. (36.1° C.). Chest: terminal congestion with generalized loose rales. C.S.F. not under pressure but turbid. A course of sulphapyridine was started at once, but the condition deteriorated rapidly. On 27/5/44 *H. influenzae* type b was isolated. The child died the same day, 24 hours after admission.

Case 4.—R. M., a boy aged 9 months. (Under the care of the late Dr. T. D. Semple, Cumberland Infirmary, Carlisle.) Was admitted to hospital on 2/5/44 after having been ill for 3 days, with meningitic symptoms for 2 days. Treatment was started with 0.25 g. oral sulphathiazole 4-hourly for 5 days. Then medication was reduced to 3 daily doses for 3 days. As all symptoms had subsided treatment was then discontinued for 5 days. When symptoms recurred medication was started again with 6-hourly and 8-hourly doses of 0.25 g. sulphathiazole. 24/5/44: *H. influenzae* type b isolated. 26/5/44: Administration of sulphadiazine in 4-hourly doses of 0.5 g. for 2 days, after which time the treatment had to be discontinued because of failure to pass urine for 16 hours. During the next 3 days meningitic symptoms became more marked and another course of 0.25 g. sulphadiazine 4-hourly was given until swallowing became difficult on 2/6/44. Death occurred on 4/6/44. The total dose of sulphathiazole was 19.5 g. and of sulphadiazine 7 g.

Case 5.—Baby A. S.; no age stated. (Under the care of Dr. M. J. Lawson, Berwick-on-Tweed.) A week before admission on 13/2/45 the boy developed a left-sided lobar pneumonia and was given sulphapyridine with satisfactory result. On 11/2/45 a renewed rise of temperature, with vomiting. Another course of sulphapyridine was started the same day. On admission to hospital on 13/2/45 there was slight neck rigidity; the fontanelles were bulging. At lumbar puncture 20 ml. of a turbid fluid was withdrawn under pressure. There was an impaired note over the left side of the chest. Sulphapyridine medication was continued together with chloral hydrate, gr. 7 (0.45 g.) at night. On 16/2/45 there were increased signs of meningitis and cerebral irritation, left internal strabismus, extreme neck rigidity, and fits. Pulse rate very rapid. After a slight improvement on 17/2/45 the child died next day. The *H. influenzae* strain isolated from the C.S.F. was subsequently found to be of type b.

Cases treated with Sulphonamides and Penicillin

Case 6.—This boy, M. L., aged 2 years 7 months (under the care of Dr. J. O'Connor, Brumby Isolation Hospital), had been ill with symptoms suggestive of tuberculous meningitis for two weeks. Two days before being admitted to hospital, vomiting, headache, and cough increased; T. 101° F. (38.3° C.), P. 140, R. 36. There was evident neck rigidity on admission on 23/6/45; 1 g. sulphanilamide was given 4-hourly. 29/6/45: No change in condition; course of sulphanilamide completed; 10,000 units antimeningococcal serum given. 30/6/45: 30,000 units intramuscular penicillin 3-hourly for 5 days. 4/7/45: No change; penicillin discontinued. 5/7/45: 0.25 g. sulphasuxidine 8-hourly. On 7/7/45, C.S.F. withdrawn under pressure. 10 ml. antimeningococcal serum given intrathecally. *H. influenzae* type b reported grown from the specimen of C.S.F. 10/7/45: 0.5 g. sulphathiazole 8-hourly for 3 days. 17/7/45: Very ill; paralysis in left arm, horizontal nystagmus; T. 105° F. (40.6° C.), pulse very rapid, R. 60. 18/7/45: Died at 4 a.m. after preceding hyperpyrexia of 109° F. (42.5° C.). Later investigation showed the strain to be completely inhibited by 0.5 unit penicillin per ml. of medium.

Case 7.—This 5-year-old girl, J. H. (under the care of Dr. L. B. Cole, Addenbrooke's Hospital, Cambridge, and Mr. D. W. C. Northfield, Chase Farm Hospital, London), had a 3-days history of headache and vomiting before admission to hospital on 14/3/45. There were marked head retraction and an acute infection of the left knee-joint. C.S.F. under pressure 350 mm.; opaque, containing 5,400 polymorphonuclear leucocytes per c.mm. Protein, 80 mg. per 100 ml.; glucose diminished. Pure growth of *H. influenzae*; the colonies of the strain had a rough surface, growth being rather dry. No agglutination with any of the 6 type sera at either 37° C. or 56° C. The strain was diagnosed as belonging to the respiratory group of *H. influenzae*. Puncture of the left knee produced thick pus containing Gram-negative bacilli. On culture a heavy growth of *H. influenzae* was obtained. Our investigations showed that the strain was inhibited by 1 unit penicillin per ml. of medium. During the first week in hospital the child was treated with sulphathiazole and penicillin, 30,000 units of the latter being administered 3-hourly by the intramuscular route and 20,000 units per day intrathecally. Sulphathiazole medication was discontinued after 8 days when it was found that the strain was sulphathiazole-resistant. In all, the child had received 93.5 g. sulphathiazole in 8 days. Penicillin therapy was continued until 4/4/45. Great irritability made administration of paraldehyde 2 ml. I.M. necessary. On 4/4/45 the general condition was still very poor; the child was drowsy and unstable, and had marked head retraction. Medication discontinued, the case

being considered as hopeless, although daily lumbar punctures were performed until 14/4/45. Slow improvement set in during April, and by 2/6/45 the general condition was such that the patient was considered fit for discharge. On the evening of that day she suddenly began to vomit. 8/6/45: Sixth-nerve palsy, flaccid limbs, especially on the right side, very drowsy, vomiting, divergent squint. On the following day the left pupil was larger than the right. There were 41,000 white blood cells per c.mm. On 12/6/45 the child was deeply comatose, with a slow pulse rate and occasional vomiting. A diagnosis of brain abscess was made and she was transferred to Chase Farm Hospital on that day for neurosurgical treatment. Examination revealed the following signs: Comatose. No papilloedema. Bilateral ptosis. Absent corneal reflexes. Fluctuating spasticity of right upper and both lower limbs. Bilateral extensor plantar responses. The C.S.F. was cloudy, the pressure too low for measurement; culture sterile. Exploratory tapping revealed a left post-frontal abscess, and 30 ml. of thick pus was aspirated with immediate improvement in her condition. Pure growth of *H. influenzae* was obtained from the pus. Aspiration was repeated on 18/6/45, and on 20/6/45 an osteoplastic craniotomy was performed and the abscess contents evacuated and drained. Considerable temporary improvement followed, but by 7/8/45 she suffered from symptoms of a further collection of pus in the abscess cavity, which was confirmed by re-aspiration. On 11/8/45 further operation was carried out, when the abscess was totally enucleated. It was extending into the temporal and parietal regions and measured 6 cm. in diameter. Gram-negative bacilli were seen in the direct film, and culture yielded *H. influenzae*. Progress after this operation was rapid. The patient started walking on 31/8/45 and was discharged on 5/9/45, walking fairly well but a little unsteady and with a slight limp. Mentally she was alert, bright, and happy. On re-examination on 12/10/45 she was normal apart from the right arm jerks being slightly brisker than the left.

Case 8.—A boy, M. E., aged 2 years (under the care of Dr. J. F. Gaskell, Addenbrooke's Hospital, Cambridge), started being sick and feverish on 16/10/45. Admitted on 20/10/45 with obvious signs of meningitis. C.S.F. turbid with clots; Gram-negative bacilli in direct film. Growth of *H. influenzae* belonging to Pittman's type b. The strain was completely inhibited by 1 unit penicillin per ml. of medium. Therapy with intramuscular and intrathecal penicillin as well as sulphamezathine was started. *H. influenzae* was isolated from the C.S.F. until 27/10/45. It is stated that from 31/10/45 to 2/11/45 the C.S.F. exerted a bacteriostatic activity in a dilution of 1 in 32. The fluid was still purulent but sterile on 1/11/45. On 4/11/45 the patient died. Post-mortem examination revealed a purulent meningitis and hydrocephalus. A total of 22.5 g. sulphamezathine was given in 8 days, of 600,000 units penicillin intramuscularly in 17 days, and of 258,000 units intrathecally in 6 days.

Case 9.—K. L., a boy aged 3 years (under the care of Dr. L. B. Cole, Addenbrooke's Hospital, Cambridge), started a cough on 20/10/45. On 24/10/45 he complained of aching bones and cold feet. He started vomiting on 25/10/45, and next day had opisthotonos, photophobia, and a squint. He was admitted on 27/10/45 with obvious meningitis and a temperature of 104° F. (40° C.). The C.S.F. was purulent and yielded a heavy growth of *H. influenzae* of type b. The strain was found to be completely inhibited by 1 unit penicillin per ml. of medium. Therapy: Sulphamezathine, penicillin intramuscularly and intrathecally. The reports on findings in the C.S.F. during treatment are as follows. 29/10/45: Bacteriostatic activity, 1 in 2. 30/10/45: Bacteriostatic activity, 1 in 4. 31/10/45: Bacteriostatic activity, 1 in 16. 1/11/45: Bacteriostatic activity, 1 in 32+. 2/11/45: Bacteriostatic activity, 1 in 32; fluid cloudy, Gram-negative bacilli in direct film; culture sterile. 3/11/45: 120 white blood cells per c.mm. Growth of penicillin-resistant *H. influenzae*. 5/11/45: Culture sterile. Patient discharged well on 14/11/45.

Total sulphamezathine given	..	..	15 g. in 3 days
„ penicillin given I.M.	..	..	995,000 units in 10 days
„ „ „ I.T.	..	..	200,000 „ „ 8 „

Case 10.—R. M., a boy aged 1 year 4 months. (Under the care of Dr. L. B. Cole, Addenbrooke's Hospital, Cambridge.) On 11/10/45 the child was unwell and drowsy, and vomited once. Admitted to hospital on the same day with obvious meningitis. The C.S.F. on 12/10/45 was cloudy and contained many pus cells and Gram-negative bacilli. The strain isolated was of type b, and was completely inhibited by 2.5 units penicillin per ml. of medium. Two courses of 690,000 units penicillin intramuscularly were necessary, the first from 13/10/45 to 19/10/45, the second from 20/10/45 to 26/10/45. Two courses of sulphamezathine were also given, the first from 12/10/45 to 18/10/45, with a total dose of 20 g., and the second from 22/10/45 to 27/10/45, with a total dose of 16.5 g. As *H. influenzae* could still be isolated from the C.S.F. one intrathecal injection of penicillin was given on each of the following days: 26/10/45 (6,000 units), 28/10/45 (8,000 units), and 30/10/45 (25,000 units). On 1/11/45 the C.S.F. showed no bacteriostatic activity. The child improved rapidly after 30/10/45,

and recovered, developing chickenpox as a complication. Discharged well on 29/11/45.

Case 11.—M. G., a boy aged 1 year 3 months. (Under the care of Dr. G. W. Anderson, Preston Hospital, North Shields.) Three weeks before admission the child had bronchopneumonia, which cleared up satisfactorily. Two weeks later he vomited and was fretful, and symptoms suggestive of tuberculous meningitis set in 2 days before admission on 10/3/45. A total of 6 g. sulphathiazole had been given by the practitioner. The course of sulphathiazole was continued with 4-hourly doses until on 17/3/45 the isolation of *H. influenzae* was reported. The strain was subsequently shown to be of type b and to be completely inhibited by 1 unit penicillin per ml. of medium. On receiving the bacteriological report 50,000 units penicillin were given intrathecally by the cisternal route and the same amount by lumbar puncture, also 20,000 units 3-hourly intramuscularly. In addition he received 4-hourly doses of 0.5 g. of sulphadiazine. On the second day the penicillin content of the C.S.F. was 100 units per ml. and the culture was sterile. This medication was maintained for 7 days with the exception of 1 day when no cisternal puncture was performed and of 2 days when the administration of sulphadiazine had to be stopped because of crystal formation in the urine. By 23/3/45 the general condition had improved; the C.S.F. had been sterile for 6 days although many pus cells were still present. During this time the penicillin content of the C.S.F. was between 50 and 100 units per ml. A total of 15 g. sulphadiazine and 720,000 units penicillin intrathecally and 480,000 units intramuscularly had by then been given. All medication was discontinued, but on 25/3/45 the temperature, which had until then been normal for 5 days, rose again to 100° F. (37.8° C.). After another 2-day course of sulphadiazine a marked improvement was noticeable in the general condition, but the child seemed to be blind. From 28/3/45 to 5/4/45 there appeared to be slow but satisfactory progress, although sight did not return. On 5/4/45 the child died. At necropsy there was a little organizing pus on the tips of the temporal lobes and on the surface under the pons. Cultures from all these accumulations of pus were sterile with the exception of one from a temporal lobe, from which 2 colonies of *H. influenzae* were grown. There was a very marked internal hydrocephalus, with the lateral ventricles grossly enlarged, reducing the cerebral tissue to a thin layer.

Case 12.—The boy, A. C., aged 3 (under the care of Dr. J. Allan, Grantham Hospital), was admitted on 3/11/45, three days after having fallen ill with drowsiness and vomiting. He presented head retraction, flexion and adduction of left leg, Kernig's sign +, convergent squint of the left eye, and twitchings of the face. T. 100° F. (37.8° C.), P. 120, R. 36. Lumbar puncture produced a cloudy fluid under increased pressure. Administration of sulphathiazole 0.75 g. 4-hourly was started. On 7/11/45 the condition had become worse. There were convulsions, biting of the tongue, violent twitchings of limbs, and the C.S.F. was thickly purulent. Fifteen ml. was withdrawn by lumbar puncture and 60,000 units calcium penicillin in 6 ml. were given intrathecally, also 20,000 units intramuscularly, followed by 10,000 units 3-hourly. On the following day another 50,000 units penicillin were given intrathecally. On 10/11/45 there were numerous pus cells, Gram-negative bacilli, and filaments. No acid-fast bacilli present. Pure growth of *H. influenzae*. The strain was subsequently found to belong to type b and to be completely inhibited by 1 unit penicillin per ml. of medium. A further 40,000 units penicillin were given intrathecally on 10/11/45 and 17/11/45. On 18/11/45 the condition had not changed appreciably. Ten ml. of rabbit *H. influenzae* type b antiserum (made in Leeds) was given intramuscularly. Sulphathiazole was discontinued. A blood sample taken next day did not show any noticeable antibody in a dilution of the patient's serum of 1 in 10. A daily dose of 6 g. sulphadiazine was given from 19/11/45 to 30/11/45. Between 20/11/45 and 27/11/45 the leucocyte count varied from 14,000 to 12,950 per c.mm. No marked change in the general condition. On 30/11/45 the condition was still without change; a cisternal puncture was performed, 10 ml. C.S.F. was withdrawn and 6 ml. of rabbit *H. influenzae* type b antiserum injected, together with 70,000 units calcium penicillin. The C.S.F. showed pus cells and Gram-negative bacilli. A moderate growth of *H. influenzae* type b was obtained on culture. On 4/12/45, when the child was comatose, another cisternal puncture, with subsequent intrathecal injection of 10 ml. rabbit *H. influenzae* type b antiserum and 80,000 units calcium penicillin, was carried out. The withdrawn C.S.F. gave only a scanty growth of *H. influenzae* type b, and it contained numerous pus cells. Henceforth treatment was discontinued. The coma deepened and the child died in the early morning of 6/12/45. A total of 37.75 g. sulphathiazole, of 66 g. sulphadiazine, of 2,160,000 units penicillin intramuscularly and 370,000 units intrathecally had been administered during the course of the illness. At necropsy thick green pus was found in the lateral ventricles. No pus elsewhere on the brain.

Case 13.—According to the history given, A. R., a boy of 1 year 2 months (under the care of Prof. W. C. Vining, General Infirmary at Leeds), had a pneumonia 6 weeks before admission on 17/12/45.

This condition cleared up satisfactorily within a week under sulphonamide therapy. At the end of the week he was allowed to get up, but started vomiting the following day and continued to do so until admitted to hospital. The child presented obvious signs of meningitis; he was very dehydrated, listless, and did not respond. T. 97° F. (36.1° C.), P. 150, R. 20. Lumbar puncture produced a cloudy fluid under pressure. Cell count in C.S.F., 760 per c.mm.; proteins, 200 mg. per 100 ml.; chlorides, 0.64%. Direct film showed pus cells and Gram-negative bacilli, of which some were filament-forming; pure heavy growth of *H. influenzae* type b. Subsequent tests showed the strain to be completely inhibited by 2.5 units penicillin per ml. of medium. On 18/12/45 a course was started of 25,000 units penicillin intrathecally per day and of 16,000 units intramuscularly every 3 hours, supported by 0.5 g. sulphadiazine 4-hourly. 19/12/45: Sugar content of C.S.F., 40 mg. per 100 ml. 20/12/45: Sugar content, 70 mg. per 100 ml. One ml. of C.S.F. contained 32 units penicillin. Only scanty Gram-negative bacilli in film. Culture gave but a small number of colonies of *H. influenzae* type b. 21/12/45: Sugar content of C.S.F., 60 mg. per 100 ml. An occasional Gram-negative bacillus was seen in the direct film, which showed numerous pus cells. Only scanty growth of *H. influenzae* type b was obtained. Agglutinating antibodies against *H. influenzae* type b were present in the undiluted serum, but not in dilution 1 in 10. 22/12/45: No change. Lumbar puncture unsuccessful. C.S.F. from cisternal puncture showed abundant pus cells. No organisms seen. No growth was obtained on culture. Penicillin content more than 1/8 but less than 1/4 unit per ml. On 23/12/45 no intrathecal treatment was given. 24/12/45: Child going downhill. C.S.F. contained pus cells but no organisms; no growth obtained on culture. Penicillin content, 1/4 unit per ml. 25/12/45: C.S.F. sterile; penicillin content, 1/2 unit per ml. On 26/12/45 the child was very weak. Lumbar and cisternal punctures and injection of penicillin by both routes were carried out. Both fluids were sterile on culture and showed only a few pus cells in the direct film. The child died shortly after the cisternal puncture. A total of 24.5 g. sulphadiazine, 992,000 units penicillin intramuscularly and 200,000 units intrathecally was administered within 9 days. At necropsy the brain was under considerable tension. The convolutions were flattened, and over both vertex and base there was a sticky fibrinous exudate of yellowish colour. No growth was obtained from the exudate. Both ventricles were extended and contained clear fluid. The pia mater of the spinal cord showed a fibrinous exudate similar to that on the surface of the brain. Death from cerebral compression.

Case 14.—A detailed account of this case has been given by McIntosh and Drysdale (1945). This girl of 2½ years had *H. influenzae* type b meningitis following closely on a meningococcal meningitis. The type b *H. influenzae* strain was completely inhibited by 0.5 unit and partially inhibited by 0.25 unit penicillin per ml. of medium. Initial symptoms observed were those of an upper respiratory catarrh suggestive of the invasive stage of measles. Two days later obvious meningitis had developed. A 7-days course of 75,000 units penicillin intrathecally and of sulphapyridine by mouth resulted in apparent success, but 2 days later a relapse occurred. A 12-days course of penicillin intrathecally and intramuscularly as well as 7 days' administration of sulphamerazine led to complete restitution. In all, 20 g. sulphapyridine, 22.5 g. sulphamerazine, 325,000 units penicillin intrathecally, and 1,200,000 units intramuscularly were administered.

Case 15.—B.A., a girl of 1 year 8 months (under the care of Dr. R. L. Langley, Bradford Children's Hospital), fell suddenly ill on 14/5/45 with vomiting, deliriousness, and temperature. On admission the following day she was semi-comatose, with neck rigidity; Kernig's sign +; abdominal and patellar reflexes absent. Lumbar puncture produced a turbid fluid under normal pressure, which contained 1,200 polymorphonuclear leucocytes, 100 lymphocytes, and 480 red cells per c.mm. The culture grown from the C.S.F. was an *H. influenzae* type b which was completely inhibited by 1 unit and partially by 0.5 unit penicillin per ml. of medium. Treatment consisted of daily lumbar punctures with intrathecal injection of 10,000 units penicillin each time for 4 days, 3-hourly intramuscular injection of penicillin for 7 days, and sulphathiazole by mouth for the first 4 days. On 19/5/45 the C.S.F. was clear for the first time; the temperature still kept moving. The child improved gradually, her temperature being normal from 29/5/45. Recovery was complete. Total amount of penicillin given intrathecally was 40,000 units, intramuscularly 259,000 units; and of sulphathiazole 9.5 g.

Case 16.—M.W., a girl aged 1 year (under the care of Dr. L. Watson, Clayton Hospital, Wakefield), was admitted to hospital on 17/1/46 with the history of a fall off a chair 3 ft. (0.9 m.) high. The fall landed her on the back of her head. She was able to play for about 50 minutes afterwards and then became drowsy. She was admitted to a surgical ward for consultation, and was transferred to a medical ward on 23/1/46, when there were signs of meningitis with neck rigidity and slight stiffness of the back. A lumbar puncture carried out 2 days previously had given the follow-

ing results: fluid under pressure, markedly turbid. Protein, 60 mg. per 100 ml.; chlorides, 750 mg. per 100 ml.; cells, 7,600 per c.mm. The centrifuged deposit showed large numbers of polymorphonuclear leucocytes, some lymphocytes, and numerous Gram-negative bacilli. Culture yielded *H. influenzae*, which subsequently was found to belong to Pittman's type b and to be sensitive to penicillin. Combined penicillin-sulphathiazole therapy was instituted as follows. Thirty thousand units of penicillin 3-hourly intramuscularly and 1 dose of 0.5 g. sulphathiazole followed by 0.25 g. 4-hourly from 23/1/46 to 26/1/46. As there was no marked improvement the dose of penicillin was increased to 50,000 units 3-hourly for a further 8 days and sulphathiazole was continued until 28/1/46. On 29/1/46 another lumbar puncture was carried out and 8,500 units penicillin given intrathecally. The pressure of the C.S.F. was 150 mm. and the fluid was slightly turbid; protein, 70 mg. per 100 ml.; chlorides, 735 mg. per ml.; glucose, 17.5 mg. per 100 ml.; abundant lymphocytes, scanty Gram-negative bacilli. No penicillin demonstrable in the C.S.F. On 1/2/46 a 4-days course of sulphamerazine was given, starting with a dose of 1 g., followed by 0.5 g. 6-hourly. Since no improvement was noticeable 50,000 units penicillin were given intrathecally for 4 days, starting on 5/2/46. A sample of serum taken on 6/2/46 was positive for agglutinating antibodies against *H. influenzae* type b, giving a marked agglutination up to a dilution 1 in 128. From 11/2/46 to 13/2/46 50,000 units penicillin were again given once daily intrathecally, and from 18/2/46 to 4/3/46 the child received 30,000 units penicillin intramuscularly at 3-hourly intervals, with only an occasional rest for 24 hours. In spite of the intensive penicillin treatment, with occasional and subsidiary sulphonamide therapy, the child died on 7/3/46. A total of 3,040,000 units penicillin intramuscularly and 358,500 units intrathecally, of 7.75 g. sulphathiazole, and of 8.5 g. sulphamerazine was given during the course of the illness.

Case 17.—M.H., a girl aged 4 (under the care of Dr. L. Watson, Clayton Hospital, Wakefield), had a history of upper respiratory infection a week before admission on 8/1/46, and three days later she developed stiffness of back and neck, headache, and some vomiting. On examination she was not very ill, and apart from slight neck rigidity there were no other physical signs. At lumbar puncture the pressure was 240 mm.; the C.S.F. was slightly turbid, and contained 45 mg. protein per 100 ml., 700 mg. chlorides per 100 ml., numerous polymorphonuclear leucocytes, and a few lymphocytes as well as some Gram-negative bacilli. Culturing gave numerous colonies of *H. influenzae*. A 4-days course of 15,000 units penicillin intramuscularly at 3-hourly intervals was given at once to be followed by a 2-days course of 1 g. sulphathiazole four times daily. On 14/1/46 3-hourly intramuscular injections of 15,000 units penicillin were given for 4 days, and on 17/1/46 this dose was doubled and continued until 25/1/46. On 18/1/46 the C.S.F. was still turbid and contained 50 mg. protein per 100 ml., 730 mg. chlorides per 100 ml., and 2,300 cells per c.mm., of which 80% were polymorphonuclear leucocytes and 20% lymphocytes. Only two colonies of *H. influenzae* were grown. After withdrawal of the C.S.F. 8,500 units penicillin were injected intrathecally. From 25/1/46 to 6/2/46 the dose of intramuscular penicillin was further increased to 50,000 units 3-hourly. On 29/1/46 lumbar puncture was performed again and 8,500 units penicillin injected intrathecally. The C.S.F. contained pus cells but no organisms and no growth was obtained on culture. The fluid contained 0.16 unit of penicillin per ml. It was at this stage that this laboratory was consulted, and as none of the previous cultures had been preserved it was impossible to determine the type of the *H. influenzae* by direct methods. A sample of blood serum was obtained, however, and was tested for the presence of agglutinating antibodies. A marked agglutination of a type b strain of *H. influenzae* was obtained to a dilution of 1 in 32 and no agglutination with any of the other 5 types. This indirect method of typing made it reasonably certain that the causative organism was of type b *H. influenzae*. Signs of meningeal irritation passed off after a final 4-day administration of sulphamerazine at 6-hourly intervals, beginning on 1/2/46. The patient was discharged on 8/3/46, after having had a normal temperature for 13 days and having been up and about the ward a week before discharge. A total of 8 g. sulphathiazole, 8.5 g. sulphamerazine, 7,280,000 units penicillin intramuscularly and 17,000 units intrathecally had been given.

Case 18.—A.T., a girl aged 2 years 4 months (under the care of Dr. R. L. Langley, Bradford Children's Hospital), fell ill with vomiting on 2/2/46. On 3/2/46 there was some deterioration; she was listless, pallid, vomited copiously, and had a temperature of 101° F. (38.3° C.). The G.P. started to give her 0.25 g. sulphapyridine at 4-hourly intervals on the same day. During the next few days there was no great change and no marked sign in any direction except missing knee-jerks. On 7/2/46 there were slight neck rigidity, convergent strabismus, and a temperature of 100.8° F. (38.2° C.). On admission to hospital on the same day she was semi-comatose, and showed marked strabismus and neck rigidity; Kernig's sign was positive, knee-jerks and abdominal reflexes were absent. Lumbar puncture produced a turbid fluid under high pressure, and 10,000

units penicillin were injected intrathecally after C.S.F. had been withdrawn. On culture the C.S.F. gave a pure growth of *H. influenzae*, which later was shown to belong to Pittman's type b and to be sensitive to penicillin. An attempt to give the child 0.5 g. sulphapyridine 4-hourly had to be abandoned after 48 hours owing to vomiting. Instead 5,000 units penicillin were given 3-hourly. After an initial fall the temperature rose again on 12/2/46, and for 3 days daily intrathecal injections of 5,000 units penicillin were given. The C.S.F. became clear on 17/2/46 and the temperature went down to normal. Intrathecal penicillin therapy was discontinued for 48 hours, but on 16/2/46 the temperature rose to 103° F. (39.4° C.), and the C.S.F. became turbid again. Recourse was had to 12-hourly intrathecal injections of 5,000 units penicillin. In all 30 such injections were given between 16/2/46 and 3/3/46. Intramuscular administration of penicillin was discontinued between 18/2/46 and 3/3/46 in favour of 0.25 g. sulphathiazole 4 times daily. On 26/2/46 the C.S.F. was free from *H. influenzae*, but on 1/3/46 another relapse occurred. A continuous plasma drip was given. The C.S.F. gave good growth of *H. influenzae*, and antibodies against *H. influenzae* type b were found to be present in undiluted serum but not in a dilution of 1 in 10. After starting renewed administration of 5,000 units penicillin intramuscularly at 3-hourly intervals and 5,000 units penicillin 12-hourly intrathecally on 4/3/46 the C.S.F. rapidly became sterile again, and the general condition improved gradually. The patient was discharged well on 3/4/46. The total dose of penicillin was 365,000 units intramuscularly and 135,000 units intrathecally. In all 3.5 g. sulphapyridine and 15 g. sulphathiazole were given.

Case 19.—P.C., a 7-months-old boy (under the care of Dr. B. A. Peters, Ham Green Hospital, Bristol), had been ill with infection of the respiratory tract, which did not respond to sulphonamide treatment, two weeks before his admission on 6/11/45. There were no symptoms apart from bronchitis and a temperature between 100° F. (37.8° C.) and 102° F. (38.9° C.), and high pulse and respiratory rates. Administration of 30,000 units penicillin daily for 4 days did not improve the general condition. On 22/11/45 signs of meningitis were noticed, and examination of C.S.F. gave the following results: protein, 55 mg. per 100 ml.; globulin, increased; sugar, 6 mg. per 100 ml.; chlorides, 690 mg. per 100 ml.; 176 red cells and 56 white cells per c.mm., mostly polymorphonuclear leucocytes. Some time later the C.S.F. was clear, and the cell count and chloride level suggested tuberculous meningitis. The child died on 4/12/45. Post-mortem examination revealed a purulent meningitis involving the whole of the meninges. A culture taken post mortem was examined in this laboratory and the strain of *H. influenzae* isolated was found to belong to type b. The strain was completely inhibited by 1 unit penicillin per ml. of medium.

Case 20.—A boy, H.D., aged 1 year 8 months. This case has been reported in great detail in an excellent recent paper by Drysdale, McIntosh, and Brodie (1946). The child had a 3-days history of meningitic symptoms before admission to hospital on 18/12/45. The *H. influenzae* strain isolated from the C.S.F. was of Pittman's type b. It was found to be sensitive to 0.7 unit penicillin per ml. of medium and insensitive to sulphapyridine, sulphamezathine, sulphadiazine, sulphathiazole, and sulphamerazine. Until this insensitivity to sulphonamides had been fully established the child had received 5 g. sulphapyridine, 5.5 g. sulphamezathine, and 12.5 g. sulphathiazole in combination with intramuscular and intrathecal injections of penicillin. Sulphonamide treatment was then discontinued and therapy was carried on with daily intramuscular and intrathecal injections of penicillin. In all the child received 10,337,500 units of penicillin intramuscularly and 1,005,000 units intrathecally within 5 weeks. This intensive penicillin treatment led to complete recovery.

Notable features of this case were: (1) The reappearance of *H. influenzae* in the C.S.F. after intrathecal administration of penicillin had been suspended temporarily. (2) The occurrence of a severe convulsion 2 hours after the eleventh intralumbar injection of 50,000 units of penicillin. No cerebral irritation had been noticed on the previous 10 occasions, nor had any symptoms occurred after any of the 7 intrathecal injections of 25,000 units which had preceded the higher dose. (3) Careful penicillin assay in the C.S.F. revealed that with daily intrathecal doses of 50,000 units an average concentration of 1.7 units penicillin per ml. of C.S.F. could be maintained, while with a daily dose of 25,000 units the concentration averaged only 0.6 unit per ml.

Discussion

The first point emerging from this survey is that 20 cases of *H. influenzae* meningitis in children, of which 19 were caused by Pittman's type b, could be collected in a small area within a period of just under two years. It would seem, therefore, that at present the condition is not as rare as the scarcity of case reports in this country would suggest. The second point is the varied nature of the symptoms with which an infection of the meninges with *H. influenzae* may manifest itself. Every

type of meningitis, from the fulminant infection leading to death in 24 to 48 hours to the protracted case typical of tuberculous meningitis, may be met with. In addition difficulties arise in diagnosing meningitis in children under 7 to 8 months of age owing to absence of the usual symptoms of meningitis, and the consequent delay in treatment is responsible for the high case fatality rate in this age group (Alexander, 1943b). Thus it is seen that in this series both the children under 1 year of age (Cases 4 and 19) died, the latter having no symptoms for a considerable time. In view of the protean nature of the symptoms of *H. influenzae* meningitis it is fortunate that the sulphonamides most effective against *H. influenzae*—i.e., sulphadiazine and sulphamezathine—have equally good bacteriostatic properties against most other organisms causing meningitis except the tubercle bacillus. Sulphadiazine and sulphamezathine should be the drugs of choice, therefore, in every case of meningitis, and particularly in children, as soon as a clinical diagnosis is made and C.S.F. has been withdrawn for culture, without waiting for bacteriological confirmation. Simultaneously penicillin should be given, since its bacteriostatic effect on a large number of strains of *H. influenzae* has now been well established. Penicillin sensitivity of *H. influenzae* strains varies to some extent, however, and determination of the sensitivity of any particular strain should be a guide to the concentration of penicillin in the C.S.F. to be aimed at (M. Gordon and Zinnemann, 1945). Penicillin should be administered both systemically and intrathecally to maintain the requisite concentrations in blood and C.S.F. As Alexander (1943b) suggests daily lumbar puncture as an essential part of treatment, the intrathecal injections cause little if any extra burden to the patient. The systemic administration also deals adequately with any possible septicaemia, which is a common accompaniment of the meningitis (Fothergill, 1937)—as Case 7 illustrates. The administration of type b specific *H. influenzae* rabbit antiserum is also indicated if the causative organism is of the b type.

It is necessary to stress the need for continuing medication without interruption until 7 days after the C.S.F. has first become sterile. Cases 1, 2, 4, 11, 14, 18, and 20 illustrate the dangers of suspending treatment too soon after the C.S.F. has become clear. Moreover, there is also the theoretical risk of producing penicillin-resistant strains of *H. influenzae* if the concentration is not maintained until the C.S.F. has remained sterile.

Under the conditions of the survey it was impossible to trace the sources of infection. Alexander (1943a) produced evidence that typable *H. influenzae* strains are harboured in the nasopharynx of children. Straker (1945) confirmed this in a number of children in this country. It is interesting in this connexion to note that in six cases of this series—namely, Nos. 5, 11, 13, 14, 17, and 19—a respiratory infection preceded the onset of meningitis. Possibly, comparative studies in adults and children might contribute to answer the question why *H. influenzae* meningitis is predominantly a disease of childhood.

The fairly wide differences as to choice and dosage of sulphonamides used should be eliminated if the American suggestions are followed (Alexander and Leidy, 1943), though the task remains of determining more accurately the dosage and route of administration of penicillin. Cases 15 and 17 recovered with comparatively small intrathecal doses—the first with 10,000 units administered daily for 4 days, and the second with 8,500 units given intermittently. In Case 20 Drysdale, McIntosh, and Brodie found, however, that 50,000 units intrathecally were required to maintain a concentration of approximately 2 units per ml. at the end of 24 hours, while 25,000 units gave a concentration of only 0.6 unit per ml. of C.S.F. Their results give a lead as to the dosage to be employed intrathecally, considering that the majority of *H. influenzae* type b strains are inhibited by approximately 2 units per ml. In view of possible cerebral reactions to such high intrathecal doses it may be worth while to give the daily dose of 50,000 units in two 12-hourly administrations. A reduction of the daily dose may be the result of such a procedure, as Case 18 suggests, in which complete recovery was the result of thirty 12-hourly intrathecal injections of 5,000 units of penicillin supported by 0.25 g. sulphathiazole 6-hourly.

In Cases 8, 11, 12, and 13 death occurred through internal hydrocephalus, probably due to adhesion or to clots in the C.S.F. Alexander (1944) suggested that this complication might

be overcome by introduction of air and heparin into the cerebrospinal canal, and it may be worth while to try her methods in such desperate cases. It need not be feared that children thus saved might prove to be crippled in one way or another for the rest of their lives. Regarding such consequences Alexander (private communication) states:

"The experience in this country when both sulphadiazine and type-specific rabbit antiserum are used in combination for the treatment of influenzal meningitis indicates that any residual damage to the brain is exceedingly rare following recovery. This appears to be true even in very chronic cases of the disease which recover over a long period of time. For example, I know, as a result of my own experience and by talking over the experiences of a number of others, of only one case in which residual damage to the brain followed a child's recovery."

In all, 5 out of 20 cases were treated with sulphonamides alone. Only one of these five recovered. Fifteen cases had combined sulphonamide-penicillin treatment and eight of them recovered. The total number of cases is too small and the methods of treatment varied too much to allow of statistical assessment. The only conclusion to be drawn is that the encouraging recovery rate suggests pushing to the limit the combined sulphonamide-penicillin treatment, perhaps supported by specific antiserum.

The sporadic occurrence of *H. influenzae* meningitis in this country makes it very difficult for any investigator, single-handed, to work out a satisfactory routine treatment. It seems reasonable to suggest that cases of *H. influenzae* meningitis of the non-fulminant type should be concentrated in a number of treatment centres. An adequate method of treatment, as in the case of subacute bacterial endocarditis, might be evolved for the majority of cases, and a substantial number of children's lives might thus be saved.

Summary

A survey of the various methods of treating *H. influenzae* meningitis is presented.

Clinical data are given of 19 cases of *H. influenzae* type b meningitis and of 1 case due to *H. influenzae* of the respiratory group. Of 5 cases treated only with sulphonamides, one recovered. Fifteen cases had combined sulphonamide-penicillin treatment. Eight of these recovered. It is suggested that the combined administration of these drugs should be used more energetically in *H. influenzae* meningitis. In view of the good therapeutic results reported from the U.S.A. specific *H. influenzae* type b rabbit antiserum, which is now available in this country, should also be given.

The establishment of a number of treatment centres to evolve a standard routine method of treatment is advocated.

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INFECTIONS OF THE NERVOUS SYSTEM OCCURRING DURING AN EPIDEMIC OF INFLUENZA B

BY

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Influenza epidemics in the past have on occasion been associated with cases presenting evidence of cerebral or cerebrospinal infection, although the relationship is obscure. During the epidemic of influenza B at the beginning of 1946 nine cases of acute infection of the nervous system, occurring at three separate levels, were observed. Two of these presented signs of brain-stem encephalitis, two of myelitis, and five of generalized polyneuritis akin to the acute toxic polyneuritis of Guillain, Barré, and Strohl (1916).

Brain-stem Group

Case 1.—A girl aged 18 complained of diplopia and right-sided ptosis. She was well until May 14, 1946, when she developed a generalized headache and extreme lassitude. She had intense sleepiness, and found it difficult to remain awake. Her neck felt a little stiff. She was bad-tempered, and had one outburst of unreasonable rage. Three days before the onset of her symptoms she had been in close contact with a girl who had a severe attack of influenza. On the 18th her vision became blurred, and she noticed diplopia in all directions. Next day the right lid began to droop, and she experienced discomfort in the right supraorbital region. The headache persisted; there was no polyuria or polydipsia; the appetite was poor; and she still felt very sleepy. She had had diarrhoea off and on for the past nine to ten days. On May 24 she was admitted to the London Hospital under the care of Dr. Russell Brain.

Examination showed the following: Right pupil a little larger, and reacting a trifle more sluggishly to light than the left; equal brisk reaction to accommodation; right ptosis; weakness of elevation, adduction, and depression of the right globe; diplopia in all directions; all tendon reflexes depressed; knee-jerks obtained only on reinforcement; equivocal right plantar response. Lumbar puncture on May 25: C.S.F. pressure, 100 mm.; 8 cells, mainly lymphocytes; protein, 20 mg. per 100 ml.; W.R. negative; Lange, 222321000. On the 28th the white cell count was 6,700 per c.mm. (polymorphs 70%, lymphocytes 25.5%, large hyalines 4.5%). June 6: No diplopia; right ptosis; very slight weakness of elevation of right globe; pupils equal, reacting sluggishly to light. On the 8th there were full ocular movements and no diplopia. The tendon reflexes were sluggish and plantar responses flexor. The patient was discharged symptom-free.

Case 2.—A medical man aged 38 complained of headache, photophobia, diplopia, dizziness, and tingling in hands of five days' duration. On March 12, 1946, he had a sore throat, cough, and general malaise, but after sulphathiazole for three days he felt fit. About March 26 he developed dizziness and photophobia, followed 24 hours later by tingling in both hands and difficulty in focusing. On the 30th he had diplopia in all directions. The left pupil was larger than the right, and both pupils reacted only sluggishly to light. Next day there was an increase in the severity of all symptoms: tingling now present in feet; headaches more severe, mainly frontal aching pain; movement of eyes painful; diplopia in all directions except to the extreme right. Left ptosis was noticed by the patient on April 1. He felt extremely drowsy, and slept eleven to twelve hours. He was admitted to the London Hospital under the care of Dr. Clifford Wilson. The patient presented a difficult diagnostic problem, as he had suffered from Hand-Schüller-Christian disease since 1932 and had had five injections of "pitressin" daily to control his diabetes insipidus.

He was seen by Dr. George Riddoch on April 2. Examination showed: Pupils moderately dilated, regular, left larger than right; very feeble reaction to light and, on convergence, right more than left; gross paresis of all external ocular movements, left more than right; severe bilateral ptosis. Upper limbs: no weakness, ataxia, or dystonia; tendon reflexes absent. Lower limbs: no weakness, ataxia, or dystonia; knee-jerks just present; ankle-jerks absent; plantar reflexes flexor. There was no cutaneous sensory change. The abdominal reflexes were present and equal. B.P. 190/120. Urine normal. Lumbar puncture: pressure 240 mm.; 4 cells; protein, 30 mg. per 100 ml.; Lange 1222100000; W.R. negative. A radiograph of the skull showed nothing abnormal. The patient was considered to be suffering from an acute infection of the nervous system, chiefly affecting the brain-stem. Daily injections of 2 ml. of "hepolon" were advised. On April 3 the left pupil was larger than the right, both fixed to light; sluggish reaction to accommodation; ptosis more severe, left worse than right. The white cell count was 7,750 per c.mm. (polymorphs 69%, lymphocytes 25%, eosinophils