tration of pituitrin and concentrated blood serum. The possible clinical application of these results is pointed out.

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SUCCESSFUL CHEMOTHERAPY FOR HAEMOLYTIC STREPTOCOCCAL MENINGITIS AND PNEUMO- COCCAL MENINGITIS IN THE SAME PATIENT

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There are many published reports of successful treatment of haemolytic streptococcal meningitis with sulphanilamide and other sulphonamides. So striking are the results that one would be justified, when recording the history of the treatment of this disease, in drawing a line between what may be called the pre-sulphonamide and the sulphonamide eras. In the former period the outlook was gloomy in the extreme. Gray (1935), in his classical analysis of the sixty-six cases of recovery from streptococcal meningitis recorded in the whole literature of the subject between 1901 and 1935, gave the mortality rate as 97 per cent. In pneumococcal meningitis the story was even more depressing, the mortality being little short of 100 per cent. With the advent of chemotherapy by sulphonamides this form of treatment was applied to streptococcal meningitis with most dramatic results. Figures such as those published by Appelbaum (1939) have become quite common. He had thirty-five cases with twenty-eight recoveries and seven deaths—the majority of the latter having other complications which might themselves have proved fatal.

Successful chemotherapy in pneumococcal meningitis was uncommon until the introduction of sulphapyridine (M & B 693), although recoveries have been reported by Caldwell and Byrne (1937), Latta (1938), Landon (1938), Young (1938), and others. Hodes, Gimbel, and Burnett (1939) report seventeen cases of pneumococcal meningitis treated with sulphapyridine and its sodium salt, eight

recovering. They contrast these results with those obtained at the Sydenham Hospital, Baltimore, before the introduction of the drug: between 1930 and 1936 twenty-seven cases were admitted and all were fatal; from December, 1936, to October, 1938, seventeen patients were treated with sulphanilamide, with one recovery. These authors state that previous to the publication of their paper eight recoveries had been recorded out of fourteen cases of pneumococcal meningitis treated by sulphapyridine alone. If these are added to their own cases we have, with the case described below, thirty-two cases of pneumococcal meningitis treated by sulphapyridine alone, with seventeen recoveries, a rate of 53 per cent. It would appear, therefore, that the introduction of sulphapyridine has so far halved the mortality rate.

A search of the literature has, however, failed to reveal any record of a patient having recovered from two distinct attacks of coccal meningitis bacteriologically different in origin, and the uniqueness of the following case in this respect would appear to justify its publication.

Case History

The patient was a girl aged 17 whose previous medical history was uneventful, except that she had had a mild attack of acute otitis media in childhood which had completely resolved.

FIRST ATTACK (STREPTOCOCCAL MENINGITIS)

On August 24, 1937, the patient was admitted to hospital with acute otitis media following tonsillitis, and six days later a Schwartze mastoidectomy was performed. Progress was satisfactory until September 8, nine days after the operation, when the temperature rose and there was headache and neck stiffness. Her condition rapidly deteriorated; within a few hours unconsciousness supervened with all the signs of a virulent meningitis. Cerebrospinal fluid withdrawn under pressure was turbid, the cell count being 11,040 per c.mm., and haemolytic streptococci were grown on culture. Chemotherapy was started on the 9th, 5 c.cm. of prontosil soluble being injected intramuscularly. On the following day two further injections were given. Mr. Terence Cawthorne converted the Schwartze to a radical operation, and released cerebrospinal fluid under extreme pressure by incision of the dura of the posterior fossa (Neumann's procedure). The next day tablets of sulphanilamide were given, being continued for eight days (see "Dosage").

The second cerebrospinal fluid specimen, withdrawn on September 12, was sterile, and the patient had regained consciousness, although still restless and averse to intervention. By the 16th her condition had improved so considerably that sulphanilamide was discontinued—a total of 27 grammes having been given. Excellent progress was maintained, the cerebrospinal fluid on October 18 being clear and containing only 30 cells. Suddenly, on October 20, severe headache, neck stiffness, photophobia, etc., recurred, the temperature rising more gradually to 102.2°. Drs. Sheldon and Denny Brown and Mr. Cawthorne all confirmed recrudescence of the meningitis, although the cerebrospinal fluid under increased pressure was sterile on culture. Sulphanilamide was again administered, and by October 25, after a further total dosage of 10.5 grammes, all signs of meningitis had once more disappeared. From that date convalescence was uninterrupted, and the girl was eventually discharged on December 17 cured—the affected ear being completely healed and dry.

In due course the patient was able to resume her duties as a nurse, and during the seventeen months which elapsed before her second illness she enjoyed very good health and experienced no sequelae. Recurrent headaches of which she complained were eliminated by the provision of glasses, and she had been free from them for some six months before the second attack.

SECOND ATTACK (PNEUMOCOCCAL MENINGITIS)

On the morning of May 13, 1939, the patient was first seen by one of us, having been complaining of vomiting, vertigo,

and photophobia. She had been perfectly well the day before, but during the preceding night had had slight pain in the right ear, without rise of temperature. Within a few hours she was unconscious, and restlessness was so pronounced that control by morphine was necessary. Intramuscular injections of sodium sulphapyridine (M & B 693 soluble) was promptly instituted, oral therapy being impracticable because of unconsciousness and vomiting. Examination of the affected ear revealed a small abscess postero-superiorly in the depths of the old radical cavity. This was incised and about half an ounce of pus evacuated. The first cerebrospinal fluid specimen withdrawn, under greatly increased pressure, on the morning of May 14 gave a growth of Type E 19 pneumococcus on culture, the second specimen taken the following day being sterile. By the evening of the 16th the patient was conscious and able to recognize people and answer simple questions. She continued to improve, and on May 20 sulphapyridine by mouth was substituted for the intramuscular injections, a previous attempt to institute oral therapy on the 18th having failed as the patient vomited the drug. Convalescence from the meningitis was from this date uninterrupted. An incidental minor disturbance was the development of deep-seated inflammation in the buttocks at the site of the intramuscular injections. A large confluent abscess in the right buttock eventually discharged pus via one or two of the needle tracks and completely cleared up. By June 26 the old radical cavity was again epithelized, healed, and dry, and the patient got up. She was discharged from hospital and went home to convalesce.

Relative Importance of Surgery and Chemotherapy

It will be evident that both the attacks of meningitis in the above case were of a very virulent nature. The rapid clinical improvement following on the administration of sulphanilamide in the first attack (streptococcal meningitis) and sulphapyridine in the second (pneumococcal meningitis) leaves little doubt that these drugs turned the scale towards recovery despite the fact that Neumann's operation was also done the first time. As regards operation, it is generally agreed that when there is reason to believe that bone disease is present in the mastoid adjacent to the dura and acting as a focus of infection eradication of the latter is essential, even though we may be shutting the stable-door after the horse is stolen. In this connexion it is interesting to note the difference between the assumed mode of infection of the meninges in the two attacks. As has been stated by Turner and Reynolds (1931), otogenic meningitis may result from infection via the blood stream, from adjacent bone disease, or through natural spaces or gaps resulting from injury. In the first attack, described above, the second route would appear to be the most likely from the sequence of events as recorded—namely, acute otitis media, cortical mastoidectomy ten days later, and then in a further ten days radical mastoidectomy; that is, apparently, a relatively slow progress to the meninges from the original focus of infection in the middle ear. Bone involvement calling for radical surgery is what one would expect and what was in fact demonstrated. On the other hand, the fulminating onset in the second attack suggests a more direct route of infection—either via the blood stream from the abscess in the old radical cavity or through the weakened barrier resulting from extensive bone removal at the previous operation. In support of this latter view Cawthorne (1939) refers to three cases in his own experience in which a second attack of streptococcal meningitis occurred and large areas of dura had previously been exposed and were lying in direct contact with the middle-ear cleft. If this were so, extensive surgery would not be called for, and it should suffice to evacuate pus from the abscess referred to and provide free drainage. This was, in fact, all that was done in our case, reliance being placed on intensive

chemotherapy, with the highly satisfactory result recorded. Chemotherapy is tending to stay the surgeon's hand to some extent, even when meningitis has actually developed, and T. B. Layton (1939) has said that the time may soon come when our practice will be to treat the meningitis first with chemotherapy and deal with the mastoid disease by operation during the convalescent period. Perhaps we should add that another possible route of infection in the second attack in our patient—namely, via the labyrinth—was ruled out, despite the suggestiveness of early labyrinthine symptoms, by the fact that the girl was subsequently found to have an active labyrinth and some hearing on that side.

In summing up the question of the relative importance of chemotherapy and surgery in the treatment of this condition we may quote the view of Long and Bliss (1939). They said: "If, however, a septic focus is present which is not draining well, and if it seems to be considered judgment of the surgeon that the focus can be drained without the operative procedure's immediately endangering the life of the patient, then sulphanilamide should be started and the focus drained."

Dosage

The dosage of sulphapyridine for the pneumococcal infection was regular and controlled in comparison with the rather haphazard administration of the sulphanilamide, which, owing to the general lack of knowledge of that aspect of chemotherapy, was a common feature at the time of treatment of the first attack. Prontosil soluble was first given parenterally (15 c.cm.), and, later, sulphanilamide was given orally (27 grammes spread over eight days). The dosage was low, the administration was not regular or sufficiently prolonged, and the level obtained in the cerebrospinal fluid was not determined. This may explain the recrudescence of the meningitis six weeks later, for which a further 10.5 grammes of the drug in tablet form was given over a period of three days. The dosage was regarded at the time as adequate in view of the rapid clinical improvement and of the fact that the cerebrospinal fluid was sterile in twenty-four hours.

For the attack of pneumococcal meningitis in May, 1939, sulphapyridine was used. In all, 68.5 grammes

was given over a period of sixteen days, and as the patient was vomiting, the soluble sodium salt was administered intramuscularly—37 grammes being given in the first seven days. On the fifth day an attempt was made to substitute tablets, but vomiting occurred despite crushing the tablets in milk and frequent administration of sodium bicarbonate.

This dosage corresponds approximately to that suggested by most writers—namely, 1 gramme per 20 lb. of body weight per twenty-four hours, given at four-hourly intervals. Estimations of free and conjugated sulphapyridine in blood and cerebrospinal fluid were done for us by Messrs. May and Baker, the method of Baines and Wien (1939) being employed, and they have incorporated their results along with the dosage of the drug in the form of the graph shown. It will be seen that on the first estimation the figures for blood and cerebrospinal fluid were respectively 15 and 10 mg. per 100 c.cm. This was after 23 grammes had been given. Dosage was then kept at 0.5 gramme four-hourly. In all remaining estimations the cerebrospinal fluid content of free sulphapyridine was approximately half that of the blood, as has been found by other writers.

Tolerance and Blood Changes

Our patient showed very little intolerance to sulphanilamide or sulphapyridine. During the attack of streptococcal meningitis cyanosis was pronounced, but caused no distress; and during the phase of aseptic meningitis there was a maculo-papular eruption situated mostly on the exposed portion of the body, but this cleared up rapidly.

Cyanosis was present with the attack of pneumococcal meningitis, but caused no distress. At the site of the injections of the sodium sulphapyridine there was a deep-seated inflammation, with later formation of pus, which, however, did not give rise to superficial ulceration but discharged along the needle-puncture tracks and cleared up in about three weeks. Intragluteal administration was continued for much longer than is usually advised, but this was thought to be justified in view of the gravity of the patient's condition and the difficulties that would have been encountered in intravenous injection.

During the course of the pneumococcal meningitis, when large doses of sulphapyridine were being given, full blood counts were done daily, and we should like to stress the behaviour of the leucocytes in a case responding to treatment which did not have to be prolonged. The total count dropped from 23,000 per c.mm. on the fourth day to 13,000 on the seventh day, a fall of 43.5 per cent.—a usual finding in all successfully treated cases. The fall in granulocytes was 25 per cent.—from 90 per cent. to 65 per cent.—when 36 grammes of sulphapyridine had been given, which suggests that on occasion granulocyte production may temporarily be disturbed even when treatment is of short duration. Against this reasoning is the fact that the infection was so very severe that it would undoubtedly have proved fatal in the days before sulphonamides; adequate comparative data do not therefore exist.

That the leucocytes were able to react well is shown by the rise on the thirteenth day to 31,000 and almost 86 per cent. granulocytes after 59.5 grammes of sulphapyridine had been given. This is due to the inflammation in the buttocks from the injections, and is analogous to the response seen in cases of pneumonia complicated by empyema.

There was a mild anaemia of the secondary type during the convalescent stage, which rapidly responded to iron therapy. Macroscopic haematuria was not observed during sulphapyridine therapy.

Cerebrospinal Fluid

During both attacks cerebrospinal fluid was withdrawn initially for confirmation of diagnosis, and thereafter only

when considered advisable to reduce pressure. It is interesting that drainage by lumbar puncture was called for on only four occasions in the attack of streptococcal meningitis and seven occasions in the attack of pneumococcal meningitis. Fluid was withdrawn once during the recrudescence. This accords with the practice of others since the introduction of chemotherapy for meningitis (Banks, 1939). It is noteworthy that at no time did the appearance of the fluid withdrawn approximate to the thickly purulent type obtained from cases of pneumococcal meningitis before the introduction of chemotherapy. These facts are further evidence of the satisfactory response of the infection to the drug, and in this connexion it is striking that in both illnesses the cerebrospinal fluid was sterile on culture at the second examination within twenty-four hours, and the cell count had fallen from 11,040 to 3,200 per c.mm. in the first attack and from a similar number (not recorded) to 2,000 per c.mm. in the case of the second attack.

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TREATMENT OF PNEUMOCOCCAL MENINGITIS WITH SULPHAPYRIDINE

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The disappointing results obtained in treating pneumococcal meningitis with moderate doses of sulphapyridine (M & B 693) led to the use of massive doses of the drug at the onset of treatment in the two cases recorded below.

Case I

A boy aged 7 was admitted to the Jenny Lind Hospital on September 30, 1939, on the third day of his illness. On September 28 he had complained of headache, had been seen to be drowsy, and had vomited once. On admission he was drowsy but conscious. He complained of pain over the vertex. The temperature was 101° and the pulse rate 100. There was neck rigidity, and Kernig's sign was positive. No physical signs were present in the chest, and the ears were normal. Lumbar puncture showed turbid cerebrospinal fluid under pressure. There were 2,500 cells per c.mm., most of them being polymorphs. Gram-positive diplococci were identified in the film.

From 10 p.m. on the day of admission he was given an injection of 3 c.cm. (1 gramme) of soluble sulphapyridine every hour for twenty-hours, and then 3 c.cm. every four hours. He vomited frequently during the first night, and next day was delirious and very noisy. Lumbar puncture showed turbid cerebrospinal fluid with 4,000 pus cells per c.mm. No organisms were found. On the third day in hospital he was still extremely ill, and difficulty was experienced in keeping him in bed. The cerebrospinal fluid was turbid but not under pressure. His delirium was controlled with paraldehyde, and he was given oesophageal feeds. The temperature had become normal twenty-six hours after admission and remained so during the third and fourth days. From noon on