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

the third day sulphapyridine was again given in doses of 1 gramme every hour for twelve doses. On the fourth day his condition had improved a little by the evening, but his urine was bright red and remained so for two days. On the fifth day there was definite improvement, but he was still delirious at times. He was pale and cyanosed, and the blood count showed 4,900,000 red cells per c.mm., 64 per cent. haemoglobin, and 12,200 white cells per c.mm. Sulphapyridine was discontinued on the morning of this day, when the total dose had reached 48 grammes, the drug having been given in doses of 1 gramme three-hourly or 1 gramme four-hourly on the fourth and fifth days. On the sixth day he was able to talk rationally and said he felt very much better.

The patient continued to do well until the ninth day, when he complained of pain over the bridge of the nose. A similar pain, he said, had been present on the first day of his illness. He also complained of frontal headache and there was slight neck rigidity. The temperature, which was 99° from the evening of the sixth day in hospital to the evening of the eighth, rose to 103° during the day. The cerebrospinal fluid was quite clear macroscopically, but contained 40 polymorphs per c.mm. No organisms were seen, but Type I pneumococci were obtained on culture. Sulphapyridine was given in doses of 1 gramme six-hourly and later 1 gramme three-hourly until the fourteenth day, the total dose during this relapse being 20 grammes.

The child never became seriously ill during the relapse, and on the eleventh day he was free from symptoms. His temperature subsided from 103° on the ninth day to 99.5° on the eleventh day, but rose to 100° till the fifteenth day. He tended to run a temperature of 99° from the fifteenth to the twenty-sixth day, when it came down permanently. The ear, nose, and throat system had appeared normal clinically throughout the illness, but a radiograph of the sinuses on the sixteenth day revealed opacity of the right antrum, and the next day antrostomy on this side by Mr. N. S. Carruthers produced thick pus. No organisms were seen in the pus, and it was sterile on culture.

On discharge from hospital at the end of five weeks the child was alert mentally. He had been taking iron since the fifteenth day, when his blood count had read: 3,120,000 per c.mm.; haemoglobin, 58 per cent.; and white cells, 12,600 per c.mm. On discharge the red cells were 4,600,000; haemoglobin, 78 per cent.; and white cells, 5,600.

On November 10, six weeks after the onset of treatment, he attended as an out-patient and appeared well. The blood count showed red cells, 4,800,000; white cells, 7,000; and haemoglobin, 82 per cent. The differential count gave 50 per cent. polymorphs, 44 per cent. lymphocytes, and 6 per cent. monocytes. On January 3, 1940, the child was seen again and still appeared very well.

Case II

This patient, a boy aged 10, was admitted to the Norfolk and Norwich Hospital on October 1, 1939. He had had a discharging right ear for some years, and this discharge was stated to have increased ten days before admission. On the day before admission he complained of severe headache at the back of the head, vomited three times, and became unconscious. On arrival he was semiconscious, with a temperature of 104° and a pulse rate of 120. Neck rigidity was present and Kernig's sign was positive. The cerebrospinal fluid was cloudy, and contained many polymorphs and pneumococci, which were identified but not cultured. From an hour after admission soluble sulphapyridine was given in doses of 3 c.cm. each hour, but the boy became more restless and died after being twenty hours in hospital. A post-mortem examination was not made.

Discussion

Five fatal cases of pneumococcal meningitis treated with sulphapyridine had been seen before these two patients. A typical unsuccessful case was that of a

woman, aged 39, admitted to the Norfolk and Norwich Hospital on January 16, 1939, on the second day of her illness. There was no response to sulphapyridine in doses of 2 grammes every four hours, and she died at the end of four days in hospital. A post-mortem examination showed extensive purulent meningitis, but no primary focus was detected. The two cases described here were treated with such massive doses because it was felt that failure in the past might have been due to the use of too small a dose. The possibility of producing toxic effects with the drug was given second place because of the seriousness of the condition and the fatal issue of cases treated in the past, when no patient had recovered. A survey of the literature provides some support for the use of a large dose as soon as the patient comes under treatment. Maclean, Rogers, and Fleming (1939) describe experiments which prove that pneumococci can, in an infected animal treated with sulphapyridine, readily establish a tolerance or fastness to the drug. Ross (1939) described a case of pneumococcal meningitis treated with sulphapyridine in which the culture of the pneumococcus (Type I) shortly after the onset of treatment was sensitive to sulphapyridine, whereas the culture obtained at the post-mortem examination was insensitive. Large doses of sulphapyridine had been used in this case. The exact dose in the first twenty-four hours is not stated, but 2 grammes was given on the first day of treatment and 10.5 grammes on the second day. No sulphapyridine was demonstrated in the cerebrospinal fluid on the second day.

The reports of cases successfully treated with sulphapyridine (see table) show great variation in the amount

Table showing Cases of Pneumococcal Meningitis Successfully Treated with Sulphapyridine

Author	Age of Patient	Type of Pneumococcus	Dose in first 24 hrs. (grammes)	Total Dose (grammes)	Day of Illness at Onset of Treatment
Cable (1939)	7	X	2	15	3rd
Robinson (1939)	3	I	1.75	3	2nd
Reid and Dyke (1938)	7	—	3.5	22.5	2nd or 3rd
McAlpine and Thomas (1939)	24	—	5.5	25.5	3rd
MacKeith and Oppenheimer (1939)	30	III	4	70	3rd
Raman (1939)	34	—	9	155	3rd
Dunlop and Laurie (1939)	9	IV	—	40.5	6th

Note.—(1) The dose for the first twenty-four hours is approximate. (2) Only cases in which sulphapyridine was used are included, since this is now the accepted form of chemotherapy.

used in the first twenty-four hours and in the total dose. The statistics in this table are not sufficient for one to arrive at a conclusion as to whether the type of pneumococcus affects the response to treatment with sulphapyridine. Hodes, Gimbel, and Burnet (1939) believe that response is good in all the types they met with. It will be noted that cures were obtained in cases in which treatment was started on the second and third days of the illness.

The number of cases reported in which sulphapyridine has been used unsuccessfully is not sufficient to allow of comparison of the dose used in the first twenty-four hours with that used in the successful cases.

The table shows cases in which the dose in the first twenty-four hours seems very small in comparison with the total dose. Considering the extreme seriousness of the diagnosis a much larger dose in the first twenty-four hours would appear justifiable, and although these cases recovered on a smaller dose, it is possible that some of those that ended fatally might not have done so if they

had received more intensive treatment at the outset. The average dose of sulphapyridine given to the adults in these cases at the onset is, in fact, less than that advocated by Banks (1940) for adults with meningococcal meningitis, whereas the more serious nature of pneumococcal meningitis would justify the use of larger doses if there is doubt as to the optimum dose, as there has been in the past. In contrast with the small initial dose in some cases, a very large total dose had occasionally to be used. The clinical accounts of some of these cases suggest that a much larger dose at the beginning might have cleared up the pneumococcal infection sooner, so that the total dose needed might not have been greater. McAlpine and Thomas (1939) believe that large doses are not necessary. The amount of sulphapyridine in the cerebrospinal fluid did not exceed 3 mg. per 100 c.cm. on the second day in their successfully treated case. At present, however, the records of the quantity of sulphapyridine in the cerebrospinal fluid in successful cases are too scanty to allow the use of this as a criterion in arriving at the optimum dose. It may be that this ideal will never be attained, since some cases are primary and others are secondary to aural or pulmonary infections, and it is not always apparent at the onset which type of case is being dealt with. In Case I, for example, there was pus in the antrum, but at a late examination it was proved not to be pneumococcal. It would be difficult to say how much sulphapyridine was "necessary" in this case, but it is significant that pneumococci were grown from the cerebrospinal fluid on the ninth day after large doses had been used.

The mortality of pneumococcal meningitis at the present moment is not easy to assess. The incidence of the disease can be gauged approximately from the experience of the Dudley Road Hospital, Birmingham (Cable, 1939), where thirty-nine cases were admitted in three years. Reports of only fourteen cases successfully treated in this country have been found since the advent of sulphapyridine. Seven of these cases had been given sulphapyridine alone. MacKeith and Oppenheimer (1939) quote five cases, with two recoveries. These considerations, and the personal experience of six cases with one recovery, indicate that the mortality rate is still very high at the present time.

Hodes, Gimbel, and Burnett (1939) treated seventeen patients, of whom four died in the first twenty-four hours and eight recovered completely. The meningitis was secondary to infection of ears, lungs, or eyes in twelve cases, and was apparently primary in five cases. One patient developed agranulocytosis, but recovered. The first six patients were treated with sulphapyridine by mouth in moderate doses, but it was found to be absorbed irregularly, as judged by the concentration in the blood and cerebrospinal fluid, and later cases were treated with sulphapyridine by mouth combined with intravenous injections of sodium sulphapyridine. The last four cases in the series reported were treated with large doses of sulphapyridine by this combined method, and all recovered. The authors believe that a concentration of 10 to 15 mg. of sulphapyridine per 100 c.cm. of cerebrospinal fluid should be maintained. The dose they now recommend is as follows. When the diagnosis is made older children and adults are given from 6 to 12 grammes at once by mouth, and a quarter of this amount every six hours, the full dose being continued by mouth until several successive cultures of the cerebrospinal fluid are sterile. In addition a 5 per cent. solution of sodium sulphapyridine is given intravenously, starting with 0.1 gramme per kg. of body weight at once and continuing with 0.03 gramme per kg.

every six hours until two successive lumbar punctures are sterile. In other words, an adult weighing 12 stone might receive 34 grammes in the first twenty-four hours.

Conclusion

In the absence of definite evidence of the optimum dose of sulphapyridine in the treatment of pneumococcal meningitis large doses should be used from the beginning. The soluble form is recommended, whether by intramuscular injection or, as Hodes, Gimbel, and Burnett recommend, intravenously. In every case of meningitis the organism should be ascertained without delay, so that, if it prove to be a pneumococcus, treatment with larger doses than would appear justifiable for meningococcal meningitis may be started. Some cases have got better with moderate doses, while others relapse after very large ones. It is possible that the use of large doses in the first twenty-four hours might reduce the present high mortality by curing patients who would die on moderate doses.

Addendum

Another patient with pneumococcal meningitis has been successfully treated with sulphapyridine. He was a man of 42 who was known to have had a chronic infection of his antra and sinuses. He attended the out-patient department of the Norfolk and Norwich Hospital on April 5, 1940, complaining of headache of a week's duration. There had been no vomiting and his temperature was normal. He was admitted under Mr. N. S. Carruthers on the same day, and a bilateral antrostomy with opening of frontal sinuses was done.

On the day after the operation he complained of more severe headache and vomited several times. His temperature rose to 102°. Neck rigidity was now present. A lumbar puncture done that evening showed a turbid cerebrospinal fluid which contained pneumococci. These were not typed. Treatment with sulphapyridine was started at once, doses of 9 grammes a day being used for the first three days. The man became very ill, so on the fourth day treatment with 24 grammes of sulphapyridine in each twenty-four hours was started. The drug was injected intramuscularly every three hours, since there is no theoretical advantage in giving hourly injections, as was done in the former cases. After treatment for two days with these larger doses the patient was still very ill, but his cerebrospinal fluid was clear and contained no pneumococci. He has since made a good recovery.

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The vascular state of the hands of five patients with Raynaud's disease has been studied by M. G. Mulinos, I. Shulman, and I. Mufson (*American Journal of Medical Sciences*, June, 1939). Treatment with histamine iontophoresis and the administration of 60 to 120 mg. of papaverine hydrochloride intravenously twice weekly has led to an increase in the blood flow in the hand and subsequently to the complete alleviation of the cyanosis and pain from exposure to cold and to the healing of trophic lesions. No addiction and very little cerebral depression followed the administration of papaverine despite the continuation of this treatment over six to eight months.