Section of Neurology

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DISCUSSION ON STREPTOMYCIN IN MENINGITIS

A Review of the Treatment of Tuberculous Meningitis with Streptomycin

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BETWEEN November 1946 and December 1948 we treated 48 cases of tuberculous meningitis at Oxford. All but one of these was bacteriologically or histologically verified.[1]

METHODS

The dosage of streptomycin was as recommended by the Medical Research Council (1948), but the duration of treatment was longer than in most other centres in this country.

Intrathecal streptomycin was given daily by lumbar or ventricular puncture for the first six to twelve weeks, without any rest periods. The dose was for adults and adolescents 100 mg., and for infants and children 50 to 75 mg. at each injection.

Systemic streptomycin was given daily for not less than six months without rest periods. The daily dose, given usually as twelve-hourly injections, was for adults and adolescents 2 grammes; for infants and children 20 mg. per lb. of body-weight.

In addition, in 8 cases streptomycin solution (1,000 μg./ml.) was injected into the cisterna chiasmatica or cisterna ambiens through indwelling polythene tubes in amounts up to 6 ml. twice daily for ten days.

One patient (Case 4) had a daily injection of 10 c.c. air with his daily lumbar streptomycin, with the idea of attempting to break down recent adhesions in the subarachnoid space.

A small maintenance dose of phenobarbitone was given for the first three to four months. The patients who did well, except the Service cases and some of the earlier civilian cases, were sent to Peppard Sanatorium under the care of Dr. Harley Stevens in the fourth to fifth month of treatment and remained there for several months, receiving graduated exercise in the latter part of their stay.

Not all our cases received the above dosage of streptomycin.

CASE 2.—When at first we had little streptomycin one patient was treated solely by the intrathecal route for 103 days, then by the intramuscular route for a further 110 days. This was a favourable case for such an experiment, since the patient had a past history of pleurisy and no evidence of active tuberculosis outside the central nervous system. This patient recovered (Smith *et al.*, 1948, Case 2)[2]

CASES 9 and 10.—In two other cases, both severe and advanced, treatment was limited to the intrathecal route; one died after twelve days, the other developed progressive hydrocephalus and died later.

CASES 12, 13 and 18.—In the early days we also tried three patients on intramuscular streptomycin alone. One died (Case 13). In the second (Case 12) a positive film on the 54th day of treatment led to institution of the usual prolonged course of intrathecal and intramuscular treatment and this patient recovered. In the other case, verified elsewhere and making a satisfactory spontaneous clinical recovery by the time he came to us, treatment was given only by the intramuscular route for 120 days (Smith *et al.*, 1948, Case 18); this patient recovered.

CASE 11.—In one patient treatment was stopped after 113 days because the patient had become completely deaf, and was doing well clinically and also as regards her C.S.F.; there was a quick relapse and the patient died.

[1]This work has been carried out by a team of workers at the Radcliffe Infirmary, especially in the Departments of Neurosurgery and Pædiatrics, and at the Military Hospital at Wheatley. Most of the bacteriological examinations have been made by Dr. R. L. Vollum, and the morbid anatomical investigations have been done by Drs. Peter Daniel and Dawn Posanquet.

[2]The case numbers refer both to this paper and the previous paper on our first 18 cases (Smith *et al.*, 1948). We have excluded one of the unverified cases of the first 18 (Case 17) because in the light of further experience we doubt the correctness of the diagnosis.

THE UNITED OXFORD HOSPITALS

CHART FOR CEREBROSPINAL FLUID FINDINGS

Reg. No. 74891/47

Name: M. R.
Age: 16 years.
Ward: Nuffield 1
Date of Admission 17.7.47

Diagnosis: Tuberculous meningitis.
Date and nature of operation (if any): Ventriculography, 25.7.47
Source of Meningitis and date of onset: Pulmonary miliary, 12.7.47

Organism: *Myco. tuberculosis.*
Sensitivity: 17.7.47 0·25 unit/c.c.
Systemic chemotherapy (*Drugs, dates, and doses*): Streptomycin gm. i, b.d. 17.7.47–7.11.47
Batch sample: Merck 665

Date	*Time*	*Route*	*Pressure*	*Films*	*Cultures*	*Content of Antibiotic*	*White cells*			*R.B.C.*	*Total Protein*	*Chlorides*	*Sugar*	*Drug.... Dose*	*Remarks*
							Total	*Polys.*	*Monos.*						
12.7.47		LP	210	No acid-fast bacilli			280	79%	21%		100	600			Done elsewhere
15.7.47		LP	280				545				125	590			
17.7.47	00·50	LP		Acid-fast bacilli present	+ve		104	59%	41%	120	175	710	Diminished	—	
	20·30	LP	260	Few acid-fast bacilli	+ve	2	550	80%	20%	50	225	590	Diminished	75,000	
18.7.47	12·30	LP	230	Very few acid-fast bacilli	+ve	16	119	36%	64%	Occ	225	580	Greatly diminished	75,000	
19.7.47	10·30	LP	200	Very few acid-fast bacilli	+ve	16	95	45	50	V.occ	225	560	Greatly diminished	75,000	
20.7.47	12·00	LP	120	Very few acid-fast bacilli	+ve	6	79	47	32	Nil	300	560	Greatly diminished	75,000	Very slow C.S.F. flow
21.7.47	17·00	LP	130	No organisms	−ve	8	30	15	15	Nil	275	580	Slightly diminished	75,000	Partial spinal block
22.7.47	12·00	LP	0	No organisms		16	45	22	23	260				75,000	
23.7.47	15·30	LP	35	No organisms	−ve	8	47	11	36	220	950	560	Normal	75,000	
24.7.47	10·15	LP	0	No organisms	−ve	32	130	34%	66%	200	—	—	—	75,000	Complete spinal block
25.7.47	15·45	Left ventricle	0	Very few acid-fast bacilli	−ve	4	8	1	7	Occ	15	630	Slightly diminished	50,000	
	15·46	Right ventricle	0	Very few acid-fast bacilli	−ve	2	6	1	5	V.occ	15	610	Slightly diminished	50,000	
26.7.47	10·00	LP	0	No organisms	−ve	0	11	4	7	V.occ	550	610	Slightly diminished	75,000	
27.7.47	11·00	LP	0	No organisms	−ve	16	101	38%	62%	330	550	610	Slightly diminished	75,000	

FIG. 1.—Chart employed in recording C.S.F. findings in meningitis (Case 11).

Pressure in mm. H_2O. Content of antibiotic in μg. per c.cm. White and red cells per cu. mm. Total protein and chlorides in mg. per cent. "Drug . . . . Dose" relates to μg. of streptomycin administered intrathecally.

In the unverified case (Case 16), which is described in full in an earlier paper (Smith *et al.*, 1948, Case 16), treatment was continued for only 68 days.

Thus, 7 of our first 17 cases did not receive their streptomycin according to our routine plan; 3 of these recovered and 4 died. All the other 41 cases, including

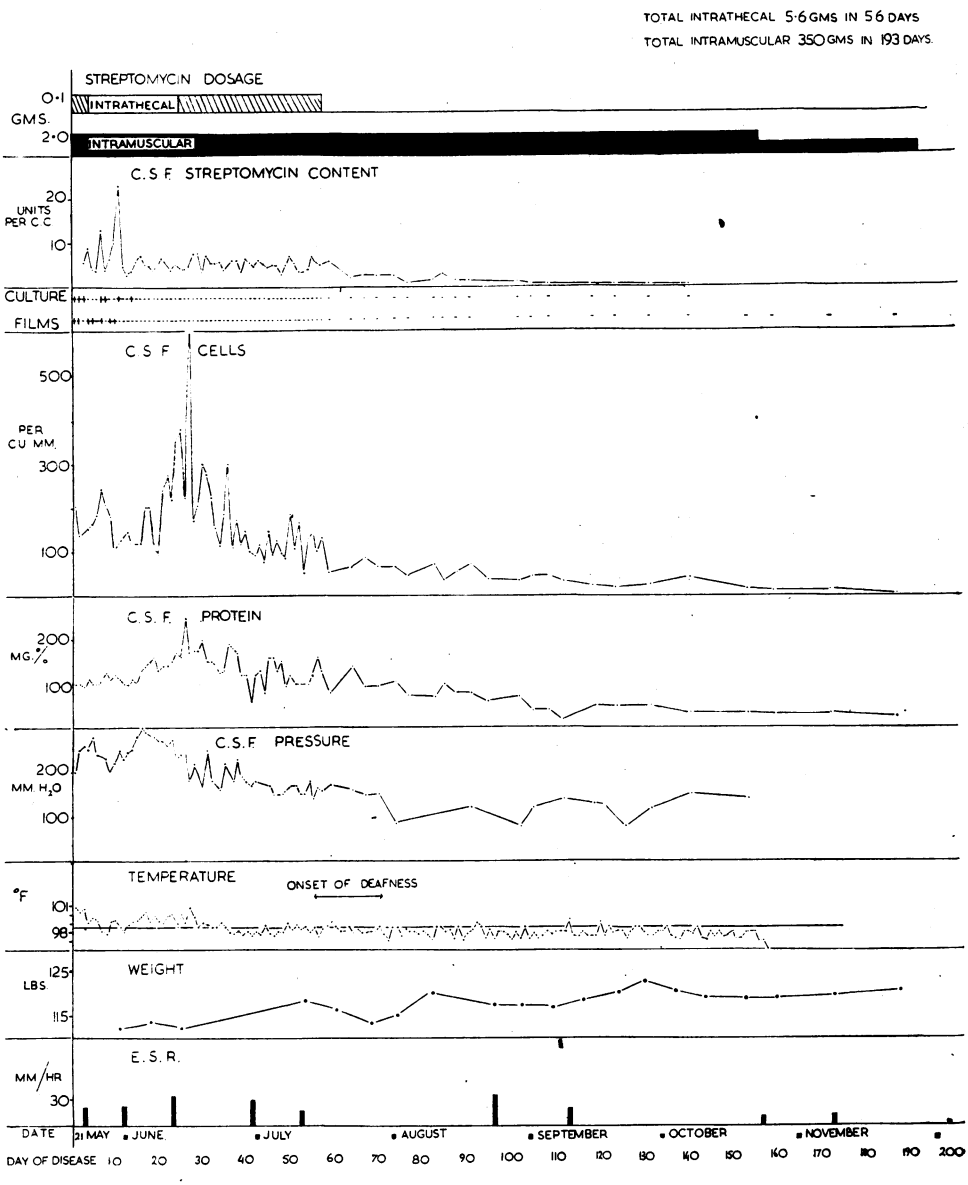

FIG. 2 (*Case* 33).—Graphic method of recording the progress of a case of tuberculous meningitis under treatment with streptomycin. The patient, a boy of 16, was given daily intrathecal streptomycin by the lumbar route for 56 days and intramuscular streptomycin for 193 days. The streptomycin levels in the C.S.F. twenty-four hours after each intrathecal treatment were at first up to 23 units/c.c. with considerable fluctuations, but soon fell below 10 u./c.c. There was a further fall in levels after intrathecal treatment was stopped; streptomycin assays ceased when the patient went to a sanatorium in the fifth month of treatment. During the first fourteen days films and cultures of the C.S.F. for *Myco. tuberculosis* were frequently positive (+) and thereafter negative (—). The white cells and protein in the C.S.F. showed characteristic fluctuations during the period of intrathecal treatment, and thereafter a very gradual fall to normal. In the first weeks of treatment pressure of the C.S.F., measured with the patient horizontal, was slightly raised. At the end of his second month of treatment the patient became completely deaf and remained so. Otherwise his recovery was complete.

Case 12 which is mentioned above, received a full course of treatment, or were in the process of doing so when they died. For a variety of reasons, it was impossible to adhere absolutely rigidly to the scheme of dosage in all of the 41 cases, but the variations were of a minor character and usually resulted in lengthening rather than shortening of the time during which streptomycin was administered.

We found it useful to record the C.S.F. findings on special forms (fig. 1) and charts (fig. 2).

Case Report

The type of result which can be obtained by these methods and some of the problems of application are best indicated by demonstration of a successful case.

Case 4.—E. C., aged 20 (69543, 1947), a young man of more than average intelligence, developed miliary tuberculosis and tuberculous meningitis in the winter of 1946–47 while in the Army in Germany. His previous health had been good, apart from whooping cough and measles at the age of 10, and there was no history of tuberculosis in the family. In Germany at the end of November 1946 he suffered from headache and fever, and spent a week in the sick-bay. He returned to work, but on January 27, 1947, he again had headache with cough, pain in the chest, and later vomiting. These symptoms were not relieved by rest in bed and so on January 31 he was admitted to hospital with a tentative diagnosis of glandular fever.

He looked pale and ill; temperature 100° to 103° F, pulse-rate 100, respiration-rate 20. His throat was reddened but there was no glandular or splenic enlargement and his blood leucocyte count was 8,100 per c.mm. X-rays of the chest early in February showed suspicion of mottling of the lung fields and enlarged hilar lymph nodes. Six specimens of sputum were negative for *Myco. tuberculosis*. E.S.R. 18 mm./hr., rising to 28 mm./hr. by February 18. He was given a six-day course of penicillin systemically with no effect.

On March 5 he complained again of headache and vomiting, and on the following day cerebrospinal fluid by lumbar puncture contained 400 white cells per c.mm., 50 mg.% protein, and 720 mg.% chlorides. On March 7 he was noted to have rigidity of the neck and a positive Kernig sign. Next day he was drowsy and acid-fast bacilli were found in his cerebrospinal fluid. He was then flown from Berlin to Oxford, and he spent the next twelve months at Military Hospital (Head Injuries) or at the Radcliffe Infirmary, being looked after for most of that time by Captain P. K. Robinson.

On admission (March 9, 1947) he was drowsy but easily roused. He would co-operate normally for a short time, but then his attention wandered. He appeared rational, but had little memory of recent events, and little idea of time. He complained of headache and showed a mild degree of meningism. His optic discs were blurred in outline and slightly swollen. There was weakness of the left external rectus which in the next few days became complete. He had slight left hemiparesis affecting face and upper limb. His deep reflexes were not obtained. X-rays of the chest showed miliary mottling throughout the lung fields, enlargement of the right hilar root shadow and some infiltration extending up into the right infra-clavicular zone (Dr. F. H. Kemp). The ventricular cerebrospinal fluid contained *Myco. tuberculosis*.

Streptomycin treatment was begun on March 10 and was continued without any free periods until October 30 (fig. 3). The intrathecal dosage (300 mg. daily) was at first larger than we have since given, the drug being administered by the ventricular as well as by the lumbar route. The patient had attacks of intense drowsiness lasting an hour or more, and these usually followed the ventricular injections. In the intervals he was alert, at times very confused but at other times able to converse intelligently. His short-term memory was profoundly affected: for example, he seemed quite incapable of remembering from hour to hour the name or appearance of any of his doctors. He was incontinent of urine and occasionally of fæces. He vomited once or twice most days and he wasted rapidly, notwithstanding a good fluid intake by stomach tube. Many of his symptoms were probably due to streptomycin but there was also some extension of the meningitis, as evidenced by the development of weakness of the right external rectus.

He continued much the same during March and April, that is, for the first seven weeks of treatment. The drowsy periods were still observed after the ventricular injections had been stopped, but they were less frequent and of shorter duration. He complained occasionally of headaches and these were usually associated with low intracranial pressure, as measured by lumbar or ventricular manometry. During most of March and April each daily lumbar injection of streptomycin was accompanied by an injection of 10 c.c. of air, with the idea of counteracting the formation of adhesions in the subarachnoid space. Frequent X-ray examination showed that this air passed into the lateral ventricles, which became increasingly dilated (fig. 4), and into the cisternæ ambiens, interpeduncularis and chiasmatica; but no air was ever seen in the sulci of the cerebral hemispheres, and thus we conclude that the pathways leading from the basal cisterns were blocked. We have no evidence that the injections of air prevented the formation of adhesions in the spinal subarachnoid space or else-

where, or that they were in other ways beneficial; but they were well tolerated, and we think they are worth a systematic trial.

Early in May the patient began to improve. He was less often drowsy, and occasionally was not incontinent. His neck became less stiff and he began to move himself about in bed. His external rectus muscles were stronger and his tendon-jerks could now be obtained. However, he was still vomiting, he still had a slight rise of temperature in the evenings and his optic discs were still slightly swollen, and he now had a marked tremor of his outstretched hands.

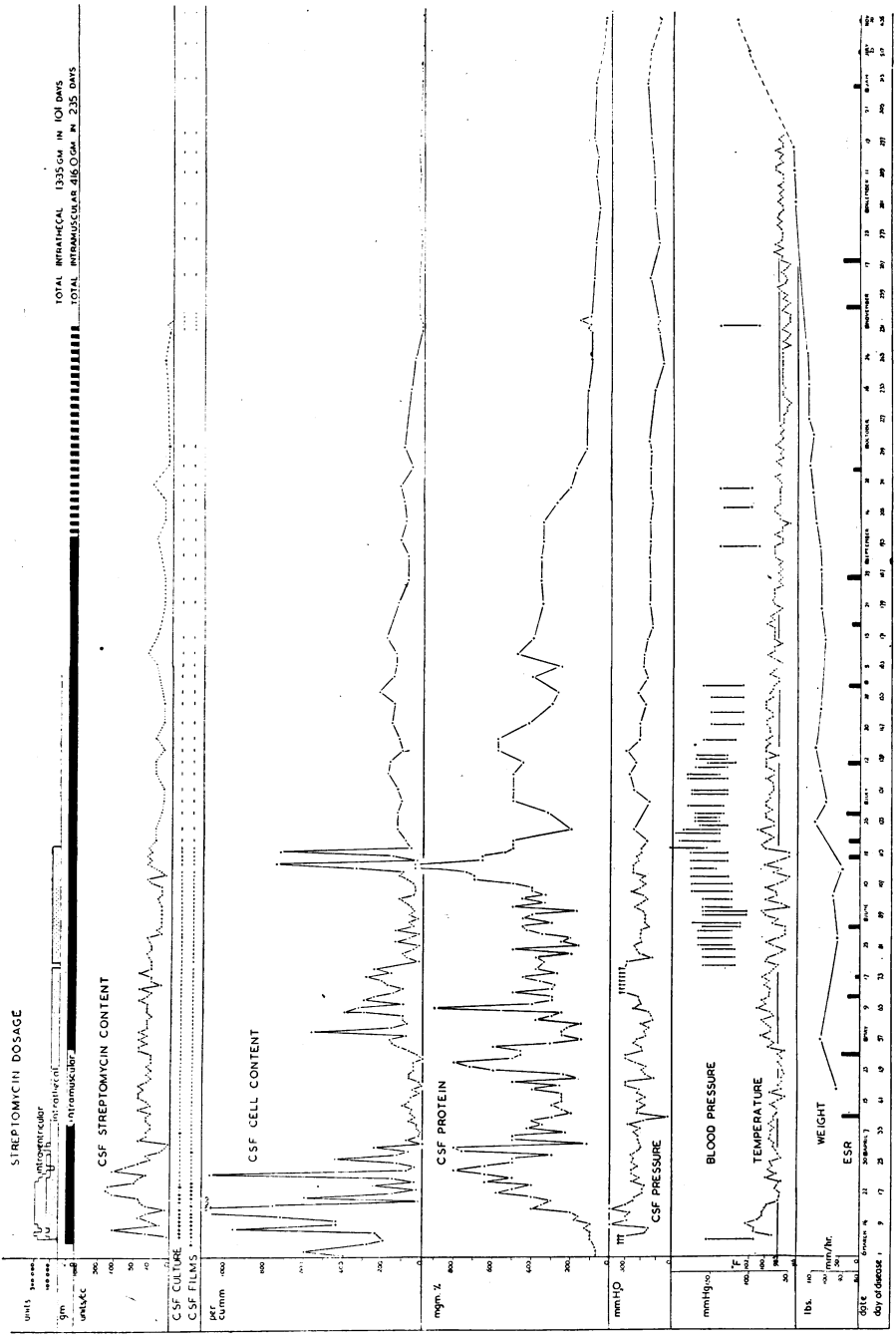

FIG. 3 (*Case 4*).—Graph showing progress of the case under streptomycin treatment. For explanation see text and the legend of fig. 2.

About the middle of May, following a rise of protein in his cerebrospinal fluid, his lumbar subarachnoid pressure rose to levels consistently over 300 mm. (fig. 3). He complained of headache and backache, and vomited intensely. He was more confused, increasingly drowsy, and after two days became unconscious. After withdrawal of cerebrospinal fluid from the lateral ventricles (initial pressure 230 mm.) he improved somewhat, but remained confused. Next day retinal hæmorrhages appeared and his papilloedema increased. Intracranial pressure was now normal (120 mm. in both lumbar space and ventricles), but his blood-pressure was raised (160/120 mm.Hg) and his urine contained a small amount of protein (less than 10 mg.%), granular casts, and 15 pus cells per c.mm. The retinal hæmorrhages and papilloedema disappeared after a week, but his blood-pressure remained high (up to 205/145 mm.Hg) for several weeks before subsiding to the previous normal level (fig. 3). Plasma proteins were for a time slightly below normal (5·85 grammes/100 c.c.) and there was some impairment of urea clearance. This attack of arterial hypertension had subsided by the middle of July; its disappearance was not hastened by cessation of intrathecal streptomycin in the middle of June.

Except in the initial stages of the attack of hypertension, intracranial pressure remained low and the patient was showing steady clinical improvement. Thus, in June he began to shave himself, and

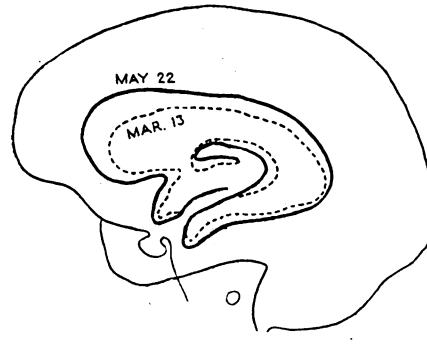

FIG. 4 (*Case* 4).—Tracings of ventriculograms 3 and 74 days after treatment was begun, showing progressive dilatation of the lateral ventricles (from *Lancet*, 1948 (i), 633).

psychometric tests showed mental improvement; his short-term memory was fuller and less confabulatory, despite poor concentration. In July he began writing letters and ceased to be incontinent. At this stage also he began to gain weight, though still troubled with nausea and vomiting, and still feverish at nights.

His mind gradually cleared. In August he was no longer confused and his performance on memory tests was entirely normal, indeed above average. He had practically no recollection of what had happened to him between his last Army leave in October 1946 and the middle of June 1947; he did not remember going to Germany. And, apart from an island of vague memory, this nine months' amnesia was still complete in December 1948, that is to say, some months after he had fully regained his health.

In September 1947 he became afebrile and began getting up after eight months in bed; as he did so he noticed transient spells of tinnitus. When towards the end of October he began walking, he was very unsteady. He had the usual high-tone deafness and loss of vestibular responses to irrigation of the ears with cold water, constant findings after streptomycin in all our patients who were old enough to be tested. Streptomycin by the muscular route was stopped on October 30, 1947. The total dosage was: intrathecal (including ventricular), 13·35 grammes over a period of 101 consecutive days; intramuscular, 416 grammes over 235 days (fig. 3).

His diplopia ceased at the end of October. During the next four months he remained in hospital taking graduated exercise and steadily gaining weight. In November, for the first time, the protein in the lumbar cerebrospinal fluid fell below 100 mg.%, and the white cells were still varying between 15 and 35 per c.mm. He was discharged from hospital and from the Army on March 16, 1948, and began work in the accounts department of a large business in May. Up to January 6, 1949, he has remained regularly at work doing a full working day. He has been free from all symptoms, except slight unsteadiness in walking, which is especially marked in the dark. His record at work, and the reports from his parents, confirm the psychometric findings that his intellectual recovery has been complete and his personality unchanged.

In July 1948 the protein of the lumbar cerebrospinal fluid was still slightly raised, but it was nearly normal at the next examination in November 1948 (6 white cells per c.mm., 35 mg. protein and 740 mg. chlorides per 100 c.c.).

X-rays of the chest, which Dr. F. H. Kemp has been kind enough to review, began to show considerable improvement in April 1947, and in November 1948 the appearances were completely normal.

(The patient was then briefly demonstrated to the meeting.)

Comment

This patient had a feverish illness for two months before he developed obvious symptoms of meningitis, and during that time X-rays showed a focus in the lungs with probable miliary spread. The miliary spread evidently preceded the onset of meningitis by several weeks. In most of our cases with meningitis and miliary tuberculosis the outcome has been fatal. In other respects this case is fairly typical of tuberculous meningitis in an adult responding successfully to streptomycin.

The first point which we wish to stress is the length of illness. Symptoms of generalized meningitis came on in March 1947, and it was twelve months before the patient was fit to leave hospital and lead a normal life again. It might be thought that this illness was maintained and extended by prolonged administration of streptomycin. This is far from being the case. Some of the patient's symptoms were due to streptomycin: for example, the drowsiness after intrathecal injections, the vomiting which only stopped when systemic streptomycin was stopped, the tinnitus and ataxia which were due to toxic damage to the vestibular and auditory pathways. But the mental symptoms were present before streptomycin was begun and cleared up after four months, that is to say, three months before streptomycin treatment was stopped. The diplopia was also present before streptomycin was started, and it lasted for seven months. The cerebrospinal fluid did not approach anywhere near the normal range as regards protein and white cells until three months after the streptomycin was stopped, that is, eleven months after the onset of the meningitis; and it did not become nearly normal until twenty months after the onset of the disease. In 9 cases the average time between the beginning of treatment and the last abnormal reading before the C.S.F. returned to normal (5 white cells per c.mm. and 35 mg.% protein, or less) was 241 days (extremes 178 and 324). In other words, it was more than eight months before the C.S.F. returned to normal. If we included cases like Case 4 in which the C.S.F. is not yet normal, the figure would be even higher.

Thus, in tuberculous meningitis, unlike most other varieties of meningitis, resolution is a very slow process taking months and months. This is in keeping with the slowness of resolution of tuberculous lesions in other parts of the body and the importance of recognizing this is twofold: first, that we should never stop streptomycin treatment prematurely because of early symptomatic improvement; and second, that after they have recovered from the severe phase of the meningitis, these patients should be treated under sanatorium conditions for several months, just like any other tuberculous patient.

The changes in the cerebrospinal fluid in this case are fairly typical (fig. 3). *Myco. tuberculosis* appeared in films and cultures for the first four weeks of streptomycin treatment and thereafter were not found. While the patient was on intrathecal streptomycin there were great fluctuations of the cells and protein, whereas once the treatment was limited to the intramuscular route these fluctuations ceased. This can be seen in fig. 3, and almost all our cases showed the same effect. In this case the final rise of protein and cells before intrathecal treatment was stopped followed immediately after a bloody lumbar tap (70,000 red cells per c.mm. in C.S.F.); we do not know the cause of the earlier rises. In our experience bleeding is the most common cause of a sudden rise of protein and it may precipitate spinal block. When spinal block occurs it is useless to continue streptomycin injections by the lumbar route and may even be harmful. Bunn (1948) has described a case in which after prolonged lumbar intrathecal therapy lumbar injection was followed by pains

down the legs, then at the next injection by paralysis of the lower limbs and bladder which lasted a month.

This brings us to the question of tapping the lateral ventricles. In our case the ventricular route was used for a variety of purposes: on admission of the patient to hospital, to exclude without delay the presence of brain abscess or tuberculoma by means of ventricular estimation or ventriculography; in the initial stage of treatment for additional intrathecal injections; during the third month of treatment to relieve an acute attack of raised intracranial pressure; as an alternative route for intrathecal injections when the lumbar region needed a rest from daily puncture; and as the disease progressed to study the size of the ventricles by repeated air injections. Further, in the early stages of Case 4 the mycobacteria were found more readily in the ventricular than in the lumbar cerebrospinal fluid, though this is unusual. Tapping the lateral ventricles through burrholes is an almost daily event in neurosurgical clinics, and since we might be unduly biased in its favour we have tried treating some 20 cases without it. In 6 of these we eventually had to make burrholes and we have come to the conclusion that the best course in all cases is to make two frontal burrholes at the beginning of treatment. Through these access to the frontal horns of the lateral ventricles can be obtained at any stage of the long illness, and this will prove of considerable use in about one-quarter of the cases. Physicians will understand how small is the risk of passing a sharp needle into the anterior horn of the lateral ventricle when we say that it is no greater and probably less than the risk of cisternal puncture; but it is of course necessary to know the topography of the lateral ventricles. In our experience streptomycin is more likely to produce a severe acute reaction when injected into the cisterna magna than when injected into the lateral ventricles.

The intrathecal dosage of streptomycin in the first four weeks of treatment in this case was considerably higher than we have employed in subsequent cases. The ventricular and, to a less extent, the lumbar injections produced attacks of drowsiness, and we have no evidence that such large doses are necessary. This was the fourth case of our series, and almost the first for which supplies of streptomycin were adequate, and we were still experimenting with dosage.

The attack of arterial hypertension in the third to fifth month of the disease was of considerable interest. It was ushered in with rise of intracranial pressure and was attended by papillœdema, retinal hæmorrhages and rise of protein in the cerebrospinal fluid. In its later stages there was a small amount of protein in the urine, also some granular casts, and kidney function was slightly impaired. A toxic effect of streptomycin may have been a contributory cause, but the condition subsided without withdrawal of streptomycin. The slight urinary infection which was observed at the onset may also have been a factor. We believe, however, that the hypertension was primarily of neurogenic origin, because we have observed it in two other patients of this series, neither of whom had renal involvement.

In one, a girl of 16 (Case 11), arterial hypertension occurred between the 8th and 17th days of treatment (highest reading, 150/115 mm. Hg) and was associated with pathological sleep. In the other (Case 13), a woman of 24 who developed severe communicating hydrocephalus, it came on on the 22nd day of treatment and persisted until death on the 82nd day (highest reading 145/125 mm. Hg). In neither case were there retinal hæmorrhages.

We have also encountered arterial hypertension in tumours of the cerebellopontine angle and other lesions of the brain-stem, though never, we must admit, in such acute form as in this case.

Other neurogenic lesions encountered in the present series of cases include glycosuria, disorders of sleep rhythm, and bulimia. The last of these is not infrequent and is a great boon since it enables the patients to maintain their weight throughout the disease. One of our patients would eat six big meals a day. Children do not

waste much unless they are soon going to die, but most of the adults lose weight during the first half of their streptomycin treatment unless they have bulimia.

Of the quality of mental recovery in this case there can be no reasonable doubt that it is complete, despite the mental disturbance in the first four months of the illness—confusion, severe loss of short-term memory, and incontinence—and despite the progressive dilatation of the lateral ventricles. Among infants and children of our series the patients who were going to die went into coma, while those who were going to recover remained conscious and, as far as we were able to detect, showed little mental disturbance, beyond the irritability and arrest of development of speech and other faculties, such as may happen with infants in any long illness. But, in adults who eventually recovered, some degree of dementia without loss of consciousness was fairly common and might last for months. The most severe forms of dementia are probably due to infarction of the basal ganglia and are, to judge from reports in the literature, evidently permanent. In our series lesser degrees of dementia were followed by complete recovery, as in this case. We have not had enough experience yet to prognosticate accurately about dementia and meanwhile it is essential that serial psychometric studies should be recorded in every case.

Dilatation of the lateral ventricles was found in every case in which the ventricles were tapped or the brain was examined at necropsy, as in every other type of meningitis. A distinction must be drawn between the relatively mild hydrocephalus which is mainly due to shrinkage of brain substance, with perhaps some partial and temporary obstruction at the basal cisterns, and which, as in this case, is compatible with complete intellectual recovery, and the severe progressive hydrocephalus which is due to complete fibrous obstruction of the arachnoid cisterns at the tentorial opening. This latter condition has been uncommon in our series, which is rather surprising in view of the fact that in all fatal cases the basal cisterns at the tentorial opening were filled with dense exudate. It is true that in all cases in the first weeks of the disease intracranial pressure, as measured by lumbar or ventricular pressure, was raised; but then it fell to normal and in most cases remained normal. Follow-up X-rays of the skulls of 8 infants and children under the age of 12 after the conclusion of treatment showed no separation of the cranial sutures and there was no enlargement of their heads.

The Results to Date

The results (Table I) are arranged chronologically, according to the date on which each patient began treatment; 20 of the 48 patients have died, all but 2 within six months of beginning treatment (Table II). It is probable that some more of those

Table I.—The Condition on December 31, 1948, of 48 Patients Treated for Tuberculous Meningitis Between November 1946 and December 1948

Treatment begun	Alive	Dead
November 1946 to June 1947 (25 to 18 months ago)	5	6
July 1947 to December 1947 (18 to 12 months ago)	5	4
January 1948 to June 1948 (12 to 6 months ago)	8	6
July 1948 to September 1948 (6 to 3 months ago)	5	2
October 1948 to December 1948 (within last 3 months) ..	5	2
Totals	28	20

Table II.—Interval Between Beginning of Treatment and Death in the 20 Fatal Cases

Interval	No. of deaths	No. at risk
Less than 3 months	14	48
3–6 months	4	29
6–12 months	2	20
12–24 months	—	10

who began treatment after June 30, 1948, will die; and some who began treatment in the previous six months may also die, for we have had two patients who relapsed and died after completing a six-months' course of treatment.

There are 19 patients alive who have completed a course of treatment. Of these 18 are well and free from symptoms apart from deafness and vestibular disturbance (*v. i. Eighth nerve symptoms*). The other patient is still severely demented after 217 days of illness, but is showing slight improvement.

Considering now the patients who completed treatment before July 1, 1948—that is, more than six months ago—there were 11 such patients. One of these soon relapsed and died. Another, with pulmonary tuberculosis of the adult type, has clinically recovered from his meningitis but still has 9 white cells per c.mm. and 85 mg.% of protein in his C.S.F.; he is at home under observation. The remaining 9 are well and, if old enough, at work, and they have normal cerebrospinal fluid. These 10 are the survivors of 20 patients who began treatment before the end of 1947 and they have been followed for twelve to twenty-five months since the onset of their meningitis. Thus, to date 50% of our patients have made a satisfactory recovery.

In our series infants under 3 did as well as older patients; but in them, as Crothers *et al.* (1942) have pointed out, the quality of the result, though seemingly good now, can only be assessed by systematic observation of their intellectual development over a period of years.

Owing to shortage of beds and of streptomycin a certain amount of selection was exercised in the choice of these 20 patients: a few late cases were refused, though some were accepted. Thus, the figures are probably more favourable than they would have been had all cases been accepted. However, early diagnosis has greatly improved since streptomycin was introduced and in consequence a 50% recovery rate at one to two years after the beginning of treatment should be attainable on unselected cases in the future.

Results of treatment of the meningitis depend to a considerable degree upon the extent and character of the tuberculous infection in other parts of the body. In our series (Table III) the outcome was unfavourable in those cases in which meningitis

TABLE III.—TUBERCULOUS LESIONS ELSEWHERE IN OUR SERIES OF CASES OF MENINGITIS

	Treatment completed		
	Recovered	Died	Still under treatment
Miliary	2	6*	3
Primary complex	8	5	—
Adult pulmonary tuberculosis	1	5†	—
Active lesions in parts other than lungs	3	3	2
Previous active lesion	4‡	—	1
No lesion found in life	2	1§	2

*In one of these the miliary spread probably developed during treatment of the meningitis.

†One of these had also general dissemination of tuberculosis; this patient died from pulmonary disease at a time when his meningitis seemed to be recovering.

‡Pleurisy 2, cervical adenitis 1, old primary complex 1.

§Necropsy not done in this case.

was associated with active pulmonary disease of an adult type, or with miliary tuberculosis. In the former group one patient died of his pulmonary disease at a time when his meningitis seemed to be recovering. In the miliary group death was invariably due to meningitis, and our unfavourable experiences agree with those of McDermott and his associates (1947) and of Bunn (1948).

Eighth nerve symptoms.—The high-tone deafness, which was present in every

patient, did not prove a serious symptom. It was observed as early as the 11th day of treatment in one patient and got slightly worse as treatment was continued: in most cases it did not encroach on the conversational tones. More serious deafness occurred in 6 patients. In 3 total deafness came on in the second to fourth month; in one of these treatment was stopped in consequence of the deafness and there was a prompt relapse of the meningitis which proved fatal; the other 2 patients are well and are learning to lip read. In 3 further patients there was a 40–60 decibel loss of hearing in one ear and retention of good hearing up to 4,096 c/s in the other ear. Four of these 6 patients were adolescents between the ages of 14 and 18, who were given the same dose as the adults; these 4 patients are one-third of the adolescents (aged 14–20) who survived long enough to develop disturbance of hearing. This indicates that the dosage which we have employed is possibly near the limit of tolerance, and that a reduction should be made for adolescents. Total deafness in our opinion is no indication for premature withdrawal of streptomycin; it is to be hoped that its incidence may be reduced by use of di-hydrostreptomycin.

Loss of vestibular function, which has been observed in our series by cold caloric test as early as the 18th day, was responsible for the ataxia which was present in all of our patients when they began to walk again some six to nine months after the onset of the meningitis. The ataxia was compensated fairly quickly by all our patients, and in none of them has it proved troublesome.

In our first successful case, a young woman who has now been under observation for over two years since the onset of meningitis (Smith *et al.*, 1948, Case 2) recovery of normal vestibular reactions and of normal hearing for high tones took place between six and nine months after cessation of streptomycin. None of the other patients has as yet shown any signs of recovery of these functions.

Some Causes of Failure

In our fatal cases the lesions included widespread meningitis, cerebral infarction, severe hydrocephalus of the communicating type, and active tuberculosis in the lungs or elsewhere. The causes of failure include starting treatment late and stopping it too soon. There are some aspects of the problem to which little attention has yet been drawn in publications on the subject.

Technical aspects of intrathecal treatment.—Intrathecal injections of streptomycin day after day may present a formidable problem, particularly in infants and young children. The complications and dangers of repeated lumbar punctures include antiseptic dermatitis of the skin, subcutaneous hæmatoma, subarachnoid hæmorrhage, spinal block, and mixed infection.

In our series the skin was prepared with 1% cetavlon and bichloride of mercury (1 : 1,000). Collodion was not used, the puncture hole being allowed to seal itself. With this method the skin of the lumbar region remained in a satisfactory state in all patients. The maximum number of punctures on successive days in one patient was 103.

Fine needles (gauge 21–23, standard wire gauge) were used and were kept sharpened. Whenever possible all punctures on one patient were done by the same individual. The three available lumbar interspaces were used in succession.

After a few weeks some of the infants and young children who are making a good clinical recovery tend to become restless on the lumbar puncture table. They may struggle violently and, if they cannot be controlled by skilful holding, it is better to give a general anæsthetic. Punctures are then done at nights so that the post-anæsthetic drowsiness interferes as little as possible with feeding. A daily ether anæsthetic seems to have no terrors for most infants, nor was it harmful. 7 of our patients of varying age between 17 months and 7 years had ether anæsthetics for up to 75 successive days. Only 2 of these 7 died, 1 during and 1 after the period of intrathecal treatment; there was no apparent connexion between the anæsthetics and their death.

Great patience and gentleness are required to avoid setting up intrathecal bleeding. Even with good technique it was uncommon to complete a course of intrathecal injections without some intrathecal hæmorrhage. There were cases in which every specimen of C.S.F. contained a few thousand red blood cells per c.mm. although the punctures went easily. When blood-vessels were injured by the needle the red cells in the C.S.F. might rise to several hundred thousand per c.mm., and this was usually accompanied by a rise of protein, as in Case 4.

Spinal block might follow severe intrathecal bleeding, but also occurred independently of it. With a block the protein was always high (1,000 mg.% or more)[1] and no positive pressure could be recorded even on bilateral jugular compression, but a small amount of C.S.F. could usually be aspirated. We believe that when there is a block it is useless to inject streptomycin and Bunn (1948) has shown that it may even be dangerous. We proceed at once to inject the streptomycin into the anterior horn of the lateral ventricle, and we continue to use the ventricular route until the spinal theca has reopened. In two cases this took several weeks.

There were other cases in which a false block occurred. At some punctures C.S.F. dripped slowly under low pressure, and it looked as though the spinal subarachnoid space might soon be blocked. But jugular compression still produced a rise of spinal pressure. A long time was needed to collect the specimen of C.S.F. and inject the streptomycin. Next day there was often a free flow of C.S.F. This slowing of the flow of C.S.F. may have been due to partial subarachnoid loculation in the cauda equina region or to partial obliteration of the subarachnoid space by extradural hæmorrhage.

In 3 infants and one adult we inserted a fine polythene tube into the lumbar theca, and left it in situ in the hopes of dispensing with daily punctures, but the result was not wholly successful. Repeated movements of the spinal column, and of the skin on the spinal column, softened and deformed the 2 cm. of tube between skin and dura, with the result that it was often impossible to obtain a flow of C.S.F. though usually it was still possible to inject streptomycin. In one of these patients an achromobacter was cultivated from the C.S.F. on one occasion while the tube was in situ; no pyogenic meningitis developed. With firmer tubes this method might be effective.

Pyogenic infection must always be borne in mind as a possible complication of intrathecal puncture and therapy. There was one case in our series (Case 6), a patient who at necropsy was found to have a subdural abscess (*Staph. aureus*) beneath a parietal burrhole which had been made for diagnostic purposes before the patient came under our care. McDermott *et al.* (1947) report that necropsy in one of their fatal cases showed purulent meningitis involving the spinal cord and minimal evidence of meningitis over the base of the brain: it is not stated whether pyogenic bacteria were found. With stringent aseptic precautions the risk of pyogenic infection should be small and would be expected to be limited to streptomycin-resistant bacteria.

Ventricular puncture carries its own risks but with care these should be minimal. We used two burrholes, one inch to either side of the middle line in the hair line at or in front of the coronal suture. The anterior horns of the ventricles lie at a depth of 5 to 7 cm. from the skin in a downward, slightly backward and very slightly medial direction. On the few occasions in which we had difficulty in finding them it was because the needle was passed in a plane too far forward. In one patient, an infant who was dying from a second attack of meningitis and progressive hydrocephalus, repeated ventricular punctures were followed by cerebrospinal fistula. Intracranial pressure was lowered by puncture of the other ventricle and of the lumbar theca, and

[1]Not all cases of high protein in the lumbar C.S.F. are associated with spinal block.

the fistula was satisfactorily closed with a stitch without the development of mixed infection. Apart from this case there were no complications from ventricular puncture.

Tuberculous lesions in other parts of the body.—Extensive active tuberculous lesions were found in other parts of the body in most of the fatal cases. As Table III shows the prognosis is evidently unsatisfactory in these cases and we believe it would be justifiable, wherever possible, to take more active steps to remove such foci surgically as soon as the acute symptoms of the meningitis have been controlled. In one of our cases (Case 18) a large mass of tuberculous glands was removed from the neck in the fourth month of meningitis without any disturbance to the patient; and we think that surgical removal of mesenteric glands, ulcerated small intestine and tuberculous disease of the vertebræ should also be considered.

Whether in such cases there is reinfection of the central nervous system from the mesenteric glands or whether the somatic focus acts mainly by lowering the patient's resistance is not known, but there can be no reasonable doubt that the patient would be better without these areas of infection. The present mortality rate in this type of case is probably around 70%. We have shown that these patients will support a major intracranial operation at the height of their meningitis (Smith *et al.*, 1948; Cairns, 1949), and also that they will tolerate ether anæsthesia well. In addition streptomycin could be used locally to prevent spread of the tuberculous process as a result of contamination of the operative field by tuberculous material. For these reasons we believe that where possible attempts should be made to eradicate large tuberculous masses or areas by surgical means.

Late relapse.—There is no evidence as yet upon the subject of late relapse, but from what is known of spontaneous recovery from tuberculous meningitis—and there are in the literature a considerable number of verified cases (A. E. Martin, 1909; Hobson, 1935; Smith and Daniel, 1947, Case 10)—late relapse of tuberculosis may be expected in some of our successful cases.

Spontaneous recovery from tuberculous meningitis. Death six years later from pulmonary tuberculosis (Rumpel, 1907).—A boy aged 9 was suddenly taken ill with meningeal symptoms. Examination showed slight stiffness of the neck, bilateral papilloedema, feeble pupillary reactions, and loss of the knee-jerks. Later there was weakness of the right external rectus, also bilateral ptosis. The C.S.F. was under raised pressure and contained tubercle bacilli. Treatment consisted of lumbar punctures, calomel by mouth, cooling baths and œsophageal feeding by tube during a period of sudden deep coma. The boy recovered, but for some months he was mentally slow; then he was able to take his place at school. Five years later he was admitted to hospital for tuberculous abscess of the axilla, and again, a year later, because of advanced pulmonary tuberculosis. His intelligence at that time was normal for his age and there were no organic signs in the nervous system. He died at the age of 17 of progressive phthisis. At necropsy the brain was normal, but the meninges of both Sylvian fissures were thickened, and on the right side showed dense adhesions. No tubercles apparent.

In this case the slow, eventually complete recovery from meningitis is remarkably like what we see in cases which recover after streptomycin. Martin (1909) cites other cases which took a similar course, and the lesson to be drawn from this experience is that our successful cases should be kept under observation for several years.

Methods of Streptomycin Therapy in Use in Various Centres

It is too early yet to compare the results of the various centres, though it seems likely that an attempt should be made as soon as enough experience has been accumulated. At present effective recovery rates in different centres range from 10% to 50%. The reports from some centres are quite inadequate to enable any assessment of their results to be made. In other centres it appears that the methods of treatment have gradually been changed so that the series of cases published does not, in fact, represent the results of the treatment in use at the time of compilation of the report. This would not matter so much if we were dealing with a method of treatment which

gave quick and lasting results, such as penicillin in the treatment of pneumococcal meningitis. Instead, we are concerned with a treatment which lasts several months and of which the results can only be assessed with any certainty twelve to twenty-four months after the start of treatment. Hence it is essential that centres should adhere strictly to a set plan of treatment until a reasonable number of cases have been treated before introducing any important new factor.

At present the main variations in different centres appear to be in the duration of streptomycin treatment (three and a half to six months +), and whether or not to have rest periods in which no streptomycin is given; also there is a claim that considerably smaller doses than have hitherto been used will be effective (Cocchi, 1947; Choremis *et al.*, 1948). All that can be said with certainty at this stage is that intrathecal as well as intramuscular treatment seems to be necessary, at least for the first month and probably for longer. Our own view is that the evidence accumulating tends to favour continuation of streptomycin treatment for a longer time than has hitherto been customary, and at moderate dosage; though whether continuously or with rest periods is not yet established. We have shown that a course of treatment can be carried through successfully without rest periods; but we are not wedded to this method and, after we have accumulated enough cases to show what it will accomplish, would be prepared to change to any other method which will produce better results.

Conclusion

At least 50% of all cases treated are dying and there is thus ample room for improvement. In the present state of knowledge there is little to recommend the occasional treatment of isolated cases by individual doctors, and any hospital which establishes a centre must be prepared to have beds occupied for months on end by the same set of patients. Each patient should have *at least* four months in hospital before going to sanatorium. And the nursing is heavy. Indeed, for all concerned the treatment of tuberculous meningitis by streptomycin is a most exacting form of therapy.

Streptomycin has already effected a considerable alteration in the outlook for patients with tuberculous meningitis and we do not feel pessimistic about its future. Meanwhile it is encouraging to note that cases are already being sent for treatment much earlier than in the past.

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