

Original Communications

FURTHER EXPERIENCE WITH STREPTOMYCIN IN THE TREATMENT OF TUBERCULOUS MENINGITIS

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IN a previous communication to this Journal Clarke (1949) reviewed our experience in the treatment of cases of tuberculous meningitis at the Military Hospital for Head Injuries. His paper dealt with the period from March 1947, when streptomycin first became available at the hospital, to the end of July 1948. The present report deals with those cases which have been under treatment in the thirteen months from August 1, 1948, to August 31, 1948.

In his Paper Clarke gave a very full and authoritative account of the history of streptomycin, its action, dosage, toxicity and methods of administration and discussed the importance of early diagnosis in relation to treatment with streptomycin. These subjects will therefore not be discussed further except in so far as they relate directly to the cases treated during the period under review.

CASES

During the thirteen months 15 patients have been under treatment (Table I). Of these, 3 (Cases 1-3) were still under treatment at the time of Clarke's report (his Cases 7-9). A fourth patient (Case 4) was also under treatment at that time but the diagnosis of tuberculous meningitis had not been established (this case is referred to on page 194 of Clarke's report). Of the remaining 11 patients, 9 were admitted during the year¹ with a presumptive diagnosis of tuberculous meningitis and 2 (Cases 5 and 6) developed tuberculous meningitis while in the hospital and receiving treatment for military tuberculosis. 11 of the patients were members of His Majesty's Forces; 10 were from the Army and 1 from the Royal Navy. The other 4 were children, sons of serving soldiers, and were admitted for treatment from Military Families Hospitals. A positive history of contact with cases of tuberculosis was obtained in only 3 cases (Cases 2, 12 and 13).

As can be seen from the data presented in Table I, in 7 cases the meningitis was part of a generalized military dissemination, in 2 it developed as a complication in patients with active pulmonary tuberculosis and in one it was secondary to caries of the thoracic spine. In 3 cases the only evident tuberculosis focus was a healed primary lung complex which was demonstrated on a radio-

¹Cases admitted during August 1949 have been excluded from this review.

graph of the chest in 1 case (Case 3) and found at autopsy in the other 2 (Cases 4 and 14). In 3 cases no primary focus could be found ; even after a full autopsy in Case 2.

The majority of the patients were admitted to hospital relatively early in the course of their illness and before they had received any treatment with streptomycin. Cases 13 and 14 were exceptional in that both had received treatment in hospitals elsewhere before coming under our care. The physical and mental state of the patients on admission varied greatly. Most had lost some weight and some were grossly emaciated (e.g. Case 9). All grades of consciousness were observed from those who were fully conscious, alert and rational, through mild euphoria and confusion to coma and delirium. All the patients with the exception of Case 6 presented the classical clinical features of meningitis at one time or another but signs indicating focal lesion of the central nervous system were observed in only about half of the cases.

PROBLEMS OF DIAGNOSIS

A diagnosis of tuberculous meningitis can be made with certainty only when the *Mycobacterium tuberculosis* is found in the cerebrospinal fluid either by direct examination of films or by culture or guinea-pig inoculation. The bacteriological methods in use at this hospital were described by Roberts (1949). Of the 15 cases at present under review, in all except 1 (Case 6) the diagnosis has been confirmed by one or more of these methods.

The problem of diagnosis may arise under two sets of circumstances :

(1) A patient with a known tuberculous infection may complain of symptoms suggestive of meningitis. In such a case if a lumbar puncture is performed and the cerebrospinal fluid is found to show an increase in cells and protein with a fall in sugar, the presumption that tuberculous meningitis has developed is so strong that it is justifiable to begin treatment with streptomycin without waiting for the demonstration of tubercle bacilli. This was the state of affairs in 5 cases in the present series (Cases 1, 5, 6, 7, and 8).

A word may be said about the development of meningitis in cases of miliary tuberculosis. It has been our practice to perform lumbar punctures once a week in every case of miliary tuberculosis once that diagnosis has been made and we have found that a slight increase in cells and protein is often the first sign of the onset of meningitis ; for example :

Case 5.—A 20-year-old private in the R.A.M.C. was admitted on 8.11.48 with a diagnosis of miliary tuberculosis. This diagnosis had been made overseas twenty-three days previously and he had already received eighteen days' treatment with intramuscular streptomycin. On admission, there were no signs of meningitis but choroidal tubercles were present in both eyes. His C.S.F. at this time showed : Cells—1 lymphocyte per c.mm.; protein—40 mg. per 100 c.c. His progress was uneventful until the seventy-third day of treatment when on a routine lumbar puncture the cells in the C.S.F. were found to have risen to 17 (12 polymorphs and 5 lymphocytes) per c.mm. ; and the protein to 100 mg. per 100 c.c. Four days later the cells were 96 per c.mm. and the protein 150 mg. per 100 c.c. At this stage there were no clinical signs of meningitis and his temperature and pulse did not indicate any change in his condition. Nevertheless the administration of intrathecal

streptomycin was begun. Three days later, he complained of headache and had neck rigidity and a bilateral positive Kernig's sign.

In this case the subsequent clinical course and the behaviour of the cellular and biochemical constituents of the cerebrospinal fluid left little doubt that the patient had tuberculous meningitis and the diagnosis was confirmed when a positive culture was obtained from cerebrospinal fluid withdrawn on the 121st day of treatment. The problem, however, is not always settled so easily, for example :

Case 6.—A 20-year-old corporal in the R.A.S.C. was admitted two days after a diagnosis of miliary tuberculosis had been made. There were no clinical signs of meningitis, no choroidal tubercles were seen and a normal C.S.F. was obtained on lumbar puncture. Treatment with systemic streptomycin was begun and weekly lumbar punctures performed. His progress was satisfactory until the twentieth day of treatment when the C.S.F. was found to contain : Cells—25 per c.mm. (52 per cent polymorphs and 48 per cent lymphocytes); protein—40 mg. per 100 c.c. There were no clinical signs of meningitis. Treatment with intrathecal streptomycin was started and although during the next week his C.S.F. showed a marked cellular response and the protein rose on one occasion as high as 110 mg. per 100 c.c. he never showed any clinical evidence of meningitis. After twenty-five days of intrathecal streptomycin his C.S.F. showed only 7 cells per c.mm. and 50 mg. of protein per 100 c.c. It was decided to discontinue the intrathecal streptomycin, and, although the cell count and protein level in the C.S.F. remained somewhat elevated for the next twenty-five days, his clinical condition gave no cause for concern. During the next six months his progress was uneventful and his C.S.F. remained normal.

The *Mycobacterium tuberculosis* was never found in this case and it may justifiably be asked whether this patient had a true tuberculous meningitis. It is known that patients with miliary tuberculosis may show transitory cellular responses and rises of protein in the cerebrospinal fluid and that these may subside spontaneously. These reactions may or may not be accompanied by clinical signs of meningitis and have been referred to as "tuberculous meningismus" (Cathie, 1949) or "serous meningitis" (Lincoln, 1947 and earlier writers). It is, however, very difficult to be certain that this was not a tuberculous meningitis which was diagnosed at the earliest opportunity and responded well to treatment.

(2) A patient who is not known to have suffered from tuberculosis or to have been in contact with cases of tuberculosis may develop tuberculous meningitis or miliary tuberculosis with a coincident meningitis. In such cases the early symptoms and signs may, as Clarke (1949) stressed, be vague and unrelated to the meninges or nervous system. At this stage, the diagnosis depends upon thinking of the possibility of tuberculous meningitis or miliary tuberculosis and taking the necessary steps to X-ray the chest and perform a lumbar puncture. The "snowstorm" appearance of the lungs or the cytological and biochemical changes in the cerebrospinal fluid will in most cases provide sufficient evidence on which to make a presumptive diagnosis and begin treatment. If there is any doubt about the diagnosis a Mantoux test can be of great help in these cases. 10 cases in the present series belonged to the group under discussion and in 8 of these a Mantoux test was performed on admission and found to be positive with dilutions of 1 : 1,000 Old Tuberculin or greater.

Sometimes there may be definite signs of meningitis and the diagnosis of tuberculous meningitis may be considered but the changes in the cerebrospinal fluid are atypical so that the diagnosis remains in doubt for some time; for example:

Case 4.—An 18-year-old private in the W.R.A.C. was admitted to hospital with a ten or twelve day history of headache, dizziness, nausea and stiff neck. She was drowsy with prominent signs of meningitis but there were no localizing signs in the central nervous system. Lumbar puncture was performed and the C.S.F. was found to be under normal pressure (110 mm.) with 172 white cells (30 per cent polymorphs and 70 per cent lymphocytes) per c.mm., protein 60 mg. per 100 c.c., chlorides 620 mg. per 100 c.c. and sugar 35 mg. per 100 c.c. A presumptive diagnosis of tuberculous meningitis was made and treatment with streptomycin commenced. The next day she had a well marked left hemiparesis which progressed during the following forty-eight hours to become a complete hemiplegia. Intrathecal and intramuscular streptomycin were given for fourteen days. During this period, her general condition improved although the hemiplegia did not and the C.S.F. showed a steady tendency towards normality so that at the end of the two weeks there were only 50 white cells per c.mm. and 70 mg. of protein per 100 c.c. As tubercle bacilli had not been found in films from the C.S.F. and the protein had never risen above 90 mg. per 100 c.c. the diagnosis of tuberculous meningitis was questioned and a decision was made to discontinue the intrathecal streptomycin and observe the effect. She continued to improve clinically and the C.S.F. also showed improvement. This was not at all what was anticipated would happen if the case were one of tuberculous meningitis and so, after seventy-four days, intramuscular streptomycin was also stopped. By 112 days she was able to be up and about despite her hemiplegia. The C.S.F. was not yet normal but contained 22 white cells (95 per cent lymphocytes) per c.mm. and 30 mg. of protein per 100 c.c. She was considered fit to go on leave. On the very day she went on leave a culture of a specimen of C.S.F. obtained on the second day of treatment was reported positive for *M. tuberculosis*. Fourteen days later she returned to hospital with a recurrence of her meningitis and on this occasion the C.S.F. findings were typical of tuberculous meningitis and numerous acid-fast bacilli were found on direct examination. Despite very intensive treatment with streptomycin this relapse ended fatally 401 days after she had originally started treatment.

This case is reported not only because it presented the most difficult diagnostic problem in the series but also because it illustrates some of the important points in treatment which are discussed later.

PROBLEMS OF TREATMENT

The present series of cases have been treated in accordance with a definite policy. Details of this policy have been given in previous publications by members of the group working in Oxford on the problem of tuberculous meningitis (Smith, Vollum & Cairns, 1948; Clarke, 1949; Taylor & Cairns, 1949). In clinical medicine, however, no policy can be rigidly adhered to since each patient presents as an individual problem. Thus, while throughout the period under review, the general policy of treatment remained unaltered, we were constantly faced with problems in the day-to-day management of each case. In this section some of the more important of these problems are discussed.

(1) *Dosage of Streptomycin and Routes of Administration.*—All the patients received treatment with streptomycin given intramuscularly and into the cerebrospinal fluid. Adult patients received 2 grm. of streptomycin intramus-

cularly in twenty-four hours. This was usually given as two injections, each of 1 grm., in the morning and evening. One patient with a very severe miliary infection received 3 grm. of streptomycin intramuscularly for thirty-four days (Case 9). As he was very emaciated this represented a very large dose of the drug and toxic effects were noted (*see below*). Two of the adult patients who were much underweight (Cases 4 and 5) were given rather smaller doses of streptomycin: 1 grm. and 1.5 grm. in twenty-four hours respectively. In the case of the children a daily intramuscular dose of rather more than 20 mg. per pound of body-weight was given.

The usual intrathecal dose for the adults was 100 mg., and, as soon as a presumptive diagnosis of tuberculous meningitis was made, this dose was given daily by the lumbar route. In one case the clinical condition of the patient was so grave and the findings of numerous bacilli in films from the cerebrospinal fluid indicated such a severe infection of the meninges that twice daily injections of 100 mg. were given intrathecally for the first thirty-eight days (Case 10). Some of the patients received one or more courses of intrathecal streptomycin by the lumbar route without any complication such as spinal block or severe bleeding arising but in others such difficulties either arose or it was suspected they might arise. In these cases it was our practice to make bifrontal burr-holes and to give streptomycin intraventricularly for a few days. It was our experience that, except in some of the children, this rest period was sufficient to allow conditions in the lumbar theca to settle down and the course could then be continued by daily lumbar punctures. The cisternal route was rarely used for giving streptomycin because we found that quite severe reactions were liable to follow the introduction of streptomycin into the cistern. On several occasions cisternal punctures were of help diagnostically, as the cerebrospinal fluid so obtained often gave a true picture of the activity of the meningitis at the base of the brain and, if such punctures were performed only occasionally during a course of intrathecal treatment, we could confirm that the lumbar cerebrospinal fluid findings were not complicated by the local traumatic effects of numerous punctures. If there was any suspicion of spinal block a cisternal puncture was performed some six to twelve hours after administration of a dose of streptomycin by the lumbar route and the streptomycin content of the cisternal fluid estimated. By this means we were satisfied that the intrathecal streptomycin was diffusing satisfactorily. If burr holes had already been made an estimation of the level of streptomycin in the ventricular fluid could likewise be used.

The dose of streptomycin given to the children by the lumbar route varied from 30 mg. for a five-month-old baby (Case 15) to 75 mg. for the older children. The amount given intraventricularly was rather less, 15 to 37.5 mg.

(2) *Duration of Streptomycin Treatment.*—The question of how long treatment should be continued is perhaps the most difficult of all problems to decide. There appears to be no doubt that, as a result of the initial wave of enthusiasm engendered by some of the immediate good results obtained with streptomycin in the treatment of tuberculous meningitis, there arose a tendency to think

in terms of the meningitis only and to forget that the condition is first and foremost an active tuberculous infection and, as such, requires prolonged treatment similar to that given to cases of active pulmonary tuberculosis or any other form of tuberculosis.

In the present series, when a presumptive diagnosis of tuberculous meningitis was made, every patient received streptomycin by both intrathecal and intramuscular routes. The first problem that had to be faced was when to stop the intrathecal injections. In the earlier cases of the series (e.g. Cases 1 and 3) a course of fifty to sixty daily injections was given and, if the patient's clinical condition was satisfactory, the course was stopped. With more experience of the disease certain more definite criteria for stopping an initial intrathecal course were later adopted.

- (i) The patient's general clinical condition must be quite satisfactory.
- (ii) At least sixty days must have elapsed since there were any definite signs of activity of the meningitis: e.g. sixty days must have passed since the last film was positive for tubercle bacilli or sixty days must have passed since any fresh neurological sign appeared.
- (iii) The white cell count and protein level in the cerebrospinal fluid must be falling or at least have maintained a "plateau" level for some days.

Using these criteria the longest continuous course of daily intrathecal injections was 123 days, for the first thirty-eight of which, as mentioned above, twice daily injections were given (Case 10).

In all cases of miliary tuberculosis with proved meningitis and in any other case in which progress was not satisfactory we have, since January 1949, given a second or even a third course of intrathecal injections (*see* Table I). Unless some untoward event occurred, thirty days' rest was given between courses and in the second and subsequent courses intrathecal injections were given every other day.

The minimal duration of systemic streptomycin treatment has been 180 days. Only two patients who have successfully completed a course of treatment have received such a short course. One of these (Case 3) relapsed thirty-six days after completing his first course (forty-eight days intrathecal and 180 days intramuscular) and has now successfully completed a second course of intrathecal (sixty days) and intramuscular (180 days) streptomycin. This patient has been exceptionally fortunate in that, neither during his initial meningitis, nor in his relapse did he develop any signs of involvement of the central nervous system. The other (Case 6) was the patient with miliary tuberculosis already referred to who may not have had a true tuberculous meningitis. Judged by recent experience it seems that the majority of patients require at least 270 days of treatment with streptomycin and many, including all cases of miliary tuberculosis with established meningitis, 365 days.

It is important to realize that the administration of streptomycin is only one aspect of the treatment of patients suffering from tuberculous meningitis. All the general measures adopted in the treatment of other forms of tubercu-

TABLE I.—SUMMARY OF CASES

Case No.	Sex	Age	Family history or history of contact	Apparent source of infection	Mantoux test on admission	Condition on admission		Focal Neurological signs	Streptomycin treatment, days			Condition on 31.8.49	
						Mental	Physical		Intramuscular Course 1	Intramuscular Course 2	Intrathecal Course 3		
1	M	19	Negative	Spinal caries D6 & 7	+1/10,000	Unconscious, restless	Poor	R. 3rd nerve palsy R. hemiplegia L. hemiparesis	270	—	57	—	Well. Off treatment 147 days
2	M	19	Positive	None found	+1/10,000	Drowsy, Incontinent	Poor	L. hemiparesis	211	46	66	—	Died 12.3.49
3	M	19	Negative	Primary lung complex	N.R.	Alert and oriented	Excellent	None	180	180	48	—	Well. Off treatment 55 days
4	F	18	Negative	Primary lung complex	+1/10,000	Drowsy	Fair	L. hemiplegia Paraplegia Deafness	74	275	14	155 ²	Died 27.8.49
5	M	20	Negative	Miliary	N.R.	Euphoric	Fair	None	312	—	60	61+	Continuing I.M. and I.T. treatment. Well
6	M	20	Negative	Miliary	+1/1,000	Alert and oriented	Good	None	180	—	26	—	Off treatment 55 days. Well
7	M	20	Negative	Miliary	+1/10,000	Euphoric.	Fair	L. hemiparesis Athetosis R. hand None	138	—	74	—	Died 4.4.49
8	M	19	Negative	Active pulmonary tuberculosis	N.R.	Alert and oriented	Fair	None	155+	—	52	8 ² +	Still under treatment. Meningitis well controlled
9	M	18	Negative	Miliary	+1/1,000	Euphoric	Very poor	Deafness	175+	—	52	8 ² +	Still under treatment. Meningitis controlled. Miliary I.S.Q.
10	M	25	Negative	Active pulmonary tuberculosis	+1/10,000	Drowsy, confused	Poor	Transient hemiparesis L.	142+	—	123	—	Still under treatment. Much improved
11	M	2	Negative	Miliary	+1/100,000	Conscious, lethargic	Dehydrated	R. hemiparesis Decerebrate rigidity None	22	—	22	—	Died 4.6.49
12	M	2½	Positive	None found	+1/1,000	Conscious, and alert	Fair	None	104+	—	89	—	Continuing treatment. Progress only fair
13	M	3	Positive	Miliary	+1/10,000	Drowsy, fretful	Fair	None	121+	—	100	8 ² +	Continuing treatment. Good progress
14	M	21	Negative	Primary lung complex	N.R.	Conscious, irritable	Poor	Blind	85*	26	26	26	Died 21.7.49
15	M	5/12	Negative	Miliary	1/100,000	Alert	Good	Spasticity of all limbs	46	—	46	—	Died 28.8.49

N.R.—Not Recorded.

Streptomycin treatment: Figures thus: 18+—course unfinished on 31.8.49.

20² —course of injections given every other day.

*This was not a continuous course but was given as four short courses of twenty-six, fifteen, twenty-one and twenty-three days.

losis should be prescribed. Ideally, after the acute stage of the disease, treatment under sanatorium conditions is advisable and certainly an effort should be made to provide this for all patients during intervals between courses of intrathecal streptomycin and after they have completed intrathecal treatment. This has not been possible with all our cases but two patients (Cases 8 and 9) in whom the systemic infection appeared to be more important than the meningitis were given a short period at a sanatorium between courses of intrathecal streptomycin.

(3) *Toxic Effects of Streptomycin.*—Clarke (1949) listed four groups of toxic reactions that have been observed in patients undergoing treatment with streptomycin; a histamine reaction, an anaphylactic reaction, disturbances of auditory and vestibular functions and irritation of the kidney. Of these the first and last have not proved troublesome in the present series. Several of the features of the anaphylactic reaction as described by Clarke have been observed. Nausea and vomiting are frequently troublesome especially during the early weeks of treatment. We found injections of hyoscine and the oral administration of benadryl both temporarily effective in reducing the incidence of vomiting which, however, usually subsided spontaneously after two to three weeks of treatment. A maculo-papular rash was seen in only one case and it was present before streptomycin therapy was begun. Eosinophilia was observed in one case (Case 6). A differential white cell count on the thirty-ninth day of treatment showed 22 per cent eosinophils; the preceding and succeeding counts showed no eosinophilia.

All patients have shown evidence of disturbance of the functions of the eighth nerve. Characteristically this takes the form of a complete loss of vestibular function demonstrable, after approximately three weeks of treatment, by absence of the caloric responses and a loss of hearing for high tones recorded by audiometry. Fortunately, in the majority of cases the deafness is above the range of conversational tones and is not a disability to the patient. In two cases in the present series, the patients became completely deaf. Case 4 developed deafness in the left ear on the 150th day of treatment and in the right ear on the 244th day, and Case 9 in both ears on the 28th day. One other patient (Case 5) has a deafness in one ear that is within the range of conversational tones. This was noted clinically on the 278th day of treatment and confirmed by audiometry the next day. Deafness is a known neurological finding in both tuberculous and other forms of meningitis and we cannot be certain that in these instances it was due to the drug and not to the disease. Nevertheless, both the patients who became globally deaf were at the time receiving larger doses of streptomycin than we normally give and it is now generally recognized that streptomycin has a specific toxic effect on the vestibular and auditory apparatus. Dihydro-streptomycin is said to be less toxic in this respect but at the time of writing our experience with it is very limited.

On three occasions after an intrathecal injection a severe reaction was observed, consisting of peripheral circulatory collapse, sweating, flaccidity of all limbs, absence of all reflexes, nystagmus, inco-ordination, dysarthria

and incontinence of urine and fæces. The first symptoms appeared about six hours after the injections and the reactions were at their maxima at about twelve hours. On one occasion the patient became deeply unconscious. The evidence that two of these episodes were due to streptomycin is that the patients recovered from the reaction in thirty-six to forty-eight hours and that the streptomycin content of the lumbar cerebrospinal fluid twenty-four hours after the incriminated intrathecal dose was abnormally high on both occasions: 230 units per c.c. and 80 units per c.c. respectively. The third episode was exactly similar to the other two but following it the patient concerned (Case 4) had clinical signs of a lesion of the cauda equina which were permanent and there was no abnormality of the streptomycin content of the cerebrospinal fluid. None of the reactions was accompanied by clinical signs suggesting a flare up of the meningitis or with a rise in cells and protein in the cerebrospinal fluid. We suspect that these reactions may have been due to an overdose of streptomycin due to some error in making up the individual doses concerned but have not been able to prove this suspicion.

Details of one of these reactions are as follows:

Case 4.—At 1400 hours on the seventh day after her relapse (*see* p. 284) this girl was given her daily intrathecal injection of 100 mg. of streptomycin by the lumbar route. At 1600 hours she vomited and complained that her lower limbs "felt funny." She was pale and had a rapid, weak pulse. The cranial nerves and upper limbs were as before but both lower limbs were flaccid. The left (hemiparetic) limb was paralysed and the right showed some general weakness but all movements could be performed. Reflexes could not be obtained from either lower limb. (As the reflexes on the left had been increased this was a most remarkable finding.) Sensation was unaffected. At 1730 hours, she volunteered the information that she felt better and that her legs were stronger. However, at 1900 hours she collapsed; her pulse was impalpable and there were pallor, sweating, and incontinence of fæces. Despite the administration of cardiac stimulants, she was still deeply comatose at 2230 hours; a response could be obtained only by strong supra-orbital pressure; the pupils were small, equal and reacted to light, all four limbs were flaccid and there was complete areflexia. Lumbar puncture was performed and the C.S.F. pressure was only 110 mm. At 0100 hours, the next day there were signs of recovery, her colour had improved and she was moving her upper limbs. Improvement continued and by 1000 hours she was talking although a little confused and very dysarthric. Nystagmus was present on lateral gaze in both directions. The limbs were still flaccid but, except for the pre-existing hemiparesis, power had returned almost to normal. There was marked ataxia of the right arm and leg. Both tendon-jerks and superficial reflexes were absent. Twenty-four hours later, her speech was normal, the reflexes had returned and apart from an amnesia for the whole episode there were no residual findings attributable to the reaction. The cerebrospinal fluid findings on the day of the reaction and the following day were as follows:

Time	Total	White blood cells per c.mm.		Protein mg. per 100 c.c.	Chlorides mg. per 100 c.c.	Strepto- mycin Units per c.c.
		Polys.	Lymphos.			
1400 hours (before reaction)	111	20%	80%	165	660	21
2300 hours (during reaction)	395	47%	53%	150	630	1020
1100 hours (day after reaction)	296	40%	60%	100	675	230

In addition to these specific toxic effects streptomycin undoubtedly has a general toxic action which is difficult to assess but is well appreciated by patients who are receiving the drug. Although during the last weeks of treatment patients whose progress is favourable may feel well, have good appetites and be gaining in weight satisfactorily, as soon as the drug is stopped they take on a new lease of life, have voracious appetites and during the first weeks of convalescence their gain in weight is much more rapid.

(4) *Causes of Failure of Streptomycin Treatment.*—6 patients in the present series of 15 died and it is of interest to consider why streptomycin treatment failed in these cases. First it may be stated that at the time of death all the patients had evidence of active tuberculous meningitis, that is to say they died of the disease and not of the effects of the disease. Failure to diagnose the disease in its early stages and hence delay in starting treatment is one reason for an unsuccessful result. In 3 of the fatal cases (Cases 2, 11, and 15) there was an interval of more than fourteen days between the onset of the illness and the administration of the first dose of streptomycin. Treatment may be ineffective because it is adequate and it may be inadequate either because insufficient streptomycin is given at each dose or because the course of treatment is too short. Case 14, in which most of the treatment was given elsewhere, comes under this heading; four short courses of systemic streptomycin, the longest being twenty-six days and two short courses of intrathecal streptomycin (twenty-six days and fifteen days) were given over a period of four months. The patient did well for a time but then relapsed. He was transferred to our care but died twenty-six days later. As already explained, failure to confirm the diagnosis led to Case 4 receiving an initial course of treatment which was inadequate judged by our standards. In view of the initial good response which was obtained it is probable that, had a full course of treatment been given then, the eventual fatal outcome might have been prevented.

In some cases despite adequate treatment, the infection rapidly gains the upper hand and death occurs in a relatively short period. Two of the children (Cases 11 and 15) died of an intense miliary infection after only twenty-two and forty-six days treatment respectively. In Case 7 an early diagnosis of meningitis was made in the presence of a previously diagnosed miliary tuberculosis. Intrathecal treatment was started immediately. Despite this he went rapidly downhill and died after seventy-four days. The presence of numerous tubercle bacilli in films made from the cerebrospinal fluid right up to the day of death showed that the meningitis had never been adequately controlled. Only two patients in the series died after surviving a long period of treatment (Cases 2 and 4). Case 4 has already been discussed above and on p. 284. In Case 2 the diagnosis of tuberculous meningitis was not made until approximately the fortieth day of the illness and when treatment started he was in very poor condition both mentally and physically. Nevertheless his progress was satisfactory for a time but then he became demented, and, after he had received sixty-six days of intrathecal treatment and 211 days of intramuscular treatment, streptomycin was stopped. He relapsed twenty-six days later and thereafter went steadily downhill.

It is thus apparent that in most of the fatal cases more than one adverse factor was present. The lessons to be learned from our fatalities are that we must endeavour to make the diagnosis early, to start treatment at once and to persevere with both systemic and intrathecal streptomycin in adequate dosage until there is good evidence that the meningitis is completely controlled.

Excluding the fatal cases only one patient in the present series relapsed after completing a course of treatment. Brief reference to this patient has already been made (p. 290).

Case 3¹.—A 19-year-old private commenced treatment on what was estimated to be the seventh day of his illness. His general condition was excellent and, apart from mild mental confusion, on one occasion, there were never any signs of involvement of the central nervous system. He was given forty-eight days of combined intrathecal and intramuscular treatment. His progress was so satisfactory that the intrathecal medication was then stopped. After fifty-seven days of treatment, he was allowed to get out of bed and at a hundred days was up all day and going out of the hospital on pass in the afternoons. Despite his good clinical condition his cerebrospinal fluid was still abnormal and intramuscular treatment was continued up to 180 days. At 203 days his C.S.F. showed 49 white cells per c.mm. (all lymphocytes), protein 65 mg. per 100 c.c., chlorides 730 mg. per 100 c.c., and sugar 52 mg. per 100 c.c. However, in view of the fact that he was well clinically and that he had been so active in the preceding weeks without any untoward result, it was decided that he should go on leave over Christmas. Fourteen days later he was readmitted with a history of headache and malaise for one week. There were signs of active meningitis and the C.S.F. now showed: white cells 212 per c.mm. (20 per cent polymorphs, 80 per cent lymphocytes), protein 210 mg. per 100 c.c., chlorides 650 mg. per 100 c.c. and sugar 55 mg. per 100 c.c. Tubercle bacilli were again found on direct examination of the fluid. Treatment was restarted and again rapid clinical improvement followed. Despite this a full course of sixty days combined treatment and 180 days intramuscular treatment was given. In view of the previous experience he was kept in bed during this period and thereafter resumption of activity was very gradual. On 31.8.49, twenty-nine days after stopping his second course of treatment and 456 days after he originally started treatment, he was apparently well and the C.S.F. showed only 5 white cells per c.mm. and 40 mg. of protein per 100 c.c.

The causes for this patient's relapse are not difficult to find. First, the all-important principle of prolonged rest as an essential part of the treatment was neglected. Secondly, we allowed ourselves to be influenced too much by the patient's general clinical condition and ignored the warning given by the cerebrospinal fluid findings that the meningitis was not yet quiescent. This case then illustrates two points which have already been stressed in this review, namely that it must not be forgotten that tuberculous meningitis is a form of active *tuberculosis* and that the administration of streptomycin should not be stopped until one is satisfied that the infection is adequately controlled.

RESULTS

Of the present series 3 patients (Cases 1, 3 and 6) have completed a course of treatment and are well at periods of up to 147 days after receiving treatment; these cases may be regarded as potential recoveries. 6 patients are still under treatment and 6 patients have died. If the 6 patients who had either completed

¹The early history of this case is given by Clarke (1949) Case 9.

treatment or died at the time of Clarke's (1949) report are also considered the following results have been obtained. From March 1947 to August 1949, 21 patients with tuberculous meningitis have been treated at this hospital. Of these 2 have recovered; they are now alive and well twenty-two months and twenty-one months after completing treatment (Clarke's Cases 1 and 2), 3 are potential recoveries (*see above*), 10 have died and 6 are still under treatment.

CONCLUSION

Further experience has confirmed the impression that streptomycin is a drug which exerts a profound influence upon the course of tuberculous meningitis. It is not an ideal drug but there is no doubt that in some cases it enables patients to recover from an illness which, before the introduction of streptomycin, was almost uniformly fatal. No hard and fast rules regarding treatment can be laid down and each case must be considered as an individual problem. To obtain the best results, streptomycin treatment should be started as early as possible in the course of the disease and the drug should be given both systemically and directly into the cerebrospinal fluid in adequate dosage and for a sufficiently long period. During treatment many problems arise and these are more easily solved if patients are treated by a specially trained team of nurses and medical officers. Nor must it be forgotten that tuberculous meningitis is an active tuberculous process and that patients suffering from it should be treated by a régime similar to that adopted for other active forms of the disease. An attitude of optimism towards the disease and perseverance with treatment will produce gratifying results even in cases which, at the outset, appear most unpromising.

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