TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN A FOUR-YEAR FOLLOW-UP

BY

**SHEENAH J. M. RUSSELL, M.D., M.R.C.P.Ed.
D.C.H.**

Former Clinical Assistant

AND

PATRICK MacARTHUR, M.D., F.R.F.P.S. D.C.H.

Assistant Visiting Physician

Royal Hospital for Sick Children, Glasgow

In 1950 we reported on the various methods of treatment with streptomycin and the results obtained after at least one year in 33 proved cases of tuberculous meningitis in the Royal Hospital for Sick Children, Glasgow (Russell and MacArthur, 1950). Because it has been recognized that certain children with tuberculous meningitis who have been treated with streptomycin and have apparently made a satisfactory recovery may subsequently suffer a relapse of the disease and die, it was thought necessary to watch the progress of these children for some years after the completion of treatment before claiming that they were cured. The present report is a further record of the 15 children who were alive at the time of the first report. The period of follow-up now ranges from 49 to 68 months. Each survivor was examined during the past year and the cerebrospinal fluid of all but one was examined. Details of these children are recorded in Table I and the case numbers correspond with those in our first report.

The main clinical features of the disease in each of the 33 original cases have already been recorded (Russell and MacArthur, 1950). These were the first patients to be treated with streptomycin in this hospital, but they were not consecutive admissions, because the accommodation available and the time required for the detailed investigations necessary ruled out the possibility of treating all cases admitted for diagnosis and found to have tuberculous meningitis. It was the practice to reserve four cots in each of the two medical units for this therapeutic trial, and when one of these cots was vacated the place was taken by the next case diagnosed. No attempt was made to select cases in which a favourable outcome might be anticipated. The results of treatment are not the best that could be obtained, because

the trial was in force at a time when little was known regarding the best method of using streptomycin, and indeed at one stage a number of patients were given only intramuscular injections.

Of the 33 patients, 12 are alive—nine are leading normal lives in their own homes and three are grossly disabled. The cerebrospinal fluid (C.S.F.) is cytologically and chemically normal in 11 of the children. One of the disabled cases (No. 25) has a low sugar content. Table II shows the results obtained in this series and in other published series.

Nine Survivors who are Well

Five of these children were under 4 years old when they developed meningitis. In only one survivor (Case 24) was there a snowstorm appearance on x-ray examination, and in one other (Case 32) there was a single choroidal tubercle, now healed. In three children the disease was in its early stages when treatment was begun, and in the other six it was in an intermediate stage. No child has survived in whom the disease was already advanced at the onset of treatment. Two children have had a relapse of meningitis and have recovered after a second course of treatment. A block in the circulation of C.S.F. from the ventricles throughout the subarachnoid space was present in Cases 14 and 22. In Case 14 the block resolved during the period of observation, while in Case 22 a partial spinal block was still present at the time of writing, although he was very well 55 months after the onset of the disease and 52 months after the block was first detected. The parents of the child with the single healed choroidal tubercle (Case 32) refused to bring him to hospital for review, but he was seen in his own home. It was impossible, however, to examine the spinal fluid or to have a skiagram taken. He appeared to be a healthy, happy boy with no abnormal signs in the central nervous system. During August and September, 1951, the C.S.F. of the other eight children was examined and cultured, and was found to be cytologically and chemically normal and sterile.

While the children were under review special attention was paid to their scholastic attainment, but unfortunately it was not possible to have intelligence tests carried out. One child (Case 14), who is of an affectionate and happy disposition, is definitely backward mentally and attends a special school, while Case 11 is probably of low average intelligence. The remaining seven, however, appear to be making good progress at school and do not exhibit any behaviour problems. Recent skiagrams of the skull show areas of calcification in six of these children.

Three Survivors Disabled

One of these children (Case 2) developed meningitis 68 months ago. Though in an early stage of the disease when treatment was begun, she did not respond satisfactorily, and

TABLE I

Case No.	Age (Years)	Stage of Disease at Start of Treatment	Duration of Observation (Months)	Snowstorm Skiagram	Choroidal Tubercles	Spinal Block (B)	Relapse (R)	C.S.F. at End of Treatment				C.S.F. Most Recent				Result	Intra-cranial Calcification
								Cells per c.mm.	Protein mg. per 100 ml.	Chloride (as NaCl) mg. per 100 ml.	Sugar mg. per 100 ml.	Cells per c.mm.	Protein mg. per 100 ml.	Chloride (as NaCl) mg. per 100 ml.	Sugar mg. per 100 ml.		
2	4	E	68					30	66	761	—	0	36	723	59	Disabled	+
9	3	I	66				R	90	43	710	—	4	36	725	59	Well	+
10	2	E	47					350	281	699	30	—	—	—	—	Dead	+
11	2	I	60				R	5	38	765	53	—	—	—	—	Well	+
12	2	I	63					12	65	770	—	1	24	743	61	Well	+
14	11	I	63			B	R	55	73	729	—	1	19	762	48	Well	+
15	3	I	58					70	277	658	—	0	42	748	73	Well	+
22	4	E	55			B	R	40	31	713	—	2	27	734	48	Disabled	+
24	6	E	55	+				1	41	713	—	0	38	—	61	Well	—
25	1	E	53				R	26	41	629	77	3	40	764	61	Disabled	—
28	3	E	52					35	82	681	—	4	27	735	37	Well	+
29	2	I	51					17	37	717	50	2	34	758	63	Well	+
32	3	I	49		+			49	50	716	56	1	30	682	53	Well	+
33	7	E	42	+	+	B	R	10	72	676	—	Refused	per mission	—	—	Dead	?
								4	4	625	32	—	—	—	—		

E=Early stage. I=Intermediate stage.

TABLE II.—*Recorded Results in Tuberculous Meningitis Treated with Streptomycin*

Author	Minimum Observation Period (Months)	No. of Cases			
		Total	Alive	Well	Disabled
Illingworth and Lorber (1951)	12	82	36 (44%)	24 (29%)	12 (15%)
Lincoln and Kirmse (1949) (promizole also given)	12	10	8 (80%)	5 (50%)	3 (30%)
Cairns <i>et al.</i> (1950)	12	60	30 (50%)	21 (35%)	9 (15%)
Cathie and MacFarlane (1950)	12	60	28 (47%)	23 (39%)	5 (8%)
McCarthy and Mann (1950)*	16	37	14 (38%)	12 (32%)	2 (6%)
Russell and MacArthur (1950)	12	33	15 (45%)	10 (30%)	5 (15%)
Present series	49	33	12 (36%)	9 (27%)	3 (9%)

* In this series six children treated with intramuscular streptomycin alone have been excluded from the figures quoted.

tubercle bacilli were still cultured from her C.S.F. two and a half months after the start of streptomycin therapy. After six months of intramuscular and intrathecal treatment her clinical condition was deteriorating and she developed convulsions and a right-sided hemiplegia. Treatment was finally stopped after 12 months, when she was hemiplegic and having convulsions. The disease is now quiescent and her C.S.F. is normal and sterile on culture, but the child is a low-grade mental defective with a right-sided hemiplegia and has frequent epileptic fits. Calcification is apparent in a recent skiagram of her skull, and is situated above and anterior to the sella and on both sides of the midline.

Case 15 has been observed for 58 months. He had intramuscular treatment alone for 60 days, after which tubercle bacilli were still cultured from his C.S.F. and he was emaciated and comatose. Ten weeks of combined intramuscular and intrathecal treatment brought improvement in the cerebrospinal-fluid findings, but his clinical disability remained severe. He suffered a relapse of meningitis 15 months after his initial attack and had a further three months of intramuscular and intrathecal treatment. The disease is at present quiescent and the C.S.F. is normal, but he is mentally defective with a right hemiplegia, has epileptic fits, and shows marked sexual precocity. Intracranial calcification began to appear 23 months from the onset of the illness, and there is now a dense mass above the sella turcica and on the left side of the brain.

Case 25 has now been under observation for 52 months. He was 12 months old and was in an intermediate stage of the disease when the diagnosis was made. He had a three-months course of intramuscular and intrathecal treatment, on the completion of which he was blind, he was having convulsions, and his C.S.F. was still abnormal. Six months later, however, his spinal fluid was normal, although he was mentally defective and was still having convulsions. Two years after his initial illness he had a relapse of meningitis, and again tubercle bacilli were cultured from his C.S.F. He was given another three-months course of intramuscular and intrathecal streptomycin with some improvement. At the present time he is mentally defective, has epileptic fits, and his C.S.F. sugar is at an ominously low level.

Changes Since last Report

Comparison of the present state of this series with the state in September, 1949, shows four changes, one for the better and three for the worse. Case 32 was reported as disabled because he was believed to be developing hydrocephalus, but he has completely recovered and attends school regularly, where his achievements are well up to the average standard. One inactive choroidal tubercle is still visible in his right eye.

Case 33, who was disabled at the time of the last report, has since died, 30 months after the onset of the disease. This boy was admitted to the centre with milinary tuberculosis and developed meningitis while on intramuscular treat-

ment. Until his death 30 months later he was under continuous observation and had four relapses, at the onset of three of which tubercle bacilli were cultured from his C.S.F. In the final episode the tubercle bacilli were still sensitive to streptomycin, but he died suddenly on the day after the start of treatment. At necropsy the brain showed hydrocephalus, with a thick gelatinous exudate at the base of the brain, and four small tuberculomata were found in the cortex.

Case 9 was classified as "well" in the original report, although nine months after the completion of treatment his C.S.F. still had a raised cell count. He remained at home, leading a normal life and attaining average success at school, but 45 months after his initial meningitis he had a relapse and in spite of treatment died within two months. This boy showed the most scattered intracranial calcification of the series, the nodules being widely spread on both sides of the brain. The course of the illness during the first six months was stormy, with episodes of convulsions, aphasia, hallucinations, facial palsy, and severe psychological upsets. Three months after stopping streptomycin it was realized that he was deaf, but gradually his deafness diminished, and a year later his hearing, by rough tests, was normal. It seems probable that his deafness was due to the disease rather than to the streptomycin sulphate with which he was treated.

Case 10 was classed as "well" in our 1949 report, but in October, 1949, he was found to have a tuberculous abscess in the anterior end of the left seventh rib. This discharged pus containing tubercle bacilli, and the child was given a four-weeks course of intramuscular streptomycin. The lesion healed completely and permanently within three months. An x-ray film of the skull in February, 1951, showed extensive intracranial calcification at the base of the brain. During 1951 the boy remained apparently well, though there was a mild right-sided hemiplegia, and he attended school regularly. On August 22 a lumbar puncture was done during routine follow-up studies. The C.S.F. was cytologically and chemically normal and he seemed very well, but it was disquieting to culture two colonies of tubercle bacilli from the C.S.F. In May, 1952, he had a relapse of tuberculous meningitis and in spite of intramuscular, intrathecal, and intraventricular treatment he died with gross hydrocephalus eight weeks later. In this relapse, three years after his primary attack, the tubercle bacilli were fully sensitive to streptomycin.

Intracranial Calcification

One of the most interesting features of the follow-up has been the detection of intracranial calcification. This has been present in the skiagrams of 8 of the 12 survivors and also of two children (Cases 9 and 10) who died of a relapse of meningitis in March, 1951, and June, 1952. In every case there have been calcified areas in the vicinity of the sella turcica. In five children central nodules were seen around the sella or just above it. In six cases there were nodules a little above the level of the sella and about one-third of the distance towards the left side of the skull, and in two cases the nodules were on both sides of the film. The majority of calcified foci appeared to be in the vicinity of the cisterna interpeduncularis and cisterna chiasmatica, and in one case the calcification extended up towards the cisterna ambiens. This localization was supported by the findings at necropsy on Cases 9 and 10, whose skiagrams showed widespread intracranial calcification. There were numerous calcified foci in the tuberculous exudate at the base of the brain, often deep in the sulci, but no calcified areas in the brain substance.

Cairns (1951) stated that "in tuberculous meningitis it is probably many months before the subarachnoid spaces are clear of exudate; in some successful cases traces of it persist indefinitely and become calcified." From the present findings it would seem that in the successful cases calcification is the rule rather than the exception, and it is probable that its appearance depends mainly upon the length of time

since active meningitis occurred. The earliest appearance of calcification in the basal cisterns was noted at 23 months from the onset of meningitis. In two of the children the areas concerned may well be within the brain parenchyma. Case 15, who shows signs of precocious puberty, has a dense mass, probably situated in the hypothalamus. Case 14, before the onset of meningitis, was admitted to a neuro-surgical unit for investigation of a cerebral tumour. At that time, in November, 1947, a skiagram of the skull showed an area of calcification in the left temporal lobe. Ventriculography revealed that there was also a large mass in the right frontal area blocking the anterior horn of the right lateral ventricle. A second area of calcification has been present on films dating from 15 months after the onset of meningitis, and the site appears to correspond with the tuberculoma found in the right lateral ventricle. It is not surprising to find that seven of the ten children showing intracranial calcification also show intrathoracic calcification.

Other published accounts of tuberculous meningitis treated with streptomycin have been searched for any reference to the presence of intracranial calcification in surviving patients. Lorber (1951) described intracranial calcification in a girl of 7 years who developed tuberculous meningitis 18 months previously. This girl showed signs of sexual precocity, and in her case there were two small foci of calcification believed to be in the wall of the third ventricle. The demonstration of intracranial calcification which is now possible in so many of these cases is a vindication of the view (Rich and McCordock, 1929) that meningitis is commonly secondary to cortical or meningeal tuberculomata.

Relapse of Meningitis

In this series there have been nine children who suffered recurrence of meningitis at intervals of 3 to 179 weeks after the completion of treatment (Table III). Six children have

TABLE III.—*Relapses of Tuberculous Meningitis*

Case No.	Interval Since Last Treatment (Weeks)	Last C.S.F. Taken Before Relapse					Present Condition
		Interval Before Relapse (Weeks)	Cells per c.mm.	Protein mg. per 100 ml.	Chloride (as NaCl) mg. per 100 ml.	Sugar mg. per 100 ml.	
3	36	9	40	76	719	38	Dead
5	3	3	20	57	764	—	„
9	179	128	31	26	727	—	„
10	(1) 4	2	130	59	695	25	Well
	(2) 179	27	1*	31	693	83	
12	80	57	12	24	702	—	Disabled
15	36	6	9	58	650	51	„
25	88	16	4	30	693	71	Dead
26	5	3	13	90	674	20	
33	(1) 5	5	42	83	686	18	Well
	(2) 4	2	15	7	667	45	
	(3) 49	12	1	—	660	58	
	(4) 32	4	2	32	604	69	
			V.P. spinal block persists				„

* Tubercle bacilli cultured. V.P. = Ventricular puncture.

died. Only in Case 25 had the C.S.F. been normal before the relapse occurred, but physically he was severely disabled. In Case 10 the C.S.F. was cytologically and chemically normal but tubercle bacilli grew on culture. One relapse which occurred after three and a half years of good health was particularly disappointing. This child (Case 9), in an intermediate stage of the disease when treatment was begun, had intramuscular and intrathecal treatment during a period of three months. Reference has already been made to the severity of the clinical picture. Ten months after the completion of treatment his C.S.F. was still abnormal, although his only physical disability was some impairment of hearing. He remained at home, and was doing well at school until January, 1951, when he had a relapse of meningitis with tubercle bacilli in the C.S.F. In spite of treatment he died six weeks later. A skiagram taken on January 30 showed extensive intracranial calcification, and at necropsy numerous calcified tubercles were found in a dense basal exudate but none were present in the brain substance. The appearance of intracranial calcification is therefore not an

infallible sign of healing of the meningitis; it does not preclude the existence of tuberculous foci which may still contain living tubercle bacilli. Cases 9 and 10 had extensive intracranial calcification when they developed a recurrence of meningitis and died.

Cortical or subcortical tuberculomata have been detected after death in only two of the six children who died after a relapse, and in only 7 of the 20 necropsies performed in the whole series. Hydrocephalus of marked degree was found in five of the six fatal cases of relapse, and the thickness of the basal exudate aroused comment in three. Tubercle bacilli were cultured from the C.S.F. withdrawn at the onset of the relapse in six of the nine children. Unfortunately, it was possible to test the streptomycin sensitivity of only two of these cultures (Cases 10 and 33). The bacilli were as sensitive to streptomycin as at the beginning of treatment more than three years previously, although there had been adequate opportunity for resistance to develop.

Type of Streptomycin and Neurotoxicity

All the children in this series were treated with salts of streptomycin—hydrochloride, sulphate, or calcium chloride complex. During their relapse three children were given dihydrostreptomycin for short periods, but no untoward effects were noted. On the basis of this limited experience of the comparative action of the two drugs we are unable to assess the relative toxicity of streptomycin and dihydrostreptomycin in the present series of cases.

Summary

Thirty-three patients with tuberculous meningitis have been treated with streptomycin and the survivors have been re-examined from four to five and a half years after the institution of treatment.

Nine (27%) are alive and well and leading normal lives, three are gravely disabled, and 21 have died after periods ranging from 2 days to 60 months.

Spinal block occurred in nine of the patients—seven are dead, and a partial block persists in one of the two survivors.

Intracranial calcification as seen in skiagrams has occurred in 10 of the 13 patients who survived long enough for it to develop. Six of these are well, two are disabled, and two have since died.

Relapse of meningitis has occurred in nine cases. Only one of these children is alive and well, two others are disabled, and six have died of the relapse.

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REFERENCES

- Cairns, H. (1951). *Arch. Dis. Childh.*, **26**, 373.
 — Smith, H. V., and Vollum, R. L. (1950). *J. Amer. med. Ass.*, **144**, 92.
 Cathie, I. A. B., and MacFarlane, J. C. W. (1950). *Lancet*, **2**, 784.
 Illingworth, R. S., and Lorber, J. (1951). *Ibid.*, **2**, 511.
 Lincoln, E. M., and Kirmse, T. W. (1949). *Ibid.*, **1**, 767.
 Lorber, J. (1951). *Proc. roy. Soc. Med.*, **44**, 726.
 McCarthy, D., and Mann, T. P. (1950). *Lancet*, **1**, 341.
 Rich, A. R., and McCordock, H. A. (1929). *Bull. Johns Hopk. Hosp.*, **44**, 273.
 Russell, S. J. M., and MacArthur, P. (1950). *Lancet*, **1**, 59.

The first report of the W.H.O. Expert Committee on Public Health Administration is now available as No. 55 in the *World Health Organization: Technical Report Series*. In the committee's opinion, the main functions of the central authority should be the formulation of policy, the giving of advice and specialized technical assistance to local authorities, and the enforcement of medical legislation and other standards of efficiency; while the main function of the local health administration should be operational.