Arch. Dis. Childh., 1964, **39**, 213.

THE SEQUELAE OF TUBERCULOUS MENINGITIS

BY

R. McLAREN TODD and JOSEPH G. NEVILLE
From The Department of Child Health, Liverpool University and Alder Hey Children's Hospital, Liverpool

(RECEIVED FOR PUBLICATION DECEMBER 19, 1963)

The classical description of the three stages in the clinical course of tuberculous meningitis was written nearly 200 years ago by Robert Whytt, Professor of Medicine at Edinburgh University; and his conclusions that 'if this disease could be known early . . . it might sometimes be cured, but as it never discovers itself . . . till the action of the brain is disturbed . . . we have little to hope from any medicine' were valid until streptomycin was introduced by Schatz, Bugie and Waksman (1944).

In February 1947, the first centre in this country for the treatment of children suffering from tuberculous meningitis was established at Alder Hey Children's Hospital, Liverpool, under the auspices of the Medical Research Council. One year later a preliminary report (Todd, 1948), based upon the response to streptomycin of 21 children with tuberculous meningitis, showed that 7 were alive, and 3 of these patients had completed streptomycin therapy and survived 19, 23 and 46 weeks after the onset of the disease. Clinically the survivors showed no evidence of meningitis, but one patient was completely deaf; a raised protein and an increased cell count were still present in the cerebrospinal fluid; psychiatric assessment showed no evidence of intellectual deterioration, change of disposition, anxiety, moroseness or apathy, but the deaf child showed some slowing of mental development not altogether accounted for by impaired hearing or a period in hospital. Such preliminary results were most encouraging, for until the discovery of streptomycin, tuberculous meningitis had been a fatal disease, most children dying within 6 weeks of the confirmation of the diagnosis.

During the 15 years that have elapsed since 1947 there have been remarkable advances in the treatment of tuberculosis; in 1947, 1,080 children under 15 years of age died in England and Wales from tuberculous meningitis, but in 1961, the latest year for which national figures are available, only 18 children died from this disease. In the City of Liverpool 24 children died from tuberculous meningitis in 1947 and only 1 in 1961. Although the fall in mortality is gratifying, what are the effects upon those children who survive? Is there still the risk of deafness or some slowing down of mental development? Are the survivors physically or emotionally handicapped? Do they attend normal schools? Are they in due course able to earn a reasonable living? Our attempts to assess the physical, social, emotional and intellectual status of children who have survived an attack of tuberculous meningitis are described in this paper.

Patients Studied and Plan of Investigation

The case records of all children under the age of 15 years who were admitted to Alder Hey Children's Hospital, Liverpool, with tuberculous meningitis during the 11-year period 1947 to 1957 were reviewed, and attempts were made to communicate with the survivors. During the 11-year period (Table 1), 194 children were treated for tuberculous meningitis; 118 of these children died, 117 from tuberculous meningitis and 1 as a result of a drowning accident several years after discharge; we were unable to trace 3 patients; 73 were alive and we have seen and investigated 65 of these survivors. We have been in correspondence with the 8 survivors we were unable to investigate; 1 is being treated for carcinoma of the bronchus, 1 lives in Western Germany, another is in the United States, another in Swansea, 1 is in the Merchant Navy, and the parents of 3 patients did not wish them to be investigated.

A preliminary contact was made by letter and this was followed by a visit from our psychiatric social worker who obtained a detailed personal and social history, obtained reports of progress at school and made arrangements for the parent and child to visit the hospital. During the morning one of us (R.McL.T.) obtained a medical history and performed a complete physical examination; this was followed by a visit to the Radiology Department for chest and skull radiographs, and a visit to the

TABLE 1
CHILDREN WITH TUBERCULOUS MENINGITIS ADMITTED TO ALDER HEY CHILDREN'S HOSPITAL, LIVERPOOL

Year	No. of Children	Alive		Dead	Unable to Trace
		Seen	Not Seen		
1947	19	3		16	
1948	20	2		18	
1949	28	6		22	
1950	25	10		15	
1951	33	6	1	24	2
1952	20	8	2	9	1
1953	13	9	2	2	
1954	13	7	1	5	
1955	8	5	2	1	
1956	8	5		3	
1957	7	4		3	
11 years	194	65	8	118	3

electroencephalography department for an EEG examination. In the afternoon an audiogram was performed, and finally one of us (J.N.) carried out a full psychiatric assessment including measurement of intelligence. We were gratified to find that our patients accepted these arrangements with enthusiasm, and some came to Liverpool from as far afield as Watford and Kilmarnock.

Initial Clinical Features, Investigations and Treatment

The case records were analysed and information obtained concerning the patient's sex, age at onset of the illness, whether or not miliary tuberculosis was present, severity of illness, examination of cerebrospinal fluid, treatment and complications encountered during the treatment phase. The *severity* of the illness when the patient was first admitted to hospital was graded according to the Medical Research Council suggestion (1948) into three categories.

Early: patients with mainly non-specific symptoms, with little or no signs of meningitis, with no pareses, in good general condition and fully conscious. Diagnosis established mainly on findings in cerebrospinal fluid.

Advanced: patients obviously extremely ill, deeply stuporose or comatose or with gross pareses.

Medium: patients in a condition between those of the first two groups.

Table 2 records that 27 (41%) of the patients were male and 38 (59%) were female; the age at onset of the illness varied from 1 to 15 years; 11 (17%) of the patients had miliary tuberculosis; the grade of severity was early in 31 (47·7%), medium in 26 (40%) and advanced in 8 (12·3%).

The initial abnormalities in the cerebrospinal fluid were those regarded as diagnostic of tuberculous meningitis; the total white cell count was raised, the cells were predominantly lymphocytes, they averaged 200 per c.mm. but varied from 18 to 484 per c.mm.; the sugar level was reduced to about 40 mg./100 ml., but in one patient it was 16 mg./100 ml.; the protein content was raised to an average of 100 mg./100 ml., but in two patients a level of 300 mg./100 ml. was recorded. There was no correlation between the clinical grades of severity and the levels of white cells, sugar and protein in the cerebrospinal fluid. Tubercle bacilli were isolated from the cerebrospinal fluid in 44 (67%) of the patients, from 17 (55%) of 31 early cases, 22 (85%) of 26 medium cases, and 5 (62%) of 8 advanced cases.

Treatment. The treatment (Table 3) which these 65 patients received was not identical; in 1947 the only specific chemotherapy available was streptomycin, but when para-amino-salicylic acid (PAS) became available in 1949, and isoniazid in 1951, these drugs were used as well as streptomycin. Additional forms of therapy, e.g. intrathecal protein purified

TABLE 2
DEGREE OF SEVERITY (M.R.C.) FOR MALE AND FEMALE PATIENTS IN EACH AGE-GROUP, INDICATING PATIENTS WHO ALSO HAD MILIARY TUBERCULOSIS

Age of Onset (yr.)	Early				Medium				Advanced	
	With Miliary		Without Miliary		With Miliary		Without Miliary		Without Miliary	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<1	1	–	–	1	–	–	–	2	–	–
1–2	1	–	1	2	–	–	–	–	1	2
2–3	–	–	1	–	–	1	–	1	1	1
3–4	–	1	–	2	–	1	3	1	–	1
4–5	–	–	1	2	1	–	1	1	1	–
5–6	–	1	1	1	–	–	–	1	1	–
6–7	1	–	2	2	–	–	2	3	–	–
7–8	–	1	–	3	–	–	1	–	–	–
8–9	2	–	–	–	–	–	–	–	–	–
9–10	–	–	1	1	–	–	–	1	–	–
10–11	–	–	–	–	–	–	2	–	–	–
11 and over	–	–	–	2	–	–	1	3	–	–
Totals	5	3	7	16	1	2	10	13	4	4

derivative (P.P.D.), intrathecal streptokinase, oral caronamide and cortisone were used in a few patients. The earlier patients received intramuscular streptomycin at 6-hourly intervals for a minimum of 12 weeks; later the injections were given at 12-hourly intervals and later still once daily. The total daily dose of intramuscular streptomycin in all patients was on the basis of 20 mg./lb. body weight, and the duration of therapy varied from a minimum of 12 weeks to a maximum of 46 weeks. Streptomycin was also given intrathecally to 52 of the patients in a dosage of 50 to 100 mg., the number of injections depending upon the discretion of the paediatrician concerned; many patients received about 50 such injections, and 3 received over 100 intrathecal injections; streptomycin was given through burr holes into the lateral ventricles in 9 patients. In later years, much to the relief of patients and staff, intrathecal therapy was discontinued, and 13 of our 65 patients did not receive a single intrathecal injection of streptomycin.

Complications. The complications that occurred during the initial treatment phase are recorded in Table 4. Hemiplegia, weakness of one limb, sixth nerve palsy, and generalized convulsions were the main nervous system defects; bone lesions developed in 5 patients, and drug sensitivity reactions occurred in 5 patients. One noteworthy feature, especially in the patients treated in the early years of the survey, was a tendency to relapse; relapse occurred in 9 patients, it developed within 7 to 13 months of the onset of the initial illness and was most probably the result of what we would now consider inadequate duration of therapy. The complications were more frequent in the more advanced cases; thus 8 of 31 early cases developed complications, compared with 23 of 26 medium and all 8 advanced cases.

The duration of *stay in hospital* averaged 35 weeks for early cases, 37 weeks for those of medium severity and 52 weeks for the advanced cases. The patients were seen at regular intervals in the Out-patient Department following discharge from hospital, and if after two years of follow-up there was no evidence of activity of tuberculous disease they were discharged.

TABLE 4

COMPLICATIONS NOTED DURING INITIAL TREATMENT PERIOD

	Total Patients	Early	Medium	Advanced
Hemiplegia	10	2	4	4
Weakness of right arm	3	1	2	
Generalized spasticity	1			1
Sixth nerve palsy	9		8	1
Seventh nerve palsy	1		1	
Generalized convulsions	4	2	2	
Gland rupture into bronchus	1	1		
Bronchiectasis	1		1	
T.B. mastoiditis	1		1	
T.B. spine	1	1		
T.B. hip	1	1		
T.B. astragalus	1		1	
Osteoporosis femoral head	1		1	
Haemolytic anaemia	1			1
Drug sensitivity	5		2	3
Total complications	41	8	23	10
Total patients in series	65	31	26	8
Relapse	9	3	4	2
Time in months after initial diagnosis		8;7;9	11;5;8;7	13;9

Long-term Follow-up

Our researches into the possible long-term effects of tuberculous meningitis were carried out on these 65 patients from 3½ to 14 years after the onset of the original illness, and their ages at the time of review varied from 6 to 27 years (Table 5a and b). The *heights and weights* of those patients under 16 years of age were recorded on standard charts prepared for the Medical Advisory Committee of the National Spastics Society; the findings for 20 boys and 26 girls (Figs. 1 and 2) show that in most patients the heights and weights are within the accepted normal limits of plus or minus 2 standard deviations from the mean. The heights of 4 boys and 2 girls are just below the lower

TABLE 3

SUMMARY OF TREATMENT OF 65 CHILDREN WITH TUBERCULOUS MENINGITIS

Treatment	No. of Children	
Streptomycin i.m. and i.th.	8	
Streptomycin i.m., i.th., and Burr holes (i.v.)	2	
Streptomycin i.m., i.th., and PAS	11	(also P.P.D. (2) and streptokinase (8))
Streptomycin i.m., i.th., PAS, and Burr holes (i.v.)	5	(also caronamide (1) and streptokinase (3))
Streptomycin i.m., i.th., PAS, and isoniazid	19	(also cortisone (1))
Streptomycin i.m., i.th., PAS, isoniazid, and Burr holes (i.v.)	1	
Streptomycin i.m., i.th., and isoniazid	5	
Streptomycin i.m., i.th., isoniazid, and Burr holes (i.v.)	1	
Streptomycin i.m. and isoniazid	4	
Streptomycin i.m., isoniazid and PAS	9	
Total	65	

TABLE 5a
AGE AT REVIEW

Age-group (yr.)	No.
6–10	18
11–15	29
16–20	12
21–25	5
26–30	1

TABLE 5b
TIME AFTER ONSET OF T.B. MENINGITIS AT REVIEW

Time (yr.)	No.
3–5	11
6–10	40
11–15	14

limits of normal, the weight of 1 boy is just below the lower limit and that of another is above the upper limit of normal. The general health of our patients following recovery from tuberculous meningitis has been good; there was no increased incidence of respiratory or other infections, appetite was average but a few had an excessive appetite. Obesity, thought to be of central origin, has been reported not infrequently in patients who have recovered from meningitis or encephalitis: it occurred in 3 of Wasz-Höckert and Donner's (1963) 103 patients.

General *clinical and neurological examination* revealed certain features, e.g. hemiplegia, weakness or incoordination of a limb, deafness and mental retardation, which are considered to be a direct consequence either of tuberculous meningitis or of specific anti-tuberculous therapy; whereas other features, e.g. migraine and asthma, are probably unconnected with meningitis. It is also of interest to note that 3 patients had married and that 2 were the parents of normal children. Delayed onset of puberty was noted in 2 patients. Table 6 records those clinical features that were found at review.

The frequency with which *physical* defects develop following tuberculous meningitis is extremely difficult to assess from many of the published reports because (1) the follow-up period has varied from a few months to several years; (2) detailed descriptions of the defects in respect of their severity are often lacking; (3) in several papers the interest of the observer has been on the effect on one particular organ, e.g. the ear; (4) the treatment prescribed has varied considerably and some of the defects may be the result of therapy rather than of the tuberculous process. Two of the most detailed surveys have been undertaken by Wasz-Höckert and Donner (1963) in Helsinki and by Lorber (1961) in Sheffield; the results recorded in these papers, together with

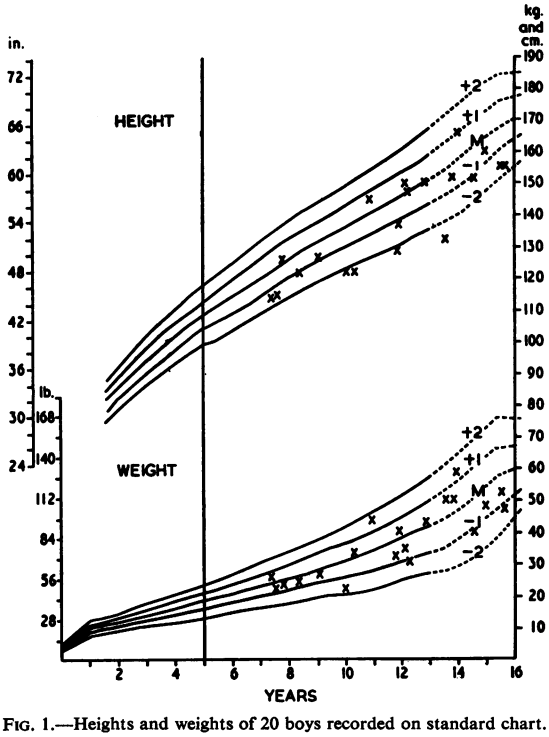

FIG. 1.—Heights and weights of 20 boys recorded on standard chart.

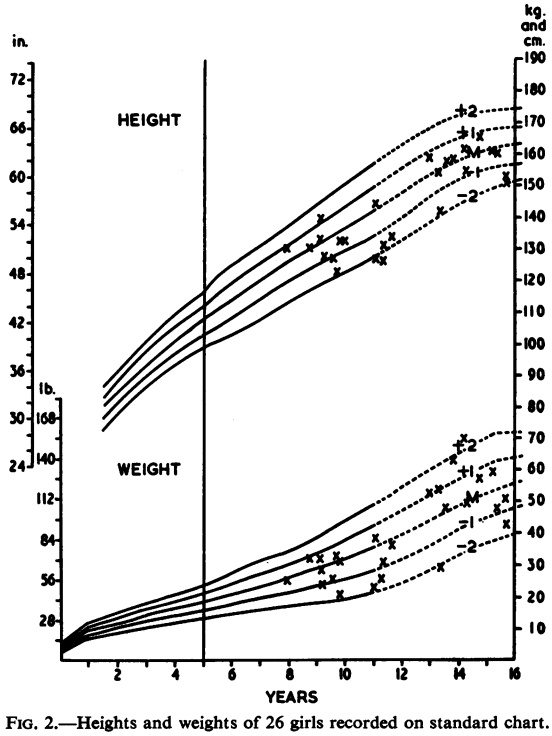

FIG. 2.—Heights and weights of 26 girls recorded on standard chart.

our own and those of Voljavec, Orton and Corpe (1959) in the United States, Pohitonova (1960) and Lapides (1962) both of the Soviet Union, have been analysed. From these six sources there is sufficient information to give an over-all picture of the incidence of sequelae in 855 children who have survived an attack of tuberculous meningitis. 529 (62%) of these patients were clinically normal 3 to 13 years after the onset of the illness; 7 were blind, 2 were partially sighted, 24 were deaf, 38 were partially deaf, 65 suffered from epileptic attacks, 39 had paralysis of varying degree and 14 had developed endocrine disturbances.

One of the most encouraging features of our series was the relatively infrequent occurrences of serious permanent neurological abnormalities. During the initial illness, 10 of our patients developed hemiplegia, 1 had generalized spasticity, 3 had weakness of an arm, 9 had sixth nerve palsy and 1 had seventh nerve palsy; at the time of review only 5 had hemiplegia, weakness or incoordination of a limb, and 2 patients had strabismus. In 7 of the patients who initially had a hemiplegia there was no spasticity, weakness or wasting of muscles, but exaggerated reflexes were present in 4 of these, and 2 who were formerly right-handed had become left-handed following a right hemiplegia. In Lorber's 100 patients 1 had facial weakness and 12 had gross defects at the time of review, but he noted that several children who had had gross neurological lesions during the active phase had made a complete recovery. In contrast, only 50 of the 103 patients reported by Donner and Wasz-Höckert (1963) were free of neurological sequelae: 30 had minor and 23 had gross neurological sequelae. *Endocrine* disturbances have been reported from time to time in patients who have survived tuberculous meningitis. One such abnormality is diabetes insipidus but it is of great rarity; so far 13 such cases have been recorded, the most recent one in a Maori child (Hay, 1960) who developed diabetes insipidus eight months after meningitis, which was responsive to intramuscular 'pitressin tannate'. Sexual precocity has also been observed (Lorber, 1951) in a girl who developed tuberculous meningitis at the age of 5½ years and who was fully developed sexually at the age of 7½ years; skull radiography showed a calcified tuberculoma in the wall of the third ventricle, and a considerable degree of hydrocephalus was demonstrated by air encephalography. Wasz-Höckert and Donner (1963) reported a similar patient, a girl who was aged 2½ years at the onset of tuberculous meningitis and in whom menarche occurred at 8 years of age. Two of our patients showed delay in the onset of puberty; one of them aged 20 years showed considerable calcification in the suprasellar area (see Fig. 7), the other showed no signs of puberty at the age of 15½ years, and calcification at the base of the brain was noted on skull radiography.

TABLE 6
CONDITIONS NOTED AT TIME OF REVIEW

Conditions	No.
Epileptic attacks	2
Hemiplegia	2
Generalized spasticity	1
Weakness of lower limb	1
Incoordination of upper limb	1
Exaggerated reflexes following hemiplegia	4
Conversion from right to left-handedness	2
Deafness (severe or moderate)	10
Strabismus	2
Shortening of lower limb	2
Gross deformity of lower limb	1
Kyphosis	1
Frontal headaches	4
Migraine	4
Asthma	1
Delayed onset of puberty	2
Married (two with children)	3

Chest and skull radiographs were taken in all 65 patients. Radiological evidence of healed pulmonary tuberculosis was obtained in 23 patients who showed calcification and in 2 others who showed fibrotic changes (Table 7). The primary tuberculous complex had developed on the left side in 12 and on the right side in 13 patients. Skull radiography showed calcification in 24 patients, but in 3 of these it was either in the choroid plexuses or in the pineal gland, and was thought to be of no significance. Calcification was near the pituitary fossa in 9 and at the base of the brain in 6 patients.

Lorber (1958) reviewed 10 published reports concerning *intracranial calcification* in patients treated for tuberculous meningitis and also recorded personal observations on 100 patients. Intracranial

TABLE 7
RADIOLOGICAL FINDINGS AT REVIEW

Findings	No.
Skull	
Calcification: base of brain	6
Near pituitary fossa	9
Left frontal area	1
Left parietal area	1
Mainly parietal area	4
Choroid plexus	2
Pineal	1
Total	24
Chest	
Calcification: left—mid zone	1
Lower lobe	6
Hilum	4
Right—upper lobe	4
Mid zone	1
Lower lobe	2
Hilum	5
Linear fibrosis: left—upper lobe	1
Right—upper lobe	1
Total	25

TABLE 8a
HEARING DEFECTS AT REVIEW

Hearing Defects	No.	Dihydro-strepto-mycin
High-tone deafness		
Bilateral	12	1
Unilateral	1	
Generalized hearing loss		
Bilateral	8	4
Unilateral—other ear normal	3	
—other ear, high-tone deafness	2	
Deficient bone conduction following T.B. mastoiditis	1	
Totals	27	5

TABLE 8b
RELATION OF HEARING DEFECTS WITH GRADE OF SEVERITY OF T.B. MENINGITIS

Hearing Defects	Early	Medium	Advanced
High-tone deafness	4	6	2
Generalized hearing loss	2	8	3

calcification was present in 177 (29%) of 610 patients who were examined up to five years after the onset of the illness. In our series significant calcification was present in 21 (32%) of the 65 patients. In all these patients calcification was most commonly found at the base of the brain, where meningeal exudate usually accumulates in tuberculous meningitis; occasionally more localized areas of calcification are found within the brain substance (Fig. 4), and they probably represent calcified tuberculomata (Rich foci). Occasionally calcification may be extensive (Fig. 7) and be associated with disturbance of hypothalamic or pituitary function. In many patients the development of calcification reflects the severity of the initial illness, the most advanced patients having the most marked calcification, but this is by no means invariable; in our 21 patients calcification was equally distributed among the early and medium patients and was not observed in the 8 advanced patients. It was also clear that calcification occurred equally in patients treated with streptomycin alone, streptomycin and PAS or streptomycin and isoniazid. Heikel and Wasz-Höckert (1963) found intracranial calcification in 26 of 101 patients and in 4 of these it was extensive; occurrence of calcification was not correlated with sex, duration of meningeal symptoms before admission to hospital or with treatment, but in opposition to our findings calcification was related to the stage of disease on admission and also occurred more commonly in patients in whom burr holes were made. *Hearing defects* were clinically obvious in 10 patients, 3 of whom were completely deaf and 7 of whom were partially deaf. Audiograms were carried out on 61 of our 65 patients; in 1 of the 4 who did not have an audiogram such testing could not be carried out because of the low I.Q., but in the remaining 3 hearing in both ears was normal on rough clinical assessment. Audiograms were abnormal in 27 of the 61 patients tested (Table 8a and b), and the tendency to abnormality increased progressively with the increasing severity of the initial illness. Thus the audiogram was abnormal in 7 (25%) of 28 early cases, 14 (53%) of 26 medium cases and 5 (71%) of 7 advanced cases. The development of hearing defect following dihydrostreptomycin is interesting; only 5 of our 65 patients received this form of streptomycin but all 5 were affected: 1 of them became completely deaf, 3 developed bilateral generalized hearing defects and 1 developed bilateral high-tone deafness. The damaging effect of streptomycin on the *eighth nerve* was recognized shortly after this drug was used in clinical practice. The calcium and sulphate salts of streptomycin affect mainly the vestibular branch, whereas the toxic action of dihydrostreptomycin is mainly on the auditory branch. Shambaugh, Derlacki, Harrison, House, House, Hildyard, Schuknecht and Shea (1959) described 32 patients with dihydrostreptomycin deafness; most of their patients were adult but one child aged 5 years and another aged 16 years were included. A total dose of as little as 1 g. was found to cause deafness, and there was often a latent period of up to six months between administration of the drug and the development of hearing loss. Severe or moderately severe deafness developed in all 5 of our patients who received dihydrostreptomycin, and audiometric deafness of major or minor degree developed in 22 of 60 patients who received streptomycin. Hearing was normal in 84 of 94 patients seen by Lorber (1961) at follow-up; 3 of the 84 had been deaf for a long period after their meningitis but subsequently hearing gradually returned to normal; 6 of 94 patients had partial deafness, and 4 were completely deaf. Ranta and Wasz-Höckert (1963) studied 103 patients and found 65 without hearing sequelae, although 27 of these had some degree of audiometric loss, 16 had slight hearing loss, 8 had severe hearing loss and 8 were completely deaf.

Electroencephalography was done in 62 of our 65 patients; normal records were obtained in 15 (24%) and abnormal records in 47. The abnormalities are recorded in Table 9 which also indicates the severity of the meningitis at the beginning of treatment. In the early group 22 (75%) of 29 patients showed some abnormality, compared with 18 (70%) of 26 patients in the medium group and all 7 of the advanced group. Although meningeal exudate at the base of the brain is one of the characteristic

features of tuberculous meningitis, the brain itself becomes involved either because of the development of increased intracranial pressure resulting from obstruction to the flow of cerebrospinal fluid or because of the onset of endarteritis and thrombosis around a tuberculoma or because of encephalitis. It is therefore not surprising that the electro-encephalogram in patients who have recovered from tuberculous meningitis should show abnormal features: it was normal in 15 (24%) of 62 of our patients; in 35 (41%) of 85 patients studied by Kauhtio, Donner and Wasz-Höckert (1963) and in 56 (57%) of 97 patients studied by Lorber (1961). The interesting finding is that in many patients without any obvious neurological lesion the EEG may be abnormal.

TABLE 9
EEG FINDINGS AND SEVERITY OF T.B. MENINGITIS

	Early	Moderate	Advanced
Total patients (65)	31	26	8
EEG abnormal	22	18	7
EEG normal	7	8	0
EEG not done	2	0	1
Abnormalities of EEG:			
Slow theta excess	11	8	3
Dysrhythmia	3	4	0
Generalized non-specific excess of theta and beta	1	0	0
Rapid beta	2	0	0
Excessive delta	3	3	1
Generalized gross abnormality	0	0	1
Paroxysmal spikes	2	3	2

Illustrative Cases

The following brief case reports illustrate the course of the illness and the outcome in 5 of our patients.

Case 1. B.R. developed tuberculous meningitis in 1949 when he was 3½ years old; the illness was of medium severity and he was treated with intramuscular streptomycin for 26 weeks, intramuscular dihydrostreptomycin for 13 weeks, with 25 intrathecal injections of 100 mg. streptomycin and 10 intrathecal injections of 100 mg. dihydrostreptomycin. The lumbar theca was punctured 127 times for therapeutic and diagnostic purposes; he developed a right spastic hemiplegia which cleared up completely and was probably due to thrombosis, and he remained in hospital for 43 weeks. When reviewed 12 years after the onset of tuberculous meningitis there were no abnormal neurological signs, but he had become left-handed following the right-sided hemiplegia; there was no evidence of the onset of puberty; he suffered from bilateral high-tone deafness; skull radiography showed calcification at the base of the brain mainly on the left side (Fig. 3), and his I.Q. on the Wechsler-Bellevue Scale Form II was 94.

Case 2. P.W. developed tuberculous meningitis in 1948 when she was 7 years old; the illness was in the early stage and she received treatment with intramuscular streptomycin (48 weeks) and with intrathecal streptomycin (110 injections each of 100 mg.) together with P.P.D. and streptokinase. Ten months after the onset of the illness she developed *grand mal* attacks which were controlled by phenobarbitone; she also had a tuberculous right hip. When reviewed 13 years after her original illness, the right leg was shorter than the left, pigmented choroidal tubercles were seen in the right fundus, her hearing was normal, skull radiography (Fig. 4a and 4b) showed a calcified area in the left frontal area and scattered calcification at the base of the brain; EEG was normal with no evidence of a focal lesion and her I.Q. was 79.

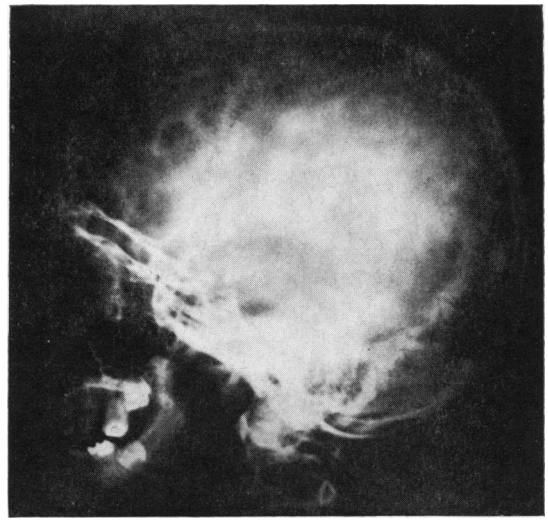

FIG. 3.—Brian R. Radiograph shows calcification at the base of brain.

Case 3. J.H. developed tuberculous meningitis of medium severity in 1950 when he was 4 years old. He received oral PAS for 26 weeks, intramuscular streptomycin for 20 weeks, 15 intrathecal injections each of 100 mg. streptomycin, 20 ventricular injections each of 100 mg. streptomycin, together with streptokinase after burr holes had been made in the skull. During the acute illness he developed generalized convulsions followed by marked spasticity of the left arm and leg, and he remained in hospital for 31 weeks. When reviewed 11½ years later there were no abnormal neurological signs, he was partially deaf in both ears (and had attended a special day school), skull radiograph (Fig. 5) showed calcification above the pituitary fossa, EEG showed excessive theta activity, and his I.Q. on the Wechsler-Bellevue Form II was 71.

Case 4. Dorothy B. developed tuberculous meningitis in 1951 when she was 9 years old, having had tuberculosis of the wrist some 9 months previously. The meningitis was in the early stage, and she received intramuscular streptomycin for 21 weeks, 62 intrathecal injections each of 100 mg. streptomycin and 21 weeks of oral PAS. One month after completing this treatment she relapsed and a

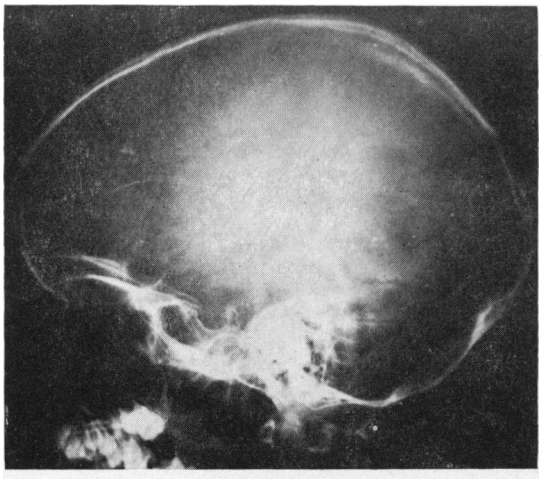

FIG. 4a.

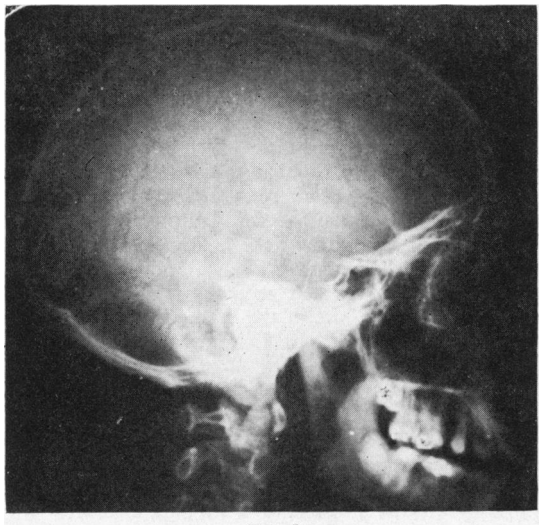

FIG. 5.

FIG. 4a and b.—Pat W. Skull radiography shows scattered calcification at base of brain and a localized calcified focus in the left frontal area.

FIG. 5.—Jeffrey H. Lateral skull radiograph shows calcified foci above the pituitary fossa.

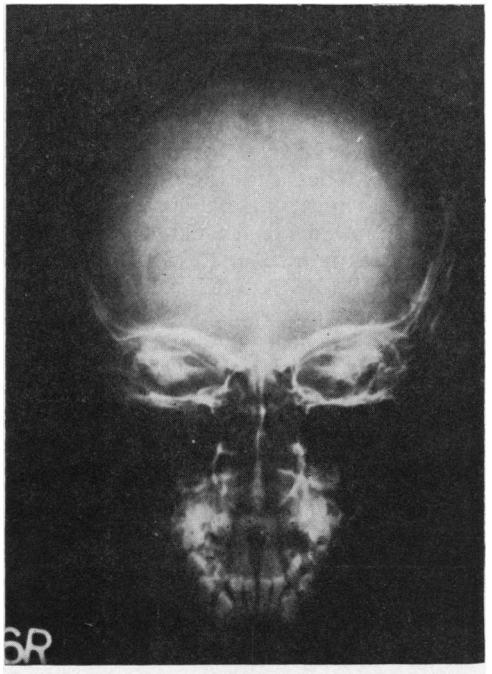

FIG. 4b.

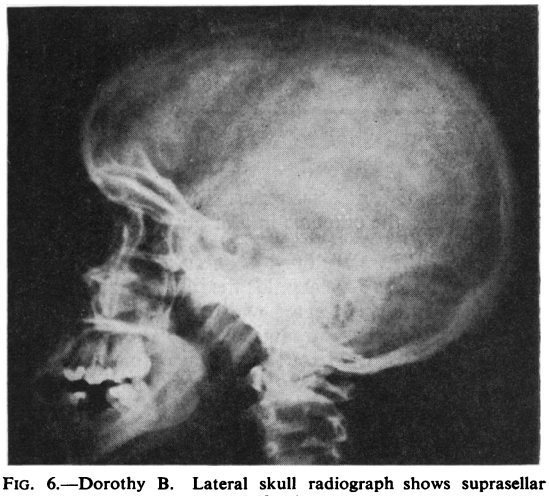

FIG. 6.—Dorothy B. Lateral skull radiograph shows suprasellar calcification.

further course of treatment of intramuscular streptomycin (25 weeks), intrathecal streptomycin (52 injections each of 100 mg.), PAS (25 weeks) and isoniazid (25 weeks) was given. Total hospital stay amounted to 74 weeks. When assessed 10½ years after the first attack of tuberculous meningitis there were no abnormal neurological signs, skull radiography (Fig. 6) showed suprasellar calcification, audiogram showed bilateral high-tone deafness, abnormal beta activity was present on the EEG and her I.Q. was 83 on the Wechsler-Bellevue Scale.

Case 5. Dennis B. developed tuberculous meningitis of medium severity in 1952 when he was 10½ years old. He was treated with intramuscular streptomycin for 34 weeks, PAS for 12 weeks, isoniazid for 22 weeks, and received 105 intrathecal injections each of 100 mg. streptomycin. When reviewed 9½ years later, at the age of 20 years, he gave a history of occasional black-outs, no pubertal changes were present, and there was exaggeration of reflexes. Audiogram showed that he had bilateral high-tone deafness, EEG showed excessive high amplitude

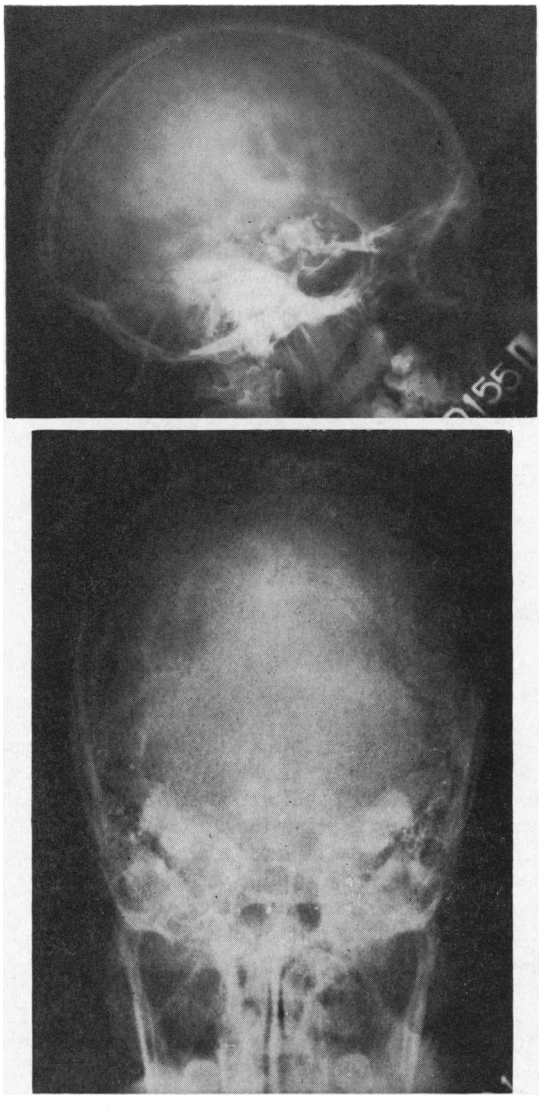

FIG. 7a and b.—Dennis B. Radiographs show considerable calcification around the pituitary fossa.

delta activity especially on the left side of the brain, I.Q. (Wechsler-Bellevue) was 72 and skull radiography (Fig. 7a and 7b) showed considerable calcification in the suprasellar area.

Level of Intelligence

(a) Methods of Assessment. In assessing the intelligence of the Liverpool survivors two scales were mainly employed, the Wechsler Intelligence Scale for Children, and the Wechsler-Bellevue Intelligence Scale (I or II) for adults, depending upon the age of the subject. Careful note was taken of any sensory and motor handicaps that might affect a patient's ability to cope with part or whole of the testing situation, and where necessary the main intelligence scales were supplemented or replaced by one or more of the following scales—the Mill Hill Vocabulary Scale, Raven's Progressive Matrices, the Arthur Point Scale of Performance Tests for Deaf Children, and the Revised Stanford-Binet Scale (form L or M). In the majority of our cases we were able to compare the reliability of our psychometric scores with the highest level of educational attainment, as recorded in their Head Teacher's reports made available to us. The benefit of the doubt was always given in the case of any physically handicapped child when widely differing I.Q.s were obtained by different tests.

(b) Results of Previous Studies. Nickerson and MacDermot (1961), working in Montreal, studied the intellectual capacity of 50 Canadian children who had recovered from tuberculous meningitis between the years 1947 to 1955, and calculated that the mean I.Q. was $73 \cdot 02 \pm 3 \cdot 88$, whereas Williams and Smith (1954) in Oxford had not been able to find any measurable deficit in intelligence in 19 patients who had contracted the disease as adults. Nickerson's calculations probably reveal a significant trend rather than representing a statistically correct mean value; the Montreal group contained Eskimos and French-Canadian children whose formal psychometric performances were likely to be adversely affected by cultural and economic differences, and it was hardly permissible to attempt to construct a frequency distribution curve or to compile mean values from I.Q.s derived from heterogeneous intelligence scales. However, allowing for the methodological approximation and for the widely differing socio-economic background of the Montreal series, it appeared very likely that tuberculous meningitis affecting the immature central nervous system of children tended to be associated with the risk of impairment of intelligence. Lorber (1961) followed the psychometric rating of 100 Sheffield children treated for tuberculous meningitis, in 33 cases for longer than 10 years after contracting the disease, and employed the Stanford Revision of the Binet Intelligence Scale for children in the great majority of the whole series. Lorber's studies confirmed that the peak of the I.Q. frequency distribution curve was shifted to the left, and Pentti, Donner, Valanne and Wasz-Höckert (1963), again employing a battery of heterogeneous intelligence scales and consequently introducing statistical difficulties in interpreting their results, also demon-

strated the abnormally high representation of below-average intelligence in their Finnish series of 103 cured children.

(c) Results of Present Series. Since it is statistically unsound to compare I.Q.s or even percentile positions obtained from different scales, the intelligence of each subject was assigned to a clinically meaningful category, i.e. mentally-defective, borderline-defective, dull-normal, average, bright-normal, and superior or very superior. The results of this classification are shown in Table 10 and compared with the expected incidence in the unselected population (Wechsler, 1949).

TABLE 10

Category of Intelligence	Number of Subjects	Approximate Percentage of Series	Expected Percentage Frequency in Unselected Population
Mentally defective	6	9·2	2·2
Border-line defective ..	6	9·2	6·7
Dull normal	13	20·0	16·1
Average	30	46·0	50·0
Bright normal	8	12·3	16·1
Superior and very superior	2	3·3	8·9

The significance of these figures merits some discussion because it cannot be taken for granted that a normal distribution of intelligence existed in our 65 subjects before they developed tuberculous meningitis, and, like Lorber's series, the Merseyside child patients were predominantly recruited from materially poor families with breadwinners who tended to be ill educated and employed in unskilled or semi-skilled occupations, and with sibs whose educational attainments suggested that they too were not of high intelligence. Despite the fact that our subjects represent a highly selected group it can confidently be asserted that tuberculous meningitis was the major factor in increasing the number of survivors with dull-defective intellect at the expense of those with average-to-very superior mental ability. All 12 subjects with manifest mental defect (amounting to idiocy or imbecility) or in the borderline category proved to have had pre-morbid developmental histories, that strongly suggested at least average-normal potentialities for future intelligence, and at least 4 had been developmentally advanced before the advent of their illness. Again, in all 12 cases the disease had been extremely severe, reaching the advanced Stage III of the Medical Research Council's classification (1948), with severe clouding of consciousness, stuporo-coma, and clinical evidence of brain damage including such features as convulsions, cranial nerve palsies, spastic weakness, involuntary movements, and gross postural abnormalities.

(d) Severity of Tuberculous Meningitis on Admission and Subsequent Intelligence. No significant correlation existed between the clinical stage *on admission* and the level of intelligence after recovery. Many children who later proved to be mentally defective or feeble-minded were admitted in Stage I of the disease, only to deteriorate despite treatment. In contrast, 6 of the 7 bright-normal survivors never exceeded Stage I in severity throughout the course of the meningitis. However, clinical evidence of major brain damage did not presage severe mental subnormality in every patient. Of the 53 survivors 24 who now have intelligence in the dull-normal to superior range were, at some phase or other during their tuberculous meningitis, in Stage III. Both subjects who are now of superior intellect were admitted gravely ill, one developing a right-sided spastic hemiplegia and a generalized coarse tremor after status epilepticus had succeeded four major convulsions.

(e) Age at Onset. Nickerson and MacDermot (1961) concluded from their studies that there was a significant (but not invariable) relation between early age at onset of tuberculous meningitis and subsequent mental subnormality. Lorber (1961) found that all severely mentally handicapped survivors had contracted the disease below the age of 3 years. In the Liverpool series 38 children contracted tuberculous meningitis below the age of 6 years and 19 (50%) are now of below average intelligence, whereas of the 27 children who developed the disease after the age of 6 years only 9 (33%) are of poor intellect. On superficial view our findings appear to support the contention that the more immature the brain, the more likely is tuberculous meningitis to limit the development of normal intelligence. However, a study of survivors with mental retardation in the regions of mental defect - to - feeblemindedness reveals a wide disparity in the age at onset: for example, 2 of the 7 children who contracted tuberculous meningitis between the ages of 12 and 15 years are now feebleminded. Both patients were certainly of normal pre-morbid intelligence, and both suffered tuberculous meningitis in a grave, advanced form.

(f) General Clinical Severity and Outcome for Intelligence. Far more important than clinical stage before treatment is commenced, or age at onset of the tuberculous meningitis, is the severity of the disease process viewed as a whole. In the Mersey-

side series the younger the patient, the greater the risk of central nervous system damage and consequent intellectual impairment because, in general, the disease tended to be more severe in infants and toddlers.

Organic Sequelae and Mental Level. (i) Residual central nervous system abnormalities.

It was to be expected that mental subnormality in survivors would be accompanied by other evidence of neurological disease, and all 6 mental defectives and one feebleminded survivor display spastic weakness or hyperreflexia. Of the 53 survivors with socially adequate intelligence, only 3 continue to display clinical signs of mild spastic hemiplegia, and another ex-patient has a persistent sixth cranial nerve weakness attributable to the meningitis.

This striking difference is also demonstrated in comparing the EEG's of the two groups. All 12 defective and borderline survivors have anomalous EEG's: 7 of these show generalized excessive slow wave activity with inadequate alpha representation, and 5 have unequivocally pathological EEG's with such features as asymmetrical activity, high amplitude slow waves, paroxysmal bursts of high voltage, theta or delta rhythm, or cascades of 'spikes'. Of the 53 survivors with reasonable-to-excellent intelligence, only 29 have abnormal EEG's, and a further 6 have recordings that are suggestive of cerebral immaturity.

(ii) Bilateral toxic nerve deafness.

Ten subjects were deaf to very high tones, but all had adequate preservation of intelligence and their high-pitch defect had clearly never been a serious social or educational handicap; indeed the hearing deficit was generally only detected by audiography. Three totally deaf survivors had normal intelligence, but of the 7 with moderate-to-severe deafness, 4 proved to be mentally subnormal. All 7 patients had been gravely ill with tuberculous meningitis, and during the course of the illness had displayed signs of brain damage; in all these patients treatment had been correspondingly prolonged with high total dosage of dihydrostreptomycin or streptomycin, or both. Every manifestly deaf child had encountered considerable educational difficulties despite the provision of special schooling, and the majority of partially deaf survivors resented and refused to wear hearing aids (except under compulsion in school), thus further restricting their opportunities for intellectual stimulation. A frequently heard comment from parents of deafened children was 'he was a bright child until he became deaf', and our clinical impression was that the single factor of auditory sensory deprivation (with its manifold consequent handicaps due to communication difficulties) may well have been mainly responsible for limiting the growth of intelligence in 4 patients when deafness had supervened under the age of 8 years.

Loss of Schooling. We were unable to determine any significant association between absence from school and present level of intelligence, apart from the fact that the average loss of schooling for the series, 11 $\pm$ 2 months, tended to be exceeded by deaf survivors. Again it is our impression, shared by Lorber (1961), that children with adequate hearing, normal-to-superior intelligence, and who came from stable and stimulating homes, very quickly made up for loss of education once they had returned to school. Deaf, feebleminded and dull children, particularly those from ignorant and restricted homes, characteristically failed to make up this leeway, and 6 children in the dull-normal category were transferred to schools for educationally subnormal pupils.

Socio-economic Status

At the time of review 35 survivors were enjoying normal education, ranging from primary schools to a Teachers' Training College. Nine were enrolled in either day or boarding schools for physically or intellectually handicapped pupils, and 2 severely mentally subnormal children were being cared for in mental deficiency institutions.

Fifteen ex-patients were in full-time employment, and 2 girls had been employed and self-supporting before marriage. Two survivors were unemployed: one lad once had a promising work record despite multiple intellectual and physical handicaps (including feeblemindedness, epilepsy, mild deafness and hypopituitary infantilism), but is likely to prove unemployable; the second patient, also feebleminded, is overrestricted by her mother, but could earn her living as a domestic or laundry worker.

Three ex-patients have married, and, in each case, courtship and marriage resulted in a leap forward in social efficiency.

Out of the total 65, 9 survivors (approximately 12%) are never likely to be employable, self-supporting financially or socially adequate, because of mental subnormality.

Behaviour and Emotional Status

Pentti *et al.* (1963) have described the psychological difficulties resulting from brain injuries caused by tuberculous meningitis, which include disinhibition, emotional lability, fatiguability, rigid and maladaptive behaviour, either as immediate accompaniments of the disease process and convalescence, or persist-

ing in association with such permanent handicaps as mental subnormality, sensory defects, fits and palsies. On the basis of follow-up studies ranging from 5 to 12½ years, the Finnish workers concluded that 80% were well adjusted, 17% mildly disturbed, and 3% severely disturbed (the percentages are approximate). Unfortunately Pentti *et al.* (1963) failed to define adequately their criteria of adjustment/maladjustment, or to indicate their method of rating each case; and their conclusion (p. 76) that adaptation problems accompanied moderate or severe intellectual and organic disabilities, is at odds with their actual findings (p. 73) that there was no correlation between late persistent behaviour disorders and residual intellectual and neurological handicaps.

Lorber's long-term studies on 100 cured cases (1961) were carried out without psychiatric assistance but: 'Much stress was laid on . . . personality, their achievement, and their adjustment to life', and his clinical impressions were supplemented by school reports and the results of psychometric testing. On the basis of this mainly subjective assessment, Lorber suggested that 88 were normally behaved at the time of review, but that a further 6 (with adequate intelligence) had displayed disordered conduct in the past. This small group of transiently disturbed children contained 4 who were physically handicapped.

(a) Method of Psychiatric Assessment of Present Series. The precise definition of the multitudinous facets of human behaviour, and their calibration and measurement in meaningful terms, free of ephemeral value judgements and applicable to all cultural and age groups, represents an impossible task, but an attempt was made to measure each survivor's ability to adapt to five cardinal 'areas' of this life-situation by constructing scales, each rated from 0-6 points, which crudely assessed the efficiency of adaptation within (1) the family, (2) the neighbourhood, (3) at school and/or at work, (4) capacity for friendship and reciprocation of affection and, (5) the survivor's degree of freedom from personal maladaptive patterns such as disorders of mood and self control, anxiety symptoms, obsessional symptoms, hypochondriasis, and psychosomatic states. The sum total of points allotted on each of the five scales was arbitrarily classified as follows:

Total Points	Behaviour Category
1–10	Severely maladapted
11–20	Mildly maladapted
21–30	Efficiently adapted

(b) Results. Table 11 indicates the levels of global adjustment obtained by the 65 Liverpool survivors. No correlation existed between long-term level of adjustment and age at onset of tuberculous meningitis, although history-taking frequently revealed the fact that many patients who had contracted the disease in the first seven years of life developed florid but transitory psychological symptoms during recovery, convalescence, and after returning to family and school life.

TABLE 11

Behaviour Category	No. of Subjects	Approximate Percentage
Efficiently adapted	38	57
Mildly maladapted	20	30
Severely maladapted	9	13

In many cases it was unnecessary to invoke the physical and psychological stresses of tuberculous meningitis, its treatment or sequelae, to account for persisting maladjustment. Such ex-patients came from insecure, neglectful, rejecting or grossly overprotective homes, and their sibs also tended to be psychologically disturbed. Many of these neurosis-inducing homes had been further stricken by the illness, absence or death from tuberculosis of one or both parents, or of some other close relation.

Apart from pathogenic family patterns our findings are that severe mental subnormality, residual cerebral dysrhythmia (even in the absence of fits) and severe-to-total bilateral toxic nerve deafness are all important contributory factors towards persistent unhappiness and maladaptation. Of the 9 survivors in the severely maladapted group 6 are grossly mentally retarded. All children rendered severely deaf have experienced great emotional suffering, and the majority remain highly vulnerable personalities.

It is generally assumed in current British children's psychiatric practice that in any large unselected group of children and young persons 10% are likely to display patterns of maladaptive behaviour that may indicate the need for psychiatric counselling and aid. Approximately 43% of the Liverpool survivors from childhood tuberculous meningitis proved to be significantly maladjusted, and, although only 13% are severely so, the high total figure of persisting social maladjustment and personal inadequacy (attributable almost invariably to combined psychological, intellectual and organic factors) affords no grounds for complacency.

Summary

Examinations were carried out 3½ to 14 years after the onset of the original illness on 65 patients who

survived one or more attacks of tuberculous meningitis. The physical, social, emotional and intellectual status of these patients has been assessed.

Physical defects, e.g. hemiplegia, weakness or incoordination of a limb, epilepsy and deafness were found in approximately one-third of the patients; significant intracranial calcification was found in 21 patients; abnormal audiograms were obtained in 26, and although hearing loss was clinically significant in few of these, obviously deaf children encountered considerable educational difficulties; abnormal EEG records were obtained in 47 patients.

Intelligence was average or above average in 40, dull normal in 13, borderline defective in 6 and mentally defective in 6 patients. Level of intelligence was not related directly to the severity of the original illness or to age, but a greater risk of intellectual impairment was apparent in the younger patients because the disease was usually more severe in this age-group.

Normal education was possible in 35 patients, 9 attended special schools for physically or intellectually handicapped pupils and 2 were in mental deficiency institutions. Of the older patients 15 were in full-time employment and 2 were unemployable as a result of their handicaps.

38 patients were emotionally well adapted, 20 were mildly maladapted and 9 severely maladapted. Thus approximately 43% of the survivors of tuberculous meningitis were either mildly or severely maladjusted, compared with the generally accepted figure of 10% for the population as a whole.

We are indebted to the patients and to their parents for the willing co-operation which made this investigation possible, to Miss Ethel E. D'Arcy our Psychiatric Social Worker for undertaking the home and school visits, to our colleagues in the Departments of Radiology, Otorhinolaryngology and Electroencephalography, Alder Hey Children's Hospital, for their assistance in carrying out the special investigations, and to the Joint Medical Research Committee of the United Liverpool Hospitals and the Liverpool Regional Hospital Board for financial assistance.

References

Donner, M. and Wasz-Höckert, O. (1963). Late neurological sequelae of tuberculous meningitis. *Acta paediat.* (*Uppsala*), Suppl. 141, p. 34.

Hay, D. R. (1960). Diabetes insipidus after tuberculous meningitis. *Brit. med. J.*, **1**, 707.

Heikel, P. and Wasz-Höckert, O. (1963). Late radiological findings after recovery from tuberculous meningitis. *Acta paediat.* (*Uppsala*), Suppl. 141, p. 88.

Kauhtio, J., Donner, M. and Wasz-Höckert, O. (1963). Late electroencephalographic findings after recovery from tuberculous meningitis. *ibid.*, Suppl. 141, p. 78.

Lapides, M. I. (1962). Clinical features, treatment and prophylaxis of residual psychic disturbances after tuberculous meningitis in children. *Abstr. Wld Med.*, **31**, 67.

Lorber, J. (1951). Sexual precocity following recovery from tuberculous meningitis with hydrocephalus. Calcifying intracranial tuberculoma. Cerebral cyst. Optic atrophy with good vision. *Proc. roy. Soc. Med.*, **44**, 726.

—— (1958). Intracranial calcification following tuberculous meningitis in children. *Amer. Rev. Tuberc.*, **78**, 38.

—— (1961). Long-term follow-up of 100 children who recovered from tuberculous meningitis. *Pediatrics*, **28**, 778.

Medical Research Council (1948). Streptomycin treatment of tuberculous meningitis. *Lancet*, **1**, 582.

Nickerson, G. and MacDermot, P. N. (1961). Psychometric evaluation and factors affecting the performance of children who have recovered from tuberculous meningitis. *Pediatrics*, **27**, 68.

Pentti, R., Donner, M., Valanne, E. and Wasz-Höckert, O. (1963). Late psychological and psychiatric sequelae of tuberculous meningitis. *Acta paediat.* (*Uppsala*), Suppl. 141, p. 65.

Pohitonova, M. P. (1960). The present and future position in the treatment of tuberculous meningitis in children. *Abstr. Wld Med.*, **27**, 189.

Ranta, J. and Wasz-Höckert, O. (1963). Late otological sequelae of tuberculous meningitis. *Acta paediat.* (*Uppsala*), Suppl. 141, p. 50.

Schatz, A., Bugie, E. and Waksman, S. A. (1944). Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. *Proc. Soc. exp. Biol.* (*N.Y.*), **55**, 66.

Shambaugh, G. E., Derlacki, E. L., Harrison, W. H., House, H., House, W., Hildyard, V., Schuknecht, H. and Shea, J. J. (1959). Dihydrostreptomycin deafness. *J. Amer. med. Ass.*, **170**, 1657.

Todd, R. M. (1948). Streptomycin. *Brit. med. J.*, **1**, 747.

Voljavec, B. F., Orton, S. P. and Corpe, R. F. (1959). Tuberculous meningitis; prognosis and treatment. *Amer. Rev. Tuberc.*, **80**, 388.

Wasz-Höckert, O. and Donner, M. (1963). Results of the treatment of 191 children with tuberculous meningitis in the years 1949-54. *Acta paediat.* (*Uppsala*), Suppl. 141, p. 7.

Wechsler, D. (1949). *Wechsler Intelligence Scale for Children.* Psychological Corporation, New York.

Whytt, R. (1778). *Observations on the Dropsy in the Brain.* Balfour, Auld and Smellie, Edinburgh.

Williams, M. and Smith, H. V. (1954). Mental disturbances in tuberculous meningitis. *J. Neurol. Neurosurg. Psychiat.*, **17**, n.s., 173.