

## THREE CHEMOTHERAPY STUDIES OF TUBERCULOUS MENINGITIS IN CHILDREN\*

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**Summary:** Chemotherapy studies were undertaken in 180 patients with tuberculous meningitis. They were treated for 12 months with 3 regimens: the first consisted of streptomycin, isoniazid and rifampicin daily for the first 2 months, followed by ethambutol plus isoniazid for 10 months; in the second, pyrazinamide was added for the first 2 months, and in the third, rifampicin was reduced to twice weekly in the first 2 months. In the first regimen alone, streptomycin was also given twice weekly from the third to the sixth month. Steroids were prescribed for all the patients in the initial weeks of treatment. Approximately 50% of the patients were aged less than 3 years. On admission, 13% of the patients were classified as stage I, 77% as stage II and 9% as stage III. Cerebrospinal fluid (CSF) culture results were available for all the 180 patients and *M. tuberculosis* was isolated in 59 (33%). CSF smear results for acid fast bacilli were available only for the 103 patients admitted to the second and the third studies, and of these, in 60 (58%) the CSF was positive either by smear or culture.

The response to therapy was similar in the 3 studies. Despite administration of rifampicin for 2 months, the mortality was high. In all, 27% of the patients died of tuberculous meningitis, 39% had neurological sequelae and 34% recovered completely. There was a strong association between the stage on admission and the mortality rate, the deaths being highest in stage III. In the first study; when isoniazid was prescribed daily in a dosage of 20 mg/kg, 39% of the patients developed jaundice however, when the dosage was reduced to 12 mg/kg, the incidence was only 16%. In the third study, where rifampicin was administered twice a week, the incidence of jaundice was low (5%).

### Introduction

Meningitis is the commonest cause of death from tuberculosis in children. While combinations of bactericidal and sterilising drugs like streptomycin, isoniazid, rifampicin and Pyrazinamide have been found to be highly effective in the treatment of pulmonary tuberculosis in adults, information about the value of these drugs in the treatment of tuberculous meningitis is limited. Three consecutive studies were therefore undertaken by the Tuberculosis Research Centre, Madras, in collaboration with the Institute of Child Health and Hospital for Children, Madras, to evolve suitable regimens for the treatment of tuberculous meningitis in children. Preliminary findings of part of the first study have already been published (Rama-chandran, 1980). A complete report of the 3 studies, including a 1 year follow-up, is presented here.

### Plan and conduct of the studies

In all, 180 patients with tuberculous meningitis, aged between 1 and 12 years, who had received not more than 4 weeks of anti-tuber-

culosis treatment and had no evidence of renal or liver disease, were admitted to the 3 consecutive studies. The majority of patients belonged to the lower socio-economic groups and came from the urban and semi-urban areas of Madras city, while a few came from rural areas. On admission, 53% of the patients were aged less than 3 years [table 1]; only 17% were aged 5 years or more. Approximately half (53%) were males.

### Criteria for diagnosis

The diagnosis was based on clinical symptoms and signs, notably fever, vomiting, irritability, apathy, refusal to play, anorexia, constipation, well-marked meningeal signs, impaired consciousness, coma and widespread paralysis. The cerebrospinal fluid [CSF] findings were also taken into consideration.

### Investigations

A 1 TU Mantoux test (PPD batch RT 23 with Tween 80) was done on admission, and read at 2 or 3 (occasionally 4) days. Antero-posterior chest radiographs were taken on ad-

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mission and at the end of treatment. Urine tests for acetylisoniazid, bile salts, bile pigments, urobilinogen, albumin and deposits were done on admission and at 1 and 2 months; then, after, tests for albumin and acetylisoniazid were done every month. Estimations of serum aspartate, alanine amino-transferase and alkaline phosphatase activities, serum bilirubin, blood urea, plasma creatinine, haemoglobin, blood platelet count and total and differential white blood cell counts were done on admission, at 1 and 2 months and the end of chemotherapy. Biochemical, cytological and bacteriological examinations of the CSF were done on admission and every 2 weeks during the first 2 months and subsequently every month until the results were normal.

*Stage I:* Patients were conscious and had mainly non-specific symptoms, with or without signs of meningeal irritation, but no focal neurological signs. Diagnosis was established mainly on CSF findings.

*Stage II:* Patients were mentally confused and/or had neurological signs.

*Stage III:* Patients were comatose and had gross neurological signs.

**Chemotherapeutic regimens**

All patients were to be treated for 12 months. The regimens in the 3 studies were as follows:

*First study: Regimen I:* 2SHR/4S<sub>2</sub>EH/6EH: Streptomycin plus isoniazid plus rifampicin daily for 2 months, followed by ethambutol plus isoniazid daily supplemented by streptomycin twice a week for 4 months, followed by etham-butol plus isoniazid daily for 6 months.

*Second study: Regimen III:* 2SHRZ/IOEH: Streptomycin isoniazid plus rifampicin plus pyrazinamide daily for the first 2 months, followed by ethambutol plus isoniazid daily for 10 months.

*Third study: Regimen III:* 2R<sub>2</sub>SHZ/IOEH: Streptomycin plus isoniazid plus pyrazinamide dully and rifampicin twice a week for the first 2 months, followed by ethambutol plus isoniazid daily for 10 months

The streptomycin dosage was 40 mg/kg body-weight, rifampicin 12 mg/kg, ethambutol 17.5 mg/kg and pyrazinamide 30 mg/kg. The first 28 patients received isoniazid in a daily dosage of 20 mg/kg, a dose used by most paediatricians for the treatment of tuberculous meningitis. However, a substantial proportion of the patients developed jaundice during the initial phase of treatment with isoniazid and rifampicin. Consequently, the dosage of isoniazid was reduced to 12 mg/kg and this dosage was prescribed to patients admitted to the second and third studies, also. In addition to anti-tuberculosis chemotherapy the patients received supportive therapy (intravenous fluids, anti-oedema measures, anti-convulsants, vitamins etc.). As a general policy, corticosteroids were administered to all the patients for a period of 6-12 weeks. Seriously ill patients (stages II and III) were given dexamethasone by the intramuscular route in a dosage of 2-4 mg every 6-8 hours for the first 3 or 4 days followed by oral prednisolone (1-2 mg/kg bodyweight).

**General management**

Patients were hospitalised for the first 2

TABLE I  
*Distribution of patients according to age on admission*

Age(year)	Patients	
	No.	%
1----	56	31
2-	39	22
3-	30	17
4-	25	14
5-	12	7
6-	9	5
7-	3	5
8-	4	
9-	1	
10-	1	
Total	180	101

**Classification according to stage of disease on admission**

At the time of admission, patients were examined in detail with special reference to the nervous system and were classified into 3 stages, adopting the following classification which is a modification of the one used by the British Medical Research Council [1948].

months of treatment. Those who were discharged during the first 2 months attended as out-patients daily for chemotherapy until they completed 2 months. After 2 months the patients attended twice or once a week (or once in 15 days if they lived outside Madras) to collect a supply of drugs. Their medication was fully supervised on the days they attended. Progress was assessed mainly by monthly clinical examination including a detailed neurological examination, and if indicated, a CSF examination. The patients were followed up for 12 months after completion of therapy.

### Surgery

Patients clinically diagnosed to have developed hydrocephalus were investigated, and surgery (ventriculo-peritoneal shunt) was performed, if indicated.

### Bacteriological procedures

CSF specimens were examined by fluorescence microscopy and cultured on Lowenstein-Jensen medium with and without pyruvate, a selective 7H11 medium with antibiotics and liquid Kirchner medium [Allen et al, 1983]. Tests of sensitivity to streptomycin, isoniazid [Tuberculosis Chemotherapy Centre, Madras 1960], rifampicin [Tuberculosis Research Centre, Madras 1983] and ethambutol [Subbammal et al, 1978] were performed. All positive cultures were identified [Marks, 1976 and Venkataraman et al, 1977].

### Definitions of drug resistance

*Streptomycin*: A resistance ratio (RR) of 8 or more on 1 culture, or 4 followed by 8 or more on a repeat test.

*Isoniazid* : (a) Growth (defined as 20 colonies or more) on 1 mg/1 or a higher concentration, or growth on 0.2 mg/1 followed by the same result on a repeat test.

*Rifampicin* ; Growth on 64 mg/1  
*Ethambutol*; Growth on 4 mg/1.

### Results

In all, 180 patients were admitted to the 3 studies. Of these, 77 patients were treated with regimen I (first study), 29 with regimen II (second study) and 74 with regimen III (third study). A tuberculin test with 1 TU yielded an induration of 10 mm or more in 50% of the patients. In all, 84 (47%) patients had a history of contact with a known case of pulmonary tuberculosis and 99 (55%) had an abnormal chest radiograph suggestive of pulmonary tuberculosis. On admission, 24 (13%) patients

were classified as stage I, 139 (77%) as stage II and 17 (9%) as stage III. There was a suggestion that the stage of the disease on admission was related to the age. Thus, the proportion of patients with stage II or stage III disease was 115 (92%) of 125 in children aged 3 years or less compared with 41 (75%) of 55 in those aged 4 years or more ( $P < 0.01$ ). A CSF protein value of more than 40 mg/100 ml on admission was observed in 96% of the patients. The nutritional status of the patients was very poor. Using growth standards set up by the Indian Council of Medical Research (Reddy et al 1976), only 2% of the patients were considered normal, while 64% had mild to moderate malnutrition and 34% severe malnutrition, based on deficit in weight for age [I.C.M.R. 1972].

CSF smear results for acid fast bacilli were available for the 103 patients in the second and third studies only. Of these, in 24 (23%) smear alone was positive, in 12 (12%) both smear and culture were positive and in 24 (23%) culture alone was positive. Thus in the 103 patients for whom both smear and culture results were available, the diagnosis was bacteriologically confirmed in 58%. Of the 180 patients, *M. tuberculosis* was isolated from the CSF in 59 (33%) patients, 9 of 24 stage I, 43 of 139 stage II and 7 of 17 stage III, the proportions in the different stages being similar. Of these 59, the culture was positive on admission in 46 patients, within 2 months in 11 and at 4 and 8 months in 2. Sensitivity test results for streptomycin, isoniazid and rifampicin were available for 56 patients and for ethambutol in 48 patients. The cultures were resistant to streptomycin in 1 (2%), to isoniazid in 3 (5%), to ethambutol in 1 (2%) and to both streptomycin and isoniazid in 9 (16%). All the cultures were sensitive to rifampicin.

### Response to treatment

Of the 180 patients admitted to the three studies, 3 died of non-tuberculous causes and 21 were discharged against medical advice before completing the therapy (see page 61). On follow up of these discharges, 7 were reported to have died within 1 week of discharge. Since the general condition of all the 7 was very poor and the cause of death was most likely to be tuberculous meningitis, they were included in the analysis. The analysis of response to treatment was therefore based on 163 patients.

The neurological sequelae were classified as follows: Mild residual damage implied such sequelae as hyperactivity, irritability, mild perceptual defects and limited motor impairment such as facial paresis or monoparesis. Moderate residual damage included such defects as hemiparesis, involuntary movements and substantial

mental impairment. Patients with severe residual damage usually remained unconscious and even if consciousness was regained, they were incapable of independent existence.

Table II gives the response to treatment in the 3 studies. It can be seen that 27% of the 163 patients died of tuberculous meningitis, 39% had neurological sequelae (including 7% with severe sequelae) and 34% made a complete recovery. The results in the 3 studies were similar.

Table III gives the response according to the stage of the disease on admission. There was a clear association between the stage on admission and tuberculous deaths, the mortality being 9% for stage I patients, 25% for stage II and 73% for stage III. Conversely, 78% of stage I patients recovered fully, compared with

29% of stage II and 7% of stage III. An interesting finding was that, in both the stage I patients who died and the one who had severe neurological sequelae, *M. tuberculosis* was grown in CSF, the strains being resistant to both streptomycin and isoniazid. There was no association between the age of the patient and tuberculous deaths (Table IV).

Of the 44 deaths, 17 (39%) occurred in the first week, 7 being from amongst the 15 stage III patients (Table V). In all, 29 (66%) died within 4 weeks, 5 (11%) in the second month, 4 (9%) in the third month, 4 (9%) between the fourth and the sixth month and 2 (5%) between the seventh and the twelfth month. The last available CSF result was biochemically abnormal in 41 of the 44 (and bacteriologically positive in 11). The other 3 patients, who died in the fifth,

TABLE IV

*Tuberculous deaths related to age on admission*

Age( years)	No. of Patients	TB deaths	
		No.	%
1—	49	16	33
2—	37	8	22
3 _	29	7	24
4—	21	6	(29)*
5 _ .	12	4	(33)
6—	9	}	
	2		
	3		
	1		
	163		

**Hydrocephalus:** Fourteen patients (2 stage I, 10 stage II, 2 stage III) were suspected of having developed hydrocephalus. Of these, 1 died before investigations could be carried out and in 5, permission for investigations was refused. Of these 5, 3 died (in the fourth, seventh and ninth months), while the remaining 2 had moderate and severe neurological sequelae respectively at the end of chemotherapy. The diagnosis of hydrocephalus was confirmed in the remaining 8, and 7 of these underwent surgery, a ventriculoperitoneal shunt (3 in the second, 1 in the third, and 3 in the twelfth month of treatment). At the end of chemotherapy 1 (stage I) of the 7 had complete recovery, 3 (I stage I, 2 stage II) had moderate sequelae, 2 (both stage II) had severe sequelae and 1 (stage III) had died of tuberculosis. The eighth patient (stage II), who did not have surgery, was reported to be alive at 24 months with mild sequelae.

**Blindness and optic disc changes ;** Sixteen patients developed varying degrees of pallor of the optic discs while on treatment (5 while receiving isoniazid plus ethambutol). Six of these died before completing the treatment. The remaining 10 recovered and had normal fundus findings and vision at 24 months.

\*Figures in brackets indicate percentages based on a total fewer than 25.

seventh and ninth months had severe neurological sequelae with normal CSF findings.

There was no association between drug resistance and response to treatment but the numbers were small (Table VI).

Twelve patients developed optic atrophy with blindness (7 during treatment with ethambutol plus isoniazid) which persisted until the end of chemotherapy. On follow up, 7 patients had died and the remaining 5 continued to have optic atrophy and blindness at 24 months.

Four patients had developed cortical blindness during the first month of therapy; all of

TABLE V *Interval between admission and*

*death, according to stage of disease on admission*

Stage of disease	No. in analysis	Tuberculous deaths									
		Total	Week of treatment				Month of treatment				
			1	2	3	4	2	3	4	5-6	7-12
I	23	2	1	0	0	0	0	0	1	0	
II	125	31	9	4	3	3	4	4	3	1	
III	15	11	7	2	0	0	1	0	0	1	
All	163	44	17	6	3	3	5	4	4	2	

TABLE VI

## Culture and sensitivity results related to response to treatment

Initial culture/sensitivity findings	Total	TB death		Complete No.	Recovery %
		No.	%		
Culture negative	108	30	28	40	37
Sensitive to <b>S, H and R</b>	39@	8	21	12	31
<b>Resistant to S,H or SH</b>	13*	5	(38)**	3	(23)
Sensitivity test result not available	3	1	(33)	0	(0)

@ 1 patient had resistance to ethambutol alone.

\*Of these, 1 had resistance to streptomycin, 3 to isoniazid and 9 to both drug

\*\*Figures in brackets indicate percentages based on a total fewer than 25.

them regained their vision by the end of 4 months.

Of the 12 patients (aged between U—7 years) who developed ocular complications during treatment with ethambutol plus isoniazid, in the first 9, treatment with ethambutol was

subsequent 3 patients, to be on the safe side, ethambutol was discontinued and PAS substituted.

In the remaining 20 patients, who developed the ocular complications in the first 2 months of therapy with streptomycin, isoniazid and rifampicin, ethambutol was given in the continuation phase.

#### Discharge against medical advice

In all, 21 patients were discharged against medical advice before completion of treatment, 15 in the first phase of therapy and the remaining 6 subsequently.

Of the former 15, 2 could not be traced. Twelve patients were reported to have died; 7 within 1 week of discharge, 1 in the second week, 1 in the third week, 1 in the second month, 1 in the third month and the last, 6 months after discharge. The last 2 patients had received anti-tuberculosis treatment from other sources after discharge. The thirteenth patient (stage I on admission), whose condition was good at the time of discharge, was found to be alive 24 months after admission, with no sequelae.

Of the remaining 6 patients (all stage II), 3 were discharged during the third month (on

follow-up, 2 had died within 2 months of discharge and 1 was alive with moderate sequelae at 24 months) and 2 during the fourth month (on follow-up, 1 had severe sequelae and the other could not be traced). The sixth patient, who was discharged in the sixth month, was reported to have died 6 months after discharge: the cause of death may not have been connected with meningitis, as she had very good clinical improvement and the CSF findings were normal at the time of discharge. Death was attributed to tuberculous meningitis in the others.

#### Non-tuberculous deaths

Three patients (all stage II) died from non-tuberculous causes. One died in the fifth month, possibly due to an anaphylactic reaction after an injection given by a private practitioner for fever and respiratory infection. The other 2 died during the ninth month: the first due to diarrhoea with dehydration; the second developed vomiting of sudden onset and died at home the next day. Since the clinical improvement was substantial and the last available cerebrospinal fluid findings were normal, the cause of death is unlikely to have been tuberculosis in either.

#### Adverse reactions

This analysis is based on all the 180 patients admitted to treatment.

*Jaundice:* This was the major problem in the first 2 studies. In all, 30 patients developed jaundice in the 3 studies, all except 1 during the first 2 months, most of them in the second and third weeks (Table VII).

TABLE VII  
Incidence of jaundice in the first 2 months\*

Study	Regimen	INHdose (mg/kg)	Total patients	Patients who developed jaun- dice		Week of onset of jaundice					
				No	%	1	2	3	4	5	6-8
First	2SHR/4S <sub>2</sub> EH/6EH	20	28	11	39	1	4	5	0	1	0
	2SHR/4S <sub>2</sub> EH/6EH	12	49	8	16	1	2	4	1	0	0
Second	2SHRZ/10EH	12	29	6	21	0	4	1	0	1	0
Third	2R <sub>2</sub> SHZ/10EH	12	74	4	5	1	0	3	0	0	0
All			180	29	16	3	10	13	1	2	0

\*One other patient (.first study) developed jaundice in the fifth month.

In the first study, when isoniazid was administered in a dosage of 20 mg/kg, the incidence of jaundice was 39% of 28; when the dosage was 12 mg/kg, the incidence was much less, namely, 16% of 49. In the second study, where pyrazinamide (30 mg/kg) was added to streptomycin, rifampicin and isoniazid (12 mg/kg), the incidence of jaundice was 21 % of 29. In the third study, the same drugs as in the second study were administered but rifampicin was given only twice a week; the incidence of jaundice with this regimen was low, namely 5% of 74.

In the patients who developed jaundice, rifampicin (first study) or both rifampicin and pyrazinamide (second and third studies) were discontinued while the other drugs were continued.

Of the 29 patients who developed jaundice during the first 2 months of therapy, 24 recovered fully, the liver function test results returning to normal; however 6 of these patients died subsequently due to tuberculous meningitis. The other 5 had died while still jaundiced. Of these, 1 patient died on the day jaundice was noticed and a definite cause of death could not be determined; 2 died while recovering from jaundice with the serial liver function test values showing considerable improvement, and death was attributed to tuberculous meningitis, jaundice being a complicating factor. The fourth patient had, in addition to tuberculous meningitis, miliary tuberculosis, enteric fever and herpes, and died of hepato-cellular failure. In the last patient, jaundice persisted up to the time of death, 10 days after terminating rifampicin and pyrazinamide; a diagnosis of viral hepatitis could not be excluded.

Only 1 patient developed jaundice after 2 months (in the fifth month) while on isoniazid and ethambutol, and was diagnosed as a case of viral hepatitis. This patient recovered fully with empirical treatment.

*Skin reactions* : Two patients, 1 in the first and the other in the third study developed skin reactions, both in the first month of treatment. The first patient developed extensive morbiliform eruptions with crusting and exfoliation. Rifampicin was stopped and the patient recovered completely. The second patient developed vesicular eruptions over the lower abdomen and groins. All anti-tuberculosis drugs were withheld for 1 week and the patient recovered fully. The treatment was resumed uneventfully.

*Arthralgia*: One patient in the second study developed swelling of the elbow and knee joints during the first month. Pyrazinamide was stopped and the swelling diminished during the next 3 weeks. He could not be followed up further as he died of tuberculous meningitis.

#### Treatment continued beyond 12 months

Of the 163 patients in the analysis of efficacy, 119 completed treatment. In 23 of these, anti-tuberculosis treatment was continued beyond 12 months for the various reasons given below. The extended period of therapy was 1-6 months in 12 patients, 7-12 months in 10, and 24 months in 1 patient.

(a) *CSF abnormality, surgery or neurological complications*: Anti-tuberculosis treatment was continued on the advice of neuro-surgeons in

9 patients of whom 5 underwent a ventriculo-peritoneal shunt. Two others had only raised CSF protein values and in the remaining 2, the parents refused permission for investigations in ! and surgery for hydrocephalus in the other. Of the 9 patients. 4 died in the thirteenth, fourteenth, fifteenth and twenty-third months and all had severe sequelae with normal CSF findings. Considering the 5 patients with a raised CSF protein value, in 3 the CSF values became normal, at the fifteenth, twenty-second and twenty-third months while in the other 2, the high values persisted until the twenty-fourth month. The neurological status of the 5 patients alive at 24 months was as follows: 1 had severe sequelae. 2 moderate and 1 mild, while the last patient recovered fully,

(b) *Persistence of abnormality on chest radiograph:* In 72 of 119 patients who completed treatment, the chest radiograph was abnormal on admission. At 12 months, the lesions had cleared completely in 47, while there were calcified lesions in 15; in 1 patient the radiograph could not be repeated. In the remaining 9 patients, the radiographic shadows did not clear completely. In 1 patient, who had a normal radiograph on admission, an abnormality (enlargement of the carinal gland) was detected at the end of therapy. In this, and the 9 patients with persistent abnormality, anti-tuberculosis treatment was continued beyond 1 year. The CSF became biochemically normal and bacteriologically negative in all the 72 patients during the course of the 12 months.

(c) *Spinal lesions:* Two patients had spinal tuberculosis in addition to tuberculous meningitis (diagnosed on admission on one and detected in the sixth month in the other). In both, chemotherapy was prolonged on the advice of the orthopaedic surgeon. The CSF at the end of 12 months was normal biochemically as well as bacteriologically in both the patients. At 24 months, both the patients had made a complete recovery.

(d) *Other reasons:* In 2 patients it was considered inadvisable to stop anti-tuberculosis treatment at the end of 1 year on account of severe respiratory infection in 1 patient with severe sequelae (the patient died, in the twenty-first month), and the detection of pulmonary tuberculosis in one of the parents of the second (patient was alive with moderate sequelae at 24 months),

#### Status at 24 months

There were 119 survivors at the end of 12 months—12 with severe sequelae, 36 with moderate sequelae, 16 with mild sequelae and 55 with complete recovery.

Of the 12 patients who had severe sequelae, 5 died, in 6 the condition remained the same and 1 had improved (to moderate sequelae). Of the 36 patients with moderate sequelae, 3 died (2 of sequelae and 1 of non-tuberculous cause), 17 showed no improvement in neurological status, 13 showed slight improvement, 1 improved to mild sequelae, while the remaining 2 recovered completely. Of the 16 patients with mild sequelae, the status remained the same in 13. 1 showed slight improvement and the remaining 2 recovered completely. In the complete recovery group of 55 patients, 1 died from a complication of typhoid fever (perforation of the gut) while the recovery was maintained in the remaining 54 patients.

The survivors at the end of 24 months are being followed, up further.

#### Discussion

The results of the present studies show a direct relationship between the stage on admission and death from tuberculous meningitis, the proportions being 9% for stage I patients, 25% for stage II and 73 % for stage III. Similar observations have been made by others (Smith 1964, Sister Gabriel, 1979 and Girgis et al, 1976, 1978). These results suggest that early diagnosis and initiation of therapy is more important than the choice of drug regimen.

Ethambutol has been used in the treatment of childhood tuberculosis in India [Mankodi et al, 1970. Bhatia et al, 1975 and Dingley et al, 1974]. In all these studies, the dosage employed was 25 mg/kg for 2-3 months followed by 15 mg/kg, and the reported incidence of ocular toxicity was negligible. In a study comparing different ambulatory regimens for spinal tuberculosis in Korea, 45 children (aged between 1 and 15 years) were treated with ethambutol ((5-25 mg/kg) plus isoniazid daily for 9 or 18 months. All the patients were assessed monthly and tests for visual acuity, colour vision and macular thresholds and visual fields were undertaken. There was no evidence from any of the assessments in any patient of ocular toxicity due to ethambutol (unpublished data from MRC Working Party on Tuberculosis of the Spine—Personal communication from Prof. Wallace Fox). A study by Leibold [1966] suggests that, on a short term basis it is safe to prescribe as much as 45 mg/kg. In the present series of studies, ethambutol was used in a dosage of 17.5 mg/kg, a dose unlikely to cause retrobulbar neuritis. Optic chiasmatic-araehmoiditis resulting in visual impairment or even blindness, with or without associated hydrocephalus, is a common complication of tuberculous meningitis. All 12 patients in the present studies who developed blindness with persistent optic atrophy had moderate to

severe neurological damage and this was most likely to have been, the cause of blindness.

The American Thoracic Society [1969] has recommended the systemic administration of corticosteroids in the management of tuberculous meningitis, a view which is supported by others [Lincoln et al 1963 and Kocen, 1977]. In the present series of studies, steroids were administered to all the patients as a routine.

Jaundice was a major problem in the first 2 studies, where daily therapy was given. The incidence was 39% in study I with isoniazid 20 mg/kg and 16% when the dose was reduced to 12mg/kg, and 21 % in study II where pyrazinamide 30 mg/kg was added to the regimen. Because of this high incidence of jaundice, in study III rifampicin was given only twice a week instead of daily during the first 2 months and the incidence fell to 5 %. The above findings suggest that the use of daily rifampicin (12 mg/kg) with a high dose of isoniazid (20 mg/kg) causes a high risk of hepatotoxicity in children with tuberculous meningitis. The addition of pyrazinamide did not appreciably alter the incidence of hepatotoxicity; a similar conclusion was reported by Girling [1978] in an extensive review of the literature. The rhythm of administration of rifampicin appeared to play a role, as regimens containing daily rifampicin carried a greater risk of hepatic toxicity than the regimen where it was given intermittently. Although the present series of studies were non-concurrent and conclusions call for caution, similar results observed in studies from this Centre on patients with spinal and pulmonary tuberculosis [Parthasarathy et al, 1986] support the above deductions. Other factors that could have contributed to the high incidence of jaundice in children with tuberculous meningitis have been dealt with by Parthasarathy and others [1986].

In conclusion, the results of the 3 studies show that, despite use of rifampicin-containing regimens, the mortality was high, especially in stages II and III, while the prognosis was good in stage I. This emphasises the need for early diagnosis and prompt treatment. The combination of isoniazid 20 mg/kg and rifampicin 12 mg/kg was associated with unacceptable levels of hepatotoxicity. Our findings suggest that, in view of the low hepatotoxicity, the third regimen consisting of 2 months of daily streptomycin, isoniazid and pyrazinamide plus twice weekly rifampicin followed by 10 months of daily ethambutol and isoniazid is a suitable regimen. It is also noteworthy that there were no relapses during the follow-up period, indicating that regular therapy for 12 months is adequate for the treatment of tuberculous meningitis.

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