TREATMENT OF TUBERCULOUS MENINGITIS*

BY

JOHN LORBER, M.D., M.R.C.P.

Reader in Child Health, University of Sheffield

The incidence of tuberculous meningitis is at last rapidly diminishing in this country, yet in 1958 there were still 369 newly notified cases in England and Wales (Ministry of Health, 1959). As the untreated disease is inevitably fatal, this incidence is still an important therapeutic challenge. We can now look back on 12 years' experience in the treatment of tuberculous meningitis. In this time three main phases occurred as new specific antituberculous drugs became available. Furthermore, various adjuvants and neurosurgical techniques have been used with varying degrees of success.

Earlier Results

To place the current methods of treatment in perspective I shall briefly summarize the three main phases, on the basis of the personal experience of 210 children admitted to the Children's Hospital, Sheffield, between 1947 and 1958 (Table I). Most of these children were referred from other hospitals, and the composition of this series is weighted by advanced cases, which make up more than a quarter of the whole group.

TABLE I.—*Results of Treatment in* 210 *Children Admitted with Tuberculous Meningitis* (1947–58)

Antibiotic Treatment	Total No. of Cases	Alive			
		Total		No Neurological Sequelae	
		No.	%	No.	%
Streptomycin	82	30	36	20	24
Streptomycin + P.A.S. ..	48	35	73	30	63
Isoniazid, streptomycin, and P.A.S.	80	66	83	55	69
All forms	210	131	63	105	50

In the first phase, up to 1950, streptomycin was the only antibiotic available, and was used in prolonged intramuscular and intrathecal courses. Relapses were common. Sometimes hundreds of intrathecal injections were given (Illingworth and Lorber, 1951). We treated 82 children this way and 30 (36%) of them are alive now, but only 20 (24%) have no neurological sequelae.

The second phase was the combination of streptomycin with P.A.S., which was introduced in 1950 (Lorber, 1954a). This combination led to a considerable decrease in the number of intrathecal injections, but, even so, 10 out of 48 children each required the frightening total of 135 injections. The results were much better: 35 (73%) are alive now, and 30 of them (63%) have no neurological sequelae. This total figure hides the fact that all the improvement occurred in children who were conscious on admission (Fig. 1). Of 58 children who were treated with streptomycin alone and were conscious on admission 41% are alive, as compared with 86% of 37 treated with streptomycin and P.A.S. The proportion of survivors among those 35 who were unconscious on admission remained the same. Only one-quarter of these have survived and all have a residual neurological lesion.

Role of Isoniazid

The third phase started with the introduction of isoniazid in 1952 (Lorber, 1954b, 1956). Isoniazid is the most potent and least toxic of the antituberculous drugs. It freely diffuses into the C.S.F., so its intrathecal administration is only rarely necessary. As a consequence the need for prolonged courses of intrathecal streptomycin has been much reduced, though I know of no evidence to suggest that its use can be entirely abandoned with safety. Between 1952 and 1958 we treated 80 new cases with the combination of isoniazid, streptomycin, and P.A.S., and we progressively reduced the arbitrary minimum number of intrathecal streptomycin injections from courses of 45 to 25, then to 20, and now to only 10 injections. More intrathecal treatment is given if the clinical condition of the patient or the C.S.F. findings are unsatisfactory at any time after the conclusion of the 10 injections. Second intrathecal courses had to be given in their first attack to 15 children out of the 66 who survive, and tubercle bacilli reappeared in the C.S.F. in several of these while receiving by mouth 20 mg. of isoniazid per kg. body weight daily, even though they were in an early stage. These observations are my strongest argument against abandoning all intrathecal treatment. The overall survival rate in the 80 isoniazid-treated children is 83%. Of the 55 who were conscious on admission 52 (95%) survived and 50 (91%) have no mental or neurological sequelae. This represents a further advance on the

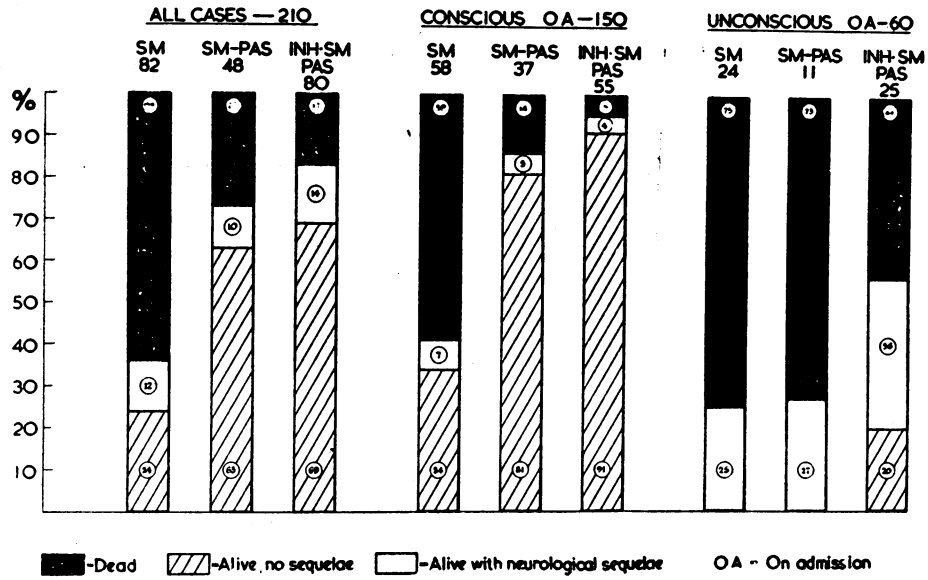

FIG. 1.—Results of treatment of tuberculous meningitis according to treatment given and the stage of consciousness on admission (1947–58). Minimum follow-up, 18 months.

*Read to the Section of Neurology and Neurosurgery at the Joint Annual Meeting of the British Medical Association and the Canadian Medical Association, Edinburgh, 1959.

good results achieved by the combination of streptomycin and P.A.S.

Of the three children who died, one was an 8-month-old infant who had combined tuberculous and influenzal meningitis; the second was an extremely emaciated boy of 7 years with advanced miliary tuberculosis and an established spinal block who went into uncontrollable status epilepticus shortly after admission. Both these received systemic and intrathecal cortisone as well, but it failed to save their lives. The third was a girl who died after a stormy course with gross disturbance of her electrolyte balance. Infarction of the adrenals was found at necropsy. This happened before the days of cortisone. It seems, therefore, that our current methods of treatment give satisfactory results in children who are conscious on admission, and uneventful recovery can be expected in almost all cases.

The situation, however, is still far from satisfactory in children who are in the advanced stage on admission (Table II). Out of 25 only 14 (56%) survive. At least,

TABLE II.—*Results of Treatment of Children Who Were Unconscious on Admission* (1947-58)

Antibiotic Treatment	No. of Cases	Alive			
		Total		No Neurological Sequelae	
		No.	%	No.	%
Streptomycin with or without P.A.S.	35	9	26	0	0
Isoniazid, streptomycin, and P.A.S.:					
Under 3 years old	16	8	50	0	0
3 years or older	9	6	67	5	55

this is a great improvement on the pre-isoniazid results, especially as five children have no neurological sequelae. All these five were over 3 years of age on admission. Of children who were unconscious and under 3 years of age on admission, we still have not been able to cure in 12 years a single child completely. It is clear that our main therapeutic efforts in the future must be directed towards finding better methods of treatment for this group.

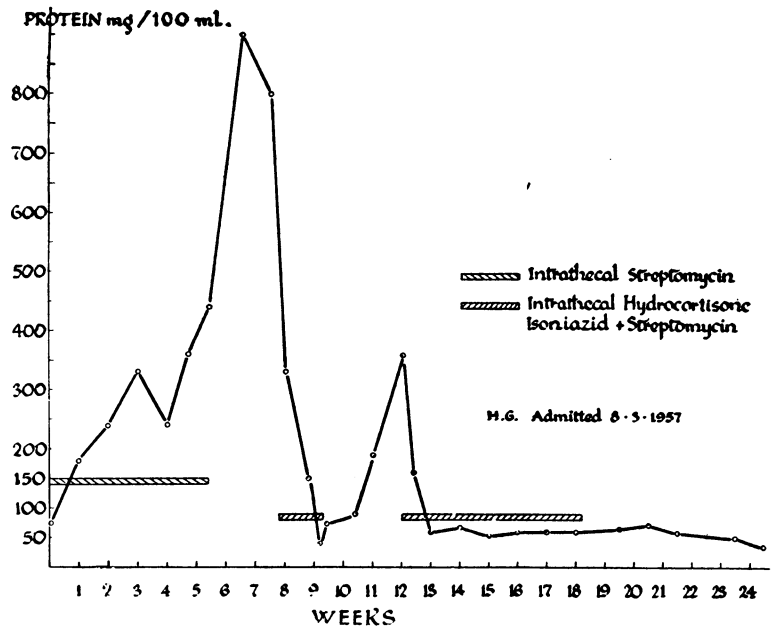

FIG. 2.—Effect of intrathecal hydrocortisone on the C.S.F. protein in a case with spinal block. The initial short course was followed by a relapse.

Seven children treated with isoniazid relapsed months or years after apparently complete recovery from their first attack. None of these were advanced cases on admission and all survived their second attack, though their clinical courses were often stormier, the duration of the disease and its treatment was longer, and in some the tubercle bacilli were much less sensitive to the main antibiotics than during their first attack. For this reason three of them were given intrathecal isoniazid to ensure a much higher C.S.F. concentration. Two children who made no headway on the three main antibiotics were given intramuscular viomycin with excellent effect when the sensitivity tests revealed that their tubercle bacilli had become very resistant to the three standard drugs.

Use of Adjuvants. Steroid Treatment

Among the important adjuvants, we used intrathecal tuberculin for several years in those patients who made poor progress on the standard treatment (Smith and Vollum, 1950). Occasionally it led to excellent results, but this form of treatment was a severe ordeal for the children, and was not without serious danger. When it appeared that cortisone or hydrocortisone might in some respects act in a similar way (Michel and Pulver, 1955) but without causing severe constitutional upset, we decided to use these drugs in selected cases in preference to P.P.D.

We now use systemic cortisone in all children who are either under 1 year of age or are unconscious on admission, as well as in all children who are severely toxic from advanced miliary tuberculosis. The duration of steroid treatment varies, but rarely exceeds one month. Intrathecal hydrocortisone is used in children with threatened or established spinal block. It is much more successful in restoring normal C.S.F. circulation in early than in well-established cases. The duration of intrathecal hydrocortisone treatment is determined by trial and error. If it is too short the C.S.F. signs of impending spinal block will reappear and can be reversed by a further course (Fig. 2). This is a very efficient treatment, but it is not free of danger. Secondary infection may be introduced, and, under cortisone cover, may remain silent both clinically and on examination of the C.S.F. For this reason we always combine intrathecal hydrocortisone with streptomycin, isoniazid, and penicillin in a "cocktail."

Altogether 15 patients have been treated with steroids up to 1958 and nine are alive (Table III). Of the six children who died I have already described two who were conscious on admission. A third baby survived, obtained a normal C.S.F., completed her treatment, and went home. She had severe mental and neurological sequelae, and died at home several months later of an unknown cause. The fourth and fifth had double meningitis, the second organism being the pneumococcus and staphylococcus respectively. These double infections were present at the time the children were admitted. Finally, the sixth child died a biochemical death. He developed a severe hypokalaemia which was not corrected even with intravenous administration of potassium. At necropsy the tuberculous meningitis

TABLE III.—15 *Children Treated with Corticosteroids as Adjuvant* (1955–8)

Route and Drug	Total	Alive and Well	Alive with Sequelae
Systemic cortisone	8	1	4
Systemic cortisone plus intrathecal hydrocortisone	5	2	1
Intrathecal hydrocortisone ..	2	1	0
	15	4	5

was found to be almost healed. This case illustrates one of the dangers of using drugs which may interfere with the electrolyte balance, and one must guard against this by frequent checks on the serum electrolytes, particularly in those treated with cortisone or viomycin.

It is not possible to show as yet in a statistically acceptable way that cortisone treatment contributed to the improvement of the results, particularly in our advanced cases. We cannot embark on a controlled trial as we no longer have sufficient cases to treat. We are satisfied, however, that used intrathecally it can prevent a threatened spinal block, and used systemically it can diminish the severe toxic state in the first few days of antibiotic treatment. None of our cortisone-treated children died in the first two weeks after admission, however deeply unconscious they were. In the past such children often died within a few days of admission and before antibiotic treatment had its full chance to exert its effect.

Current Treatment

To summarize our present routine of treatment (Table IV), it consists of a minimum six-months course of isoniazid by mouth, in divided doses of 20 mg./kg. daily together with 40 mg. of streptomycin per kg. given intramuscularly in a single daily dose. P.A.S. is given initially, but is continued for six months only if there are no side-effects. Viomycin is given twice weekly intramuscularly to children whose organisms are proved or strongly suspected to be resistant to at least one of the main antibiotics. Selected children are treated with cortisone according to the indications already outlined. The oral dose is up to 300 mg. daily, gradually reducing to 100 mg. daily, or its equivalent if any other corticosteroid is used. The dose of hydrocortisone intrathecally is 10–25 mg. according to age.

All children receive 10 intrathecal injections of streptomycin in doses of 20 to 50 mg. per injection. The first six are given daily, the others follow on alternate days. More injections are given if necessary. Intrathecal isoniazid is given to those who are given intrathecal hydrocortisone or whose organism is less sensitive to isoniazid. Pyridoxine (vitamin B_6) is given routinely in doses of 40 mg. daily to all children to guard against the neurotoxic effects of isoniazid. This is an essential precaution, as all the toxic manifestations of isoniazid, such as fits, disorientation, blindness, and paralysis, could easily be attributed to the complications of the meningitis itself. Finally, to guard against convulsions, which often have such disastrous effects, one must give full doses of anticonvulsants, at least until the child is well on the way to recovery.

TABLE IV.—*Current Treatment of Tuberculous Meningitis*

	Systemic	Intrathecal
Specific treatment:		
Isoniazid ..	20 mg./kg. daily for 6 months or longer	Occasional: 20–50 mg. per dose
Streptomycin ..	40 mg./kg. daily for 6 months or longer (maximum 1 g. daily)	10 injections (more if necessary): 20–50 mg. per dose
P.A.S.	If well tolerated: up to 5 g. daily	—
Adjuvant treatment:		
Cortisone (or other steroids)	1. In infants under 1 year of age 2. In all advanced cases for about 1 month	—
Hydrocortisone	—	In threatened or established spinal block
Pyridoxine ..	40 mg. daily	
Anticonvulsants	For 1–2 months	

The C.S.F. should be checked weekly at first, and later, when progress is obviously very satisfactory, at less frequent intervals, until one month after the discontinuation of treatment. No further examination is then necessary, unless there is the slightest suspicion on clinical grounds that all may not be well and a relapse is feared. If the child relapses, the second course of treatment should be longer, usually at least a year, and he will often require more intensive intrathecal treatment.

All this still sounds formidable, though it is trivial compared with the treatment which was given 10 years ago. Nevertheless, one would give a totally erroneous impression if one finished the description of our treatment with these technical details. In practice, things are much more cheerful. The large majority of children are much better within a week of admission, are afebrile, and are allowed to get up and play in a very pleasant ward which used to be the conservatory of a stately mansion. They wander into the adjoining playroom with its full array of toys and books for all ages and its television set. Alternatively, in good weather they will go through the french windows into an extensive garden where they play games. Teachers look after children of school age and they start their lessons within a week or two of admission. We have even had children taking their 11-plus examination while still under treatment.

We do not like to keep small children in hospital and away from their families a day longer than is essential. Pre-schoolchildren who live in the city or not too far out are therefore sent home after the first month of treatment if they are well, and they receive their daily injections from a health visitor. Their treatment is supervised from the out-patient clinic and the C.S.F. is checked at their attendances. This policy is very popular, and we had good co-operation from the family doctors, health visitors, and the parents, and so far have had no cause to regret this liberal approach. We prefer to keep children of school age in hospital longer, because otherwise their education would be unnecessarily interrupted. When we do send them home they are ready to resume ordinary attendances at school the next day.

Summary

In the course of 12 years 210 consecutive children were admitted and treated for tuberculous meningitis. Of these 131 (63%) survived, and 105 (50%) have no neurological or mental sequelae. The results progressively improved with increased experience in management, and with the introduction of P.A.S. followed by isoniazid as specific anti-tuberculous drugs and P.P.D. and corticosteroids as adjuvants. Since the introduction of isoniazid 66 out of 80 children (83%)

survived, and 55 of them have no sequelae. The most difficult patients are those who are under 3 years of age and are unconscious on admission, and none of those so far have made a complete recovery. Intrathecal streptomycin treatment has not been abandoned, but the minimum course is now reduced to 10 injections. The total duration of treatment is six months or longer, but most of this time the children are ambulant and either are treated at home or receive regular schooling in hospital. Systemic corticosteroids are used in children under 1 year of age or in those who are unconscious on admission; intrathecal hydrocortisone is of value in threatened or established spinal block.

The work on which the paper is based has been continuously in progress over 12 years. It would never have been possible without the continuous help and confidence of Professor R. S. Illingworth and without the selfless contribution of many colleagues in the region who referred their patients to us for treatment.

REFERENCES

Illingworth, R. S., and Lorber, J. (1951). *Lancet*, **2**, 551.
Lorber, J (1954a). Ibid., **1**, 1104.
—— (1954b). Ibid., **1**, 1149.
—— (1956). *Brit. med. J.*, **1**, 1009.
Michel, F., and Pulver, W. (1955). *Schweiz. med. Wschr.*, **85**, 717.
Ministry of Health (1959). *Monthly Bull. Minist. Hlth Lab. Serv.*, vol. 18, Nos. 1–12.
Smith, H. V., and Vollum, R. L. (1950). *Lancet*, **2**, 275.

UNILATERAL EMPHYSEMA

BY

R. F. FOUCHÉ, M.R.C.P.Ed., D.M.R.D.
Registrar, Radiodiagnostic Department, London Hospital

J. R. SPEARS, F.F.A. R.C.S.
Senior Registrar in Anaesthetics, London Hospital

AND

COLIN OGILVIE, M.D., M.R.C.P.
Consultant Physician, United Liverpool Hospitals and Regional Thoracic Surgical Centre; Late Lecturer in Medicine, London Hospital

An apparent increase in the transradiancy of one lung may be due to rotation, to diminished contralateral transradiancy, to giant cysts or bullae, to compensatory emphysema, or to obstructive emphysema resulting from incomplete bronchial occlusion. Macleod (1954) described a group of cases showing abnormal transradiancy of one lung in which none of these causes was apparent. The purpose of this paper is to report the radiological and physiological characteristics of seven patients conforming to Macleod's original description. These patients had all been referred with respiratory symptoms to the out-patient clinics of the London Hospital over a period of two years.

Methods

The study of each patient included clinical history and examination, postero-anterior radiographs in inspiration and expiration, fluoroscopy, whole-lung tomography, and either bronchography or bronchoscopy. The following physiological measurements were made:

1. The subdivisions of the lung volume, residual volume being measured by a closed-circuit helium-dilution technique (Bates and Christie, 1950).

2. The maximum breathing capacity expressed as the maximum voluntary ventilation at a respiratory rate of 80 per minute (M.V.V.80). This was repeated after an inhalation of 1% isoprenaline sulphate to assess the degree of reversible bronchial obstruction.

3. The maximum inspiratory and expiratory flow rates, derived from the spirometric tracing of a forced inspiration and expiration respectively.

4. Mixing efficiency, calculated from the helium-dilution curve (Bates and Christie, 1950).

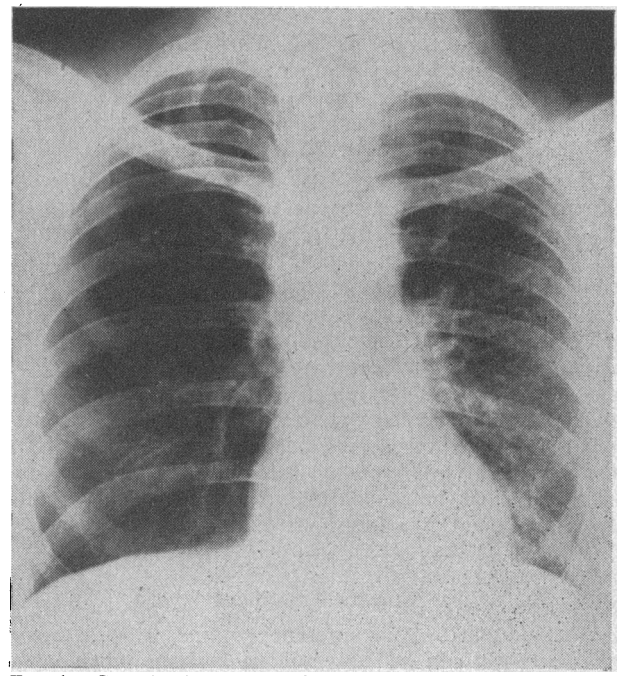

FIG. 1.—Case 4. Postero-anterior radiograph showing increased transradiancy of right lung.

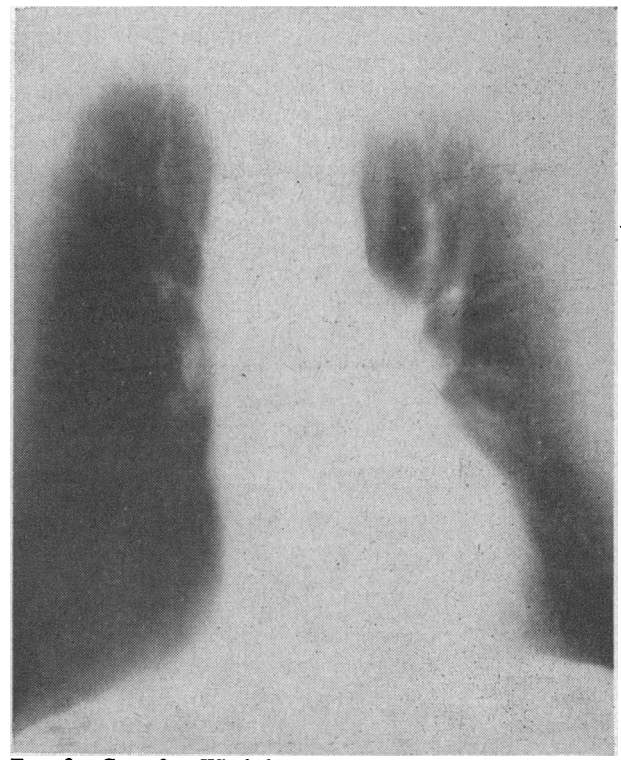

FIG. 2.—Case 2. Whole-lung tomogram showing diminished vascularity of right lung most marked in middle and lower zones. Note also low flat diaphragm on this side.