CURRENT RESULTS IN TREATMENT OF TUBERCULOUS MENINGITIS AND MILIARY TUBERCULOSIS*

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The purpose of this paper is to present the results of treatment of tuberculous meningitis in children who were admitted to the Children's Hospital, Sheffield, during 1954. Fifteen of these were admitted to the professorial unit, while five were under the care of Dr. T. Colver. The study is a direct continuation of earlier work (Illingworth and Lorber, 1951; Lorber, 1951; Lorber, 1954a, 1954b). In the last paper I reported the results of a controlled therapeutic trial in which the use of isoniazid was compared with that of streptomycin and P.A.S., and in which all patients received a minimum of 45 intrathecal streptomycin injections.

Present Investigation

Plan.—On account of the progressively diminishing number of cases it was not feasible to run a new trial with two concurrent groups. It was therefore decided to reduce the minimum number of intrathecal streptomycin injections from 45 to 25 by giving daily injections for six days, followed by three injections weekly, until a total of 25 injections had been reached by the end of the seventh week of treatment. The total duration of intrathecal treatment remained as in the earlier series. Subsequent similar intrathecal courses were given if the clinical condition of the patient or the state of the C.S.F. demanded it, according to the criteria outlined in a previous communication (Lorber, 1954a). In all other respects the treatment remained as in the preceding series (Lorber, 1954b) (Table I). Dr. Colver's patients continued to receive a minimum of 45 intrathecal injections.

TABLE I.—*Treatment of Tuberculous Meningitis, 1954-5*

Drug	Route	Dose	Minimum Duration
Isoniazid	Oral	20 mg./kg.	6 months
Streptomycin	Intramuscular	40	"
"	Intrathecal	25-50 mg.	25 injections
P.A.S. "	Oral	0.5 g./kg.	6 months
Tuberculin	Intrathecal	Where indicated	"

Material.—During 1954, 20 new patients were admitted to the hospital with tuberculous meningitis, and all were included in the study. They were between 4 months and 13 years of age, three being 12 months old or less. Seventeen patients were conscious on admission, two being particularly early cases, and three were in an advanced stage of the disease. Five had associated miliary tuberculosis. The diagnosis was established by the usual clinical features, a positive tuberculin test, and the characteristic C.S.F. in all cases. Tubercle bacilli were seen in a direct smear of the pre-treatment specimen of C.S.F. in every case, and were subsequently recovered on culture in 16 cases and from inoculated guinea-pigs in 17 cases. In two cases both culture and guinea-pig inoculations were negative.

Treatment

No patient required more than the planned minimum period of six months of systemic treatment. The C.S.F. showed a significant deterioration in four children after the completion of a course of 25 intrathecal injections, and in two of these tubercle bacilli reappeared in the C.S.F. during

treatment with oral isoniazid and intramuscular streptomycin. All four children made an uneventful recovery after a further course of 25 intrathecal injections. Neither on admission nor at the conclusion of the first course of intrathecal treatment was there any indication that these four children were more likely than other children to need a second course. The survivors on this regime received an average of 32 intrathecal injections, as compared with 65 in the previous group treated with isoniazid and 90 injections in those treated without isoniazid.

One child relapsed six months after the completion of all treatment. She was re-treated on the same plan, and made an uneventful recovery without sequelae. Thus the halving of the number of intrathecal injections has not led to more frequent resort to second courses, nor have there been more relapses.

One child was treated with intrathecal tuberculin. This 4-months-old infant failed to make satisfactory progress on the standard treatment, and by the twelfth day developed obvious and rapidly increasing hydrocephalus. This was confirmed by a pneumoencephalogram (Fig. A). Following the introduction of intrathecal tuberculin treatment he greatly improved, and eventually made a full recovery. His head circumference became normal, and objective evidence of the regression of the hydrocephalus was obtained by a second pneumoencephalogram five months after the beginning of treatment (Fig. B). Two years after the beginning of the illness he was physically and mentally normal.

Ancillary treatment by anticonvulsants and by physiotherapy and occupational therapy was carried out as in the

FIG. A.—Pneumoencephalogram showing considerable hydrocephalus 12 days after admission. FIG. B.—Regression of hydrocephalus five months later.

*Based on a paper delivered at the Séminaire sur le Traitement de la Tuberculose de l'Enfant (International Conference on Infantile Tuberculosis), Paris, December, 1955.

earlier series. The introduction of regular schooling into the unit has been an important development in the management of children of school age.

C.S.F. Changes

In the present series none of the children developed a spinal block. In our total experience with 51 cases treated with isoniazid, only one case has been seen in which a temporary spinal block developed.

The reduction in the total intrathecal treatment has not resulted in any delay in the return of the C.S.F. to normal as compared with the previous series, and, if anything, the protein returned to normal one to two months earlier (Table II). With our treatment it still takes some six to seven

TABLE II.—C.S.F. Changes in Patients Treated with Isoniazid (Averages)

	At End of Months				
	3	4	5	6	7
Cell count per c.mm.:					
1952-3 series	56	28	21	11	8
1954 "	45	35	20	19	10
Protein, mg. per 100 ml.:					
1952-3 series	96	102	65	51	48
1954 "	110	68	49	41	38

months for the C.S.F. to return to normal. This does not seem to matter, as there have been no late deaths or late complications. It has been found unnecessary to continue with intrathecal treatment until the C.S.F. is normal.

Results of Treatment

After a period of observation of 15 to 25 months (average 21 months) 19 patients were alive and all had concluded their treatment (Table III). The only child who died was

TABLE III.—Results of Treatment of Meningitis, 1954

Total treated	20
Alive	19
No subjective sequelae	16
Minimal hearing loss*	2
Severe mental defect	1
Dead	1

* Possibly present before treatment began.

a girl of 3. She was admitted in the advanced stage, in status epilepticus. She never recovered consciousness, and died within a week of admission. Eighteen children, including three infants, are well and have no neurological or detectable mental sequelae, although two of these are convalescent from a concurrent tuberculous disease of the vertebrae. Two others have a minor hearing loss which is demonstrable only by audiometry, but both of them attend ordinary school and manage without a hearing-aid. We have no information about their hearing before the meningitis developed. One child had two fits during treatment, and as her electroencephalographic pattern is still abnormal she is being treated with anticonvulsants, although she has had no fits since her recovery.

Routine intelligence tests are being carried out on all survivors, but it is too early to attempt to give final figures of I.Q.s in this group of children. The lowest figure to date is 89. The girl who relapsed and had a second complete course of treatment is an intelligent child. She attends a grammar school and easily holds her own with children of her own age, in spite of over a year's absence from school. Her I.Q. is 122.

One child is a mentally defective hyperkinetic idiot. The condition of this child was fair on admission, but a few hours later he had a prolonged succession of convulsions, from the effects of which he never recovered. He received 45 intrathecal injections. It is seen that the only two bad results were directly related to prolonged convulsions.

Miliary Tuberculosis

Treatment of acute generalized miliary tuberculosis without meningitis was the same as for tuberculous meningitis, except that no intrathecal treatment was given. Before

isoniazid became available more than one-third of such patients developed meningitis while on streptomycin treatment. The prognosis in these cases was poor, in spite of early diagnosis with routine lumbar punctures. Since the introduction of isoniazid no case of frank meningitis occurred in any of 11 cases treated up to the end of 1954, and the C.S.F. changes of "serous meningitis" (Lincoln, 1947) have all regressed without recourse to intrathecal treatment. All 11 children survived. The youngest of them was a 3-months-old infant, who had serous meningitis, enlarged liver and spleen, tuberculous otitis media, and generalized lymphadenopathy in addition to the miliary dissemination and a massive lung lesion. She is now perfectly well, 24 months after the beginning of her treatment.

Use of Anti-tuberculous Drugs

The results of treatment of tuberculous meningitis are now far superior to those obtained before the introduction of isoniazid. We now possess two potent specific drugs in isoniazid and streptomycin, as well as several other less efficient but none the less useful drugs, such as P.A.S. Different workers use these in different combinations, and so long as isoniazid is included in the regime the results show high survival rates. It is, however, difficult to compare the results obtained by different methods of treatment, because adequately controlled investigations are extremely rare and because the data provided by most authors are either not comparable or not sufficiently detailed. It is impossible to draw conclusions from those series of cases in which (a) the diagnosis is in doubt because of the absence of bacteriological confirmation from the C.S.F.; (b) the period of observation is short (less than one year) and patients are included who are still being treated; or (c) patients are excluded from the analysis either because they died within the first few days or weeks of treatment or for any other reason.

The large majority of workers agree that oral isoniazid should be given in combination with intramuscular streptomycin and that other tuberculostatic drugs—for example, P.A.S.—may be given in addition. Most agree that intrathecal isoniazid is harmless but unnecessary, because adequate concentrations are present in the C.S.F. after oral administration. The major controversy is centred in intrathecal streptomycin treatment. Many have abandoned its use, but others think that it should be used either in all cases or in a selected group. There is no doubt that since the introduction of isoniazid the need for prolonged courses of intrathecal injections has been greatly reduced, but no one knows the best line of treatment.

We have continuously and successfully reduced the number of intrathecal injections from an average of over 100 in those treated with streptomycin alone to 32 in this series, in which isoniazid was used together with streptomycin and P.A.S. We have, however, not discontinued the routine use of intrathecal streptomycin, for the following reasons: (1) The high survival rate and the good quality of the survivors with the present line of treatment. (2) A significant deterioration in the C.S.F. occurred in 10 patients after the conclusion of one intrathecal course (45 or 25 injections), and in three of these tubercle bacilli reappeared in the C.S.F. while they were receiving 20 mg./kg. of isoniazid daily. These changes were all successfully reversed by further intrathecal treatment. (3) We have been unable to find criteria which would indicate which patients would not require intrathecal treatment, or which patients would need more than one course. Some of the 10 children who had to have more than one course were among the earliest cases, and some advanced cases did well on a single course. (4) It would be undesirable to omit intrathecal treatment and then start it later if the course of the disease were unfavourable, because of the risk of irreversible cerebral changes.

We have not found convincing evidence from the literature that intrathecal streptomycin is unnecessary. There are some who claim a high proportion of survival rates, but these rates are on the whole lower than those obtained with

intrathecal treatment. It is not possible to be dogmatic about this, as there has been no report of a properly controlled investigation in which concurrent cases were treated with or without intrathecal streptomycin, while receiving streptomycin systemically together with isoniazid. It is noteworthy, however, that in some series treated without intrathecal injections the number of deaths in the first four weeks of treatment is unduly high. These deaths cannot be regarded as inevitable, as the patients did not have the benefit of intrathecal treatment.

For these reasons it is thought that at present the optimum treatment of tuberculous meningitis should include intrathecal streptomycin therapy, although it might be possible to reduce the number of injections even further. As we cannot foretell which patients will survive without intrathecal treatment, it is preferable to give it to some of them unnecessarily rather than to withhold it from those who need it.

Use of Cortisone

We have no experience with cortisone or corticotrophin as adjuncts in the treatment of tuberculous meningitis. It is claimed that these drugs are useful in the prevention of obstructions in the C.S.F. pathways. There has not been, however, a single paper describing a controlled study of the value of cortisone. This does not mean that cortisone may not be of benefit in some cases or that it may not replace the intrathecal use of tuberculin. It must be borne in mind, however, that obstructions in the C.S.F. pathways very rarely develop with modern treatment. Only one case with a temporary spinal block has been seen in the 51 cases treated with isoniazid. Astonishing recoveries can occur from apparently hopeless situations without the use of cortisone, and such occurrences need not be attributed to cortisone treatment.

Effects of Earlier Diagnosis

Of the 69 consecutive unselected patients who were treated in the Children's Hospital, Sheffield, during 1952-4 inclusive, 59 (85.5%) are alive (Table IV). These figures include those

TABLE IV.—Results of Treatment of Tuberculous Meningitis, 1952-4

Year	No. of Cases	Survivors
1952	26	21 (80.8%)
1953	23	19 (82.6%)
1954	20	19 (95%)
1952-4:		
All cases	69	59 (85.5%)
Conscious on admission ..	59	54 (91.5%)

who died within a few hours of admission. The proportion of patients who are admitted in an advanced state has been progressively decreasing in the last few years, but some still arrive so late in the course of the illness that no method of treatment can be expected to restore them to normal health. Early diagnosis and efficient treatment should now result in a recovery rate which approaches 100%. In 1954 we lost no child who was conscious on admission, and of 59 consecutive children who were conscious when admitted between 1952 and 1954 inclusive, 54 (91.5%) are alive, although 18 of them received no isoniazid treatment. The need to refer cases to special centres has not been lessened by recent advances in treatment.

Summary

During 1954, 20 new patients were admitted with tuberculous meningitis. Of these only one child died. He was in status epilepticus on admission and never recovered consciousness. A reduction in the number of intrathecal injections to a minimum of 25 and an average of 32 did not result in any deterioration in the results of treatment as compared with a previous series, and the C.S.F. returned to normal as quickly as before. Only one of the survivors has serious neurological and

mental sequelae. As the reappearance of tubercle bacilli in the C.S.F. may still occur after a course of intrathecal treatment during isoniazid therapy it is thought unwise to abandon intrathecal treatment. Cortisone was not used.

Of 69 consecutive children who were admitted during 1952-4 inclusive, 59 (85.5%) are alive. Of the 59 who were conscious on admission, 54 (91.5%) survived.

All the 11 children who were admitted during this period suffering from uncomplicated miliary tuberculosis survived. None developed meningitis during or after treatment with isoniazid and streptomycin.

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MURMURLESS BACTERIAL ENDOCARDITIS

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In 1870 Wilks pointed out that bacterial endocarditis may exist "even though we fail to detect any morbid sounds in the heart." The cases which he mentioned had neither signs nor history of a "primary heart affection," and several of them were examples of acute bacterial endocarditis. Rarely, subacute bacterial endocarditis also occurs in patients with no detectable heart disease, when, for instance, the infection involves a bicuspid aortic valve. To diagnose these cases before a murmur appears is obviously difficult, but it is particularly desirable, since prompt treatment could prevent them from developing valve lesions. In this paper the histories of four patients in whom bacterial endocarditis was at first murmurless are reviewed in an attempt to discover how the disease may be diagnosed before the valves become damaged. In two cases the condition was suspected and treatment was started before a murmur appeared, but in neither of them soon enough to avert valve damage.

Case 1. Acute Bacterial Endocarditis

In 1948 a 39-year-old policeman developed sudden fever, with severe malaise and headache. He had no symptoms of a respiratory infection, no joint pains, and no history of previous rheumatic fever. On treatment with salicylates he failed to improve, and later began to have rigors. When admitted to hospital after two weeks' illness, he was pale and sweating profusely (temperature 103° F.—39.4° C.) but no abnormal signs were found apart from tachycardia. The haemoglobin was 68%, the white blood count 9,800, and