ISONIAZID IN THE TREATMENT OF MILIARY TUBERCULOSIS IN CHILDREN

BY

W. P. SWEETNAM and E. F. MURPHY

From the Huddersfield and Halifax Hospital Groups

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The treatment of miliary tuberculosis in children by a long course of streptomycin injections raises obvious difficulties. The possibility of treating the disease successfully with a drug which is readily taken by mouth must be considered a big advance. This paper reports the results of the treatment of four children with miliary tuberculosis. All received isoniazid alone in a dosage of 10 mg. per kg. of expected weight in 24 hours. The cases were unselected consecutive admissions. Treatment was continued for a year.

Case Reports

Case 1. A girl aged 4 was admitted with a month's history of anorexia and cough. Her weight was then 28 lb. There was marked wasting. The spleen was

palpable and there were many moist sounds over both lung fields and signs of fluid over the right base. A radiograph (Fig. 1) showed generalized miliary mottling of the lung fields with a right pleural effusion. The Mantoux reaction was strongly positive, tubercle bacilli were recovered from gastric washings, and a diagnostic paracentesis revealed a typical tuberculous pleural effusion. The mother was found to have active pulmonary tuberculosis. Examination of the cerebrospinal fluid revealed no abnormality.

The child improved clinically within a few days of the start of treatment. At the end of a week she was eating well and had gained $\frac{1}{2}$ lb. During the next month she continued to gain weight at the rate of nearly a pound a week; after six months she had gained 14 lb. in weight. Treatment was discontinued at the end of a year by which time she weighed 42 lb. She continued to gain and now (17 months after admission) weighs 44 lb. and appears in all respects a normal child.

Radiological improvement became obvious after eight weeks' treatment (Fig. 2) and progressed steadily. The miliary mottling had disappeared after six months. On the cessation of treatment 12 months after admission the lung fields were clear save for a small area of collapse at the right base (Fig. 3).

Case 2. A girl aged 5 was admitted with a three weeks' history of increasing listlessness. She had had severe headaches on and off for the previous week and had vomited on several occasions.

On examination she was pyrexial and apathetic. Her weight was 37 lb. A choroidal tubercle was seen in one fundus. Examination of the cerebrospinal fluid showed 250 cells (90% lymphocytes) 160 mg. protein and 30 mg. of sugar. The Mantoux test was strongly positive. A radiograph showed fine miliary mottling. Tubercle bacilli were recovered from gastric washings. The child's mother was discovered to have pulmonary tuberculosis.

Clinical progress was rapid, the pyrexia subsided in two days, her appetite returned quickly and she began to gain weight at the rate of $\frac{1}{2}$ lb. a week. Improvement in the x-ray picture occurred after six weeks' treatment and the C.S.F. became normal after 20 weeks, by which time she was running happily around the ward. When

FIG. 1.—Miliary mottling throughout lungs; right pleural effusion.

FIG. 2.—After eight weeks, there is some clearing of the lung fields, absorption of the pleural effusion, and consolidation of the right middle lobe (Case 1).

FIG. 3.—After 12 months' treatment the lung fields are clear save for a small area of collapse at the right base (Case 1).

FIG. 4.—Miliary mottling throughout the lungs (Case 3).

FIG. 5.—After 12 weeks' treatment miliary mottling is less pronounced (Case 3).

FIG. 6.—After 12 months' treatment the lung fields are clear. (Case 3).

FIG. 7.—Miliary mottling throughout the lungs (Case 4).

FIG. 8.—After six weeks' treatment the miliary mottling is less pronounced with consolidation of the right upper lobe (Case 4).

FIG. 9.—Lung fields are clear (Case 4).

treatment was discontinued at the end of 12 months, she weighed 47 lb., and a radiograph of the lungs was clear. She continued to gain weight and now 15 months after admission weighs 50½ lb.

Case 3. A boy aged 9 was admitted with a fortnight's history of anorexia, loss of weight, and intermittent

abdominal pain. Except for some wasting there were no abnormal physical signs. His weight was 48 lb. The Mantoux reaction was strongly positive. A radiograph of the chest (Fig. 4) showed typical miliary mottling. Tubercle bacilli were recovered from the gastric washings. The C.S.F. findings were normal. The boy's father was known to have pulmonary tuber-

culosis. Appetite returned slowly, he continued to have some abdominal pain and occasional vomiting for 10 days, after which he began to gain weight rapidly. Six months after admission he had gained 14 lb. in weight. Shortly afterwards he suddenly complained of severe abdominal pain and vomited copiously and signs of obstruction of the small intestine became apparent. Laparotomy revealed a tuberculous stricture of the ileum, 2 ft. from the caecum. This was relieved by a lateral anastomosis, and the boy made a rapid recovery. Treatment was discontinued after 12 months. He then weighed 68 lb. and was back at school. He continued to gain weight and two months later weighed 70 lb.

Radiological improvement was slow, the first signs of clearing occurring after three months of treatment (Fig. 5). A radiograph taken at the cessation of treatment (Fig. 6) showed no abnormality.

Case 4. A boy aged 2 had measles six weeks before admission. His cough had persisted and he failed to pick up. On examination he was found to be a miserable, flabby child, weighing 23 lb. There were many moist sounds over both lung fields, and the spleen was enlarged. He had an extensive papular erythema which gave the appearance of a papular tuberculide. The Mantoux reaction was strongly positive and a radiograph showed a typical miliary mottling of the lung fields (Fig. 7). Tubercle bacilli were recovered from gastric washings. The father was found to have pulmonary tuberculosis. The C.S.F. findings were normal.

The response to treatment was good at first and his rash gradually disappeared. After six weeks' treatment he weighed 24½ lb. His cough then became troublesome again; he developed signs of consolidation in the right upper lobe and his weight remained stationary. A radiograph taken at this time (Fig. 8) showed consolidation of the right upper lobe, the generalized miliary mottling being less marked. The C.S.F. examination was again normal. A further sustained improvement then took place. The child is now clinically well, and after 12 months' treatment weighs 30 lb., the lung fields being radiologically clear (Fig. 9).

Discussion

Miliary tuberculosis provides an ideal situation for assessing an antibacterial drug. The disease untreated is almost uniformly fatal, and the interpretation of the radiological progress is not complicated by the presence of large areas of necrotic lung tissue. Clinical improvement occurred in all four cases within a few days of the start of treatment. Radiological clearing of the lung fields was slow; improvement became obvious after about six to 12 weeks' treatment and progressed steadily; all had

a normal radiological appearance after a year. The clinical and radiological findings support the histological evidence of Ritchie, Taylor and Dick (1953) that the lesions of miliary tuberculosis undergo resolution during treatment with isoniazid and do not become fibrosed or calcified as often happens with streptomycin. A constant feature was the rapid return of the appetite which, in some cases, became voracious. This feature was so striking as to suggest that isoniazid may have some specific effect on the appetite. Appetite and weight gain continued, however, after the cessation of treatment.

The Medical Research Council (1953) found that a third of all patients treated with isoniazid alone developed resistant variants within three months, and have recommended that isoniazid should not be used by itself in the treatment of pulmonary tuberculosis. This recommendation is based on the use of the drug in chronic 'open' pulmonary tuberculosis. In miliary tuberculosis, the lesions are acute, 'closed', usually minute, and should provide no great barrier to the action of the drug or the promotion of healing. The development of drug-resistant variants and their dissemination is therefore unlikely.

The treatment of miliary tuberculosis, in children especially, by a long course of injections is unpleasant for all concerned. Isoniazid (in the form of syrup) is in contrast readily taken by children. This ease of administration probably more than compensates for the risk of drug resistance which, in the case of miliary tuberculosis is, at present, largely theoretical.

Summary

Four children with miliary tuberculosis have been treated with isoniazid alone on a dosage of 10 mg. per kg. daily for a year. One case was complicated by tuberculous meningitis, and another by tuberculous enteritis. Clinical improvement was rapid and all remained well after treatment was stopped. Radiological improvement was slow but progressed steadily, the lung fields being clear after 12 months' treatment. No toxic effects were observed.

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