THE PROBLEM OF INDICATIONS FOR TREATMENT OF
ASYMPTOMATIC PRIMARY TUBERCULOSIS

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A brief review of present concepts of the fate of the primary complex may serve as a useful introduction to the problem of treating the infant or child with asymptomatic primary tuberculosis.

The primary lesion persists for months and gradually disappears, usually leaving calcification in the site of the primary focus and the corresponding lymph nodes. In most instances recovery is uneventful despite the almost universal occurrence of a hematogenous or lympho-hematogenous spread of tubercle bacilli, but this accounts for most of the severe complications of primary tuberculosis such as tuberculous meningitis and skeletal tuberculosis. The spread may be of various types and degrees but is usually an occult hematogenous dissemination from the primary lesion, which may take place during the incubation period or during the first few months after the appearance of the primary complex. Hematogenous spread also may be massive, resulting in miliary tuberculosis. Tubercle bacilli in the tracheo-bronchial lymph nodes may spread to other lymph nodes or other areas of the body through lympho-hematogenous dissemination. Common sites of invasion are the cervical lymph nodes and tonsils. The primary lesion may progress locally by excavation and by bronchogenic dissemination; it is then often called locally progressive primary tuberculosis.

The majority of the complications appear within the first year of infection in an infant or a child who has previously been asymptomatic.

In children, reinfection or chronic, adult type of tuberculosis is most common in adolescence. It may be of exogenous or...
endogenous origin. The endogenous type might be considered a distant complication of primary tuberculosis, since it is believed to occur as a result of activation of a dormant focus.

The child with a positive tuberculin reaction and a negative roentgenogram of the chest usually has a pulmonary primary complex which is minimal in extent. Experience has shown that such children are less likely to develop meningitis or other early complications, as well as less likely to develop reinfection tuberculosis at adolescence, than children with roentgenographic evidence of primary pulmonary tuberculosis. Aside from this difference, which is probably due to extent of disease, the incidence of complications cannot, at present, be accurately predicted. It may vary with socio-economic conditions, degree of exposure, virulence of the bacillus, diet, stress, ethnic group, general care of the patient or other undetermined factors. Certainly it is within the experience of pediatricians that many patients recover uneventfully.

Isoniazid is highly effective in the treatment of complications of primary tuberculosis. Unlike streptomycin, isoniazid suppresses tuberculous disease to the extent that further spread is a rare occurrence among tuberculous children receiving isoniazid. This observation has been made in children clinically ill with tuberculosis, but among the children with asymptomatic primary tuberculosis, the role of isoniazid is not so clearly established.

The peculiarities of primary tuberculosis account for the difficulties in evaluating the effectiveness of therapy. Unlike tuberculous meningitis in which even a few cures are highly significant, accurate evaluation of therapy of primary tuberculosis requires prolonged observation of large numbers of patients, divided into two comparable groups—one group treated and the other not treated. The importance of including control cases may be illustrated by the widely divergent reports in the literature on the incidence of tuberculous meningitis among children with primary tuberculosis; for example, Wallgren reported a meningitis rate of 0.7%, Price, 0.3%, Miller, 3%, and Walker, 19%. Equally divergent observations have been made on the mortality from all complications of primary tuberculosis. Before antimicrobial agents were available, Lincoln reported a mortality of 23.4% among children with primary pulmonary tuberculosis seen at Bellevue Hospital; on the other hand, Myers in Minnesota reported only 0.5% mortality. Regardless of the varying material, which partially explains the difference in these observations, it is clear that a study of the therapy of primary tuberculosis without control cases would be inconclusive.

In a controlled study it is also possible to evaluate the disadvantages in treating all children with primary tuberculosis. Some of the possible disadvantages, such as interference with the immune process, have already been pointed out. The possibility of creating bacterial resistance without accomplishing cure may be a valid objection to treatment and an important reason for a carefully planned investigation.

Because of these problems, a large scale co-operative investigation was organized and co-ordinated by the U. S. Public Health Service. This project is called the Tuberculous Meningitis Prophylaxis Study, but the over-all objective includes investigation of the effects, both immediate and long range, of the price as well as the gain, of treating children with asymptomatic primary tuberculosis with isoniazid.

A large number of infants and children from different geographic areas and ethnic groups are under observation. The children have been selected at the local level in more than 30 pediatric clinics, in the United States, Mexico, Puerto Rico, and Canada. The children included in the study fulfill the following criteria: (1) positive tuberculin reaction; (2) visible hilar or parenchymal lesion on roentgenogram except in children under 3 years of age who are accepted without roentgenographic evidence of tuberculosis; (3) absence of symptoms due to tuberculosis.
In each clinic, half of the children selected for study receive isoniazid in doses of approximately 5 mg/kg, and half receive a placebo. The investigators do not know whether a child is receiving isoniazid or placebo, a precaution which helps to remove bias in the selection of patients and in the evaluation of results of therapy. All children receive therapy for 1 year but will be kept under observation a number of additional years. At the beginning of the study it was expected that the effect of isoniazid could be evaluated after a thousand children had been observed; but when this goal was reached the incidence of complications was so low that it seemed unlikely that a reliable comparison between treated and untreated groups could be made. For this reason, it was decided to increase the number of patients to 2,000 or more.

The number of cases necessary to prove the effectiveness of a given drug in preventing complications depends upon whether the drug will be completely effective or not. Until recently it had been generally accepted that tuberculous meningitis did not occur in patients treated with isoniazid. Lincoln and Lythcott have reported one case of tuberculous meningitis developing in a 3-year-old child after 8 months of therapy with isoniazid in doses of 3.5 to 4 mg/kg. Mitchell, Anderson, Ohr and Middlebrook reported a fatal case of tuberculous meningitis in an adult during the tenth month of therapy with isoniazid and streptomycin.

In Puerto Rico, after observing more than 500 infants and children with all forms of tuberculosis treated with isoniazid combined with streptomycin or para-aminosalicylic acid, we encountered the first case of tuberculous meningitis developing in an adult during the tenth month of therapy with isoniazid and streptomycin.

A 3-year-old child had contact with a tuberculous adult who still had a positive sputum after 3 years of treatment with isoniazid and streptomycin. Six months after exposure the child was toxic and febrile, had a parenchymal lesion in the right lung and a positive tuberculin reaction. He received therapy in the hospital with isoniazid and streptomycin for 6 months. Because the child was not doing well, I checked repeatedly and confirmed that he was receiving and retaining the correct medication. The dose of isoniazid was gradually increased from 10 mg/kg to 30 mg/kg. On the fifth month of therapy he developed osseous lesions, visible by roentgenogram, in the skull, tibia, metatarsals, ulna and vertebra and a lumbar cold abscess, followed a month later by meningitis and death despite administration of isoniazid by the intramuscular and intrathecal routes. The necropsy findings were typical of miliary tuberculosis, tuberculous meningitis and osseus tuberculosis. All material for culture was obtained during isoniazid therapy. Now growth of Mycobacterium tuberculosis had been observed after 5 months of incubation.

These reports emphasize the fact that meningitis can occur in patients treated with isoniazid and warn us not to assume that further studies are superfluous. Another question needing clarification concerns the optimum duration of isoniazid therapy. Cases of tuberculous meningitis and miliary tuberculosis have been described which occurred in tuberculous children after receiving short courses of therapy.

More precise indications for treatment may be established by analysis of various characteristics among children in the controlled study. These characteristics might include: Size of the tuberculin reaction, age, height and weight of the patient, roentgenographic appearance of the lesion and presence of superficial adenitis. All of these have been discussed previously by many authorities, however, definite proof of their significance by means of large controlled studies has been lacking. An example of the importance of further observations is the fact that in the meningitis-prophylaxis study the rate of complications among children with tuberculin reactions, with induration less than 10 mm in diameter, was five to seven times lower than that of children with larger reactions. It also has been observed that the rate of complications varies with
age; children under 1 year of age developed complications at a rate three to five times higher than older children up to the age of 11 years. If these observations are confirmed at the end of the study, the size of the tuberculin reaction and age of the patient might serve in the future to establish indications for therapy. Thus, it appears that the answer to this problem might not be simply treat or not treat. Through analysis of the results of the Public Health Service investigation it may ultimately be possible to select the children who are most likely to develop complications and obviate the necessity of treating all children.

How long shall we have to wait before the results of this study are considered significant? We are hoping that within another year part of the answer will be available. If isoniazid is found to be effective in preventing early complications, it will certainly be indicated in the treatment of primary tuberculosis. Whether the treated child is less likely to develop late complications, especially reinfection or chronic adult pulmonary tuberculosis, can only be learned after prolonged follow-up. If it is found that reinfection tuberculosis can be prevented by treating the primary lesion with isoniazid, we will have the tools for preventing tuberculosis in the next generation.

CONSIDERATIONS BASIC TO TREATMENT AND PROPHYLAXIS OF TUBERCULOSIS IN CHILDREN

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[The following is based on a transcription of the remarks of Dr. McDermott—Ed.]

Certain basic concepts, which have been discussed by Dubos,* with respect to the triangular relationship between the drug, the parasite and the host, have generality not only in the field of tuberculosis but in the field of other infections. It might be of value to consider these principles in relation to the specific situation of the child who may have, or may have been exposed to, tuberculous infection.

Relationship between tubercle bacilli and isoniazid could conceivably occur in three different sets of circumstances: In the first circumstance the drug would be present before the bacilli, which is the situation in the United States, but only in circumstances in which one administered isoniazid in an area of high prevalence of tuberculosis with the notion that contacts of an infectious patient might have to be protected.

Nevertheless, if these circumstances should obtain some of the tubercle bacilli received by the drug-treated host presumably might survive and if they did survive they would make no contribution to the acquisition of resistance by that host. By the same token, they would produce no active disease, so long as the drug therapy was administered. Once the therapy was stopped, in these

*Presented by Dr. Dubos as part of this symposium and previously published elsewhere (Dubos, R. J.: Childhood tuberculosis. Am. Rev. Tuberc., 74:1, 1956).

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