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.]

Certainly 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 in the extracellular and other fluids of the body before the tubercle bacilli were implanted. The second would be the circumstance in which the tubercle bacilli had already been implanted but the administration of the drug was started within a few hours or a few days of the implantation. The third would obtain if the tubercle bacilli had been present for a matter of more than a few days, and their multiplication had resulted in cutaneous sensitivity to tuberculin.

The first case, in which the drug was present before the bacilli, would not obtain 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 situations...

* Presented by Dr. Dubos as part of this symposium and previously published elsewhere (Dubos, R. J.: Childhood tuberculosis. Am. Rev. Tuberc., 74:1, 1956).
circumstances, the child would face the implications of having tubercle bacilli and a primary infection. Whether postponement of primary infection by such means would serve any useful purpose or not would depend on the circumstances.

In the second set of circumstances, the tubercle bacilli would be present first, but for only a short period of time, before the initiation of therapy with isoniazid. This might occur in an infant delivered of a mother with highly infectious tuberculosis or in a medical worker, professional or non-professional, who suffered some sort of traumatic injury, such as a needle puncture with infectious material. In these circumstances, too, the administration of isoniazid would result in a “freezing” of the total situation. The bacilli would not multiply to any great extent, and so would not produce disease. Neither would they produce or call forth any acquired resistance until such time as one ceased the administration of the drug. At that point, again, the host would face the implications of a primary tuberculous infection. Again, whether any useful purpose is served by postponing or by arranging things so the child has a primary infection at one age rather than at another, in the absence of more precise data, is a matter of opinion. It is assumed that drug resistance in the circumstances cited is not a problem.

It is the third situation, in which the child has developed a positive reaction to tuberculin, which causes concern, and to all intents and purposes it is this situation which is the one of practical significance.

It is by no means clear to what extent the various general principles discussed by Dubos apply to this practical situation of the child with the positive tuberculin reaction. In administering isoniazid to a person who is a cutaneous reactor one is treating an established infection, which is almost certainly a tuberculous lesion in the lungs and in the lymph nodes. Moreover, clinical and roentgenographic tests are such that it is difficult to distinguish between the child with the enlarged lymph nodes and perhaps a collapsed lung as a consequence, and the child who has an extensive necrotic lesion which simply happens to be in the lymph nodes. The problem is just as great whether one can put one's finger on the site of the lesion or not. In either case, all that is really known is that the child has developed a cutaneous reaction to tuberculin, which means the presence of a tuberculous lesion, and that the presence of this primary infection has changed the child to a certain extent with respect to the handling of fresh implantations of tubercle bacilli.

What can one hope to accomplish in this situation by administration of isoniazid, not for a matter of a few months, but for a matter of 18 months to 2 years, or for a protracted period of time? The local extension of the lesion can be prevented. Secondly, metastases from that lesion to the brain, to other parts of the lung and to the kidney can be prevented, if they have not already occurred at the time the therapy was started.

Thirdly, if metastasis has occurred before treatment with isoniazid, the full evolution of the metastatic lesion can be prevented and it can be kept under control for a long period, presumably sufficient to permit healing. In short, a child is placed in a most favorable situation with respect to the unpleasant consequences of the primary infection, and to some extent would be receiving protection against fresh implantations so long as the therapy continued to be administered.

What could be harmful in the administration of isoniazid in exactly these circumstances? One would obviously be treating a large number of children who did not really need such treatment by virtue of the fact that the majority of people can handle tuberculous infection without its becoming tuberculous disease. Second, there would be some risk of drug toxicity, though the toxicity of the drug is relatively unknown. Third, in at least some of the children, isoniazid resistant strains of tubercle bacilli might develop. Fourth, as Dubos mentioned, the increased resistance to subsequent infection produced by the primary infection might be
reduced to an extent greater than would occur naturally in the hemming in of the primary infection.

What are the relative possibilities? With respect to a reduction in the acquisition of resistance, it is possible, as in the first two sets of circumstances mentioned, to administer a drug too early. But no one knows and this is the crux of the situation—whether by the time a person has become a cutaneous reactor to tuberculin everything has happened that is going to happen in relation to the acquisition of resistance, or whether fresh increments of host resistance are to be anticipated thereafter, increments which could be prevented by the drug. I would venture a guess, that in some circumstances the acquired immunity from the primary infection probably would be reduced, but I also wonder whether the reduction would be any greater than that which occurs in the natural course of things if the infection is successfully handled by the host.

In so far as drug toxicity and drug resistance are concerned, weighing drug toxicity in this situation today is imponderable. In certain circumstances neurotoxic manifestations can occur with isoniazid. The incidence of such toxic signs among a group of young children is unknown, and until such information is available we cannot have a sound opinion. On the basis of the absence of evidence, thus far one would say that the risks are quite low.

It is the same with drug resistance, in that drug resistance is a factor with tubercle bacilli as it is with other bacteria. In the particular situation cited here it presumably would not be a factor in most of the situations faced, but there would remain an occasional lesion, an occasional child, in whom drug-resistant tubercle bacilli might emerge. It would be my guess that the incidence of such would be quite small.

Thus, I can sum up my own position by saying that I am in complete agreement with Dubos about what can or cannot be accomplished by antimicrobial therapy in the tuberculous subject. I believe that in the first two sets of circumstances, when treatment is given either before infection or shortly thereafter, one is simply “freezing” a situation which has to be faced later on; that in the third set of circumstances, which I consider to be the common problem, the probabilities of drug toxicity or the emergence of drug resistance and the possibilities of lowering acquired resistance by use of the drug are sufficiently unlikely that I would strongly favor administration of the drug. If subsequent information shows that the incidence of drug toxicity or drug resistance is impressively high, then that position would obviously have to be reconsidered.

INDICATIONS FOR TREATMENT OF ASYMPTOMATIC TUBERCULOSIS IN CHILDREN

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From 1915 until 1930, medical literature was filled with discussions concerning the necessity of the treatment of patients whose roentgenograms showed open cavities but who in other respects were relatively asymptomatic. In many instances such patients were offered little or no treatment. From 1925 to 1945 authors questioned the necessity of the treatment of minimal, but otherwise asymptomatic tuberculosis. Now all agree that such cases should be treated.

In the early days after the discovery of streptomycin, antimicrobials were reserved for those patients who showed progressive pulmonary tuberculosis while under other forms of treatment. It was common to save chemotherapy until it was needed. Today, in any tuberculosis hospital, approximately

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