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...
100% of the patients admitted, and proven to have tuberculosis, will be treated with chemotherapy.

It is a well-established fact that a primary infection confers a certain degree of resistance to reinfection. The good effects of the primary infection have been so fully studied both in experimental animals and in humans, particularly in regard to the program of vaccination, that the deleterious effects have been frequently overlooked.

A person who is a recent tuberculin converter undoubtedly has living tubercle bacilli in his body. No one has yet proven what happens to these bacilli either in the experimental animal or in the human. For years it was assumed, but without positive proof, that they slowly or rapidly died. It is now realized that while they may not multiply, they may remain dormant but living in the lymph node component of the primary complex. Many studies, both in this and in other countries, have shown the dangers of a primary infection. The reports of Miriam Brailey in 1938 from the Johns Hopkins Hospital showed that of 223 patients who had a positive tuberculin test at an average age of 13 months, with or without roentgenographic changes, 30% of those showing parenchymal lesions died. Of those showing either enlarged nodes or negative roentgenograms of the chest, 7.5% died. In 1939, Zacks pointed out the tendency of tuberculosis to progress in the 5 to 9-year-old group and even more in the 10- to 14-year-old group. The very detailed and still continuing studies of Dr. Edith Lincoln have demonstrated this point.

In 1955, Nils Levin reported an 18-year follow-up on children with primary tuberculosis. He gave findings from other investigators quoting mortality rates of 5 to 24%, and in his own group of 254 children who initially showed active tuberculosis, 5% had active disease and 13% had died of tuberculosis.

The recent studies done by the United States Public Health Service in Puerto Rico and in Muscogee County, Georgia have again emphasized this point. About 100,000 persons in Puerto Rico were followed for an average of about 4 years. The rate of development of tuberculosis per 100,000 person-years of observation was 160 for the reactors as compared with 46 for the controls and 31 for the vaccinated group. In Muscogee County, Georgia where 68,000 persons were tested and examined roentgenographically, three-fourths of the new cases came from the originally tuberculin-positive group.

The majority of the cases developed within the first 2 years after conversion of their tuberculin test. An appreciable number, however, continued to develop at yearly intervals.

These figures are based on untreated cases and are comparable to figures for untreated minimal tuberculosis in the adult. It is on the basis of this evidence that we routinely treat tuberculosis in adults with drugs.

The infant or the child with tuberculosis does not present the so-called classical shadows in the upper one-third of both lungs so commonly seen in the adult. Pulmonary tuberculosis in the infant may involve any segment. Lincoln has recently shown that it frequently involves the anterior segment of the upper lobe, an area not commonly associated with the adult type of tuberculosis. The roentgenographic appearance may vary from that of bronchopneumonia to a localized area of atelectasis. Shadows from day to day vary more than they do in adults. Fibrosis and cavity formation is rare. It is frequently difficult to determine if an abnormal shadow is or is not present, particularly in the mediastinal area. Symptoms of extrapulmonary tuberculosis rarely develop before the lesion is far advanced.

One reason previously advanced for not treating these infants was that streptomycin and para-aminosalicylic acid (PAS) did not prevent the development of meningitis. It has also been frequently pointed out that the atelectatic lesion or the enlarged glands may not respond more rapidly to streptomycin and PAS than expected otherwise.
The toxicity of streptomycin and PAS, the difficulty of obtaining co-operation of the patient and family, and the lack of definitive result were, therefore, quoted as reasons against treatment.

What should one do when a patient is referred with a positive tuberculin test? I believe the following steps should be followed.

1. Repeat the tuberculin test. The patch test is widely used in mass surveys; it is easy to apply, and meets with wide-spread approval. Unfortunately, it is not as easy to read as other tests. Recently, cases have been reported in which a definitely positive patch test was not confirmed subsequently by the use of intradermal methods using either P.P.D. or old tuberculin.

For this reason, we routinely repeat any positive patch test using either purified protein derivative or old tuberculin. Old tuberculin varies widely depending upon the source of the tuberculin. P.P.D., on the other hand, is a relatively stable tuberculin.

While all agree that a positive tuberculin reaction to the first strength (0.00002 mg, or .01 mg O.T., 1 tuberculin unit), and the intermediate strength (.0001 mg, or 5 tuberculin units) is uniformly a specific reaction, many physicians now feel that a reaction to second strength P.P.D. (250 tuberculin units) is not necessarily a specific reaction to tuberculin. This is particularly true in those areas of the country where histoplasmosis and coccidiomycosis are endemic, and it is necessary to test with antigens with these substances.

If the tuberculin test is positive to 10 or less tuberculin units, then a complete study of the patient should be done. An adequate history and physical examination must be done. The history should include, if possible, the dates of all other tuberculin tests given, and their reaction. It is quite important, for example, to know if a person is a recent converter or if it is possible that the tuberculin test has been positive over a long period of time. It should include a careful inventory of systems to try to detect any possibility of an extrapulmonary lesion.

2. Laboratory studies should include gastric lavage and culture. In any case with genitourinary symptoms a urine sample should be cultured. If glands are available they should be biopsied and studied both microscopically and by culture. Routine blood studies must be done as a base line for further observation if treatment is to be carried out.

3. A roentgenogram of the chest is routinely obtained.

4. After all studies have been completed the patient should then be evaluated as to the advisability of treatment.

All of us agree that patients with the more severe forms of tuberculosis, that is, miliary and meningeal, must be treated intensively with combined antimicrobial agents. The American Trudeau Society Committee on Therapy, in a detailed statement, recommended isoniazid, streptomycin, and PAS for these infants or children.

In the group of children showing clinically active pulmonary or extrapulmonary tuberculosis, all agree that combined antimicrobial therapy, including isoniazid, should be used. The remaining groups, that is, those children with positive tuberculin tests with or without parenchymal shadows or mediastinal involvement, are the ones under discussion.

I believe treatment should be considered in these patients. This is particularly true in those infants below the age of 3 years, and in all children known to have converted their tuberculin test in less than 1 year. It is equally true if the general level of resistance of the child is low.

Treatment, if started, should use an effective drug of the lowest possible toxicity. At this moment, isoniazid fulfils this requirement better than other forms of treatment. Isoniazid used alone has been proven effective in primary infection in experimental animals, in many cases of tuberculosis in adults, and in glandular tuberculosis. In the minimal and closed forms of tuberculosis, there has been no series of cases reported in which the development of resistance to isoniazid was considered an important
factor in the outcome of treatment. Its toxicity at the effective dose level of 4 to 5 mg/kg is quite low. For these reasons I believe that these cases should be treated with isoniazid alone using 4 to 5 mg/kg/day.

Such treatment, once started, must be continued without interruption for a minimum period of 12 to 18 months. In every reported study of tuberculosis in adults under any treatment regimen, it has been pointed out that long-term therapy is superior to short, and that every effort must be made to maintain continuous therapy because interrupted therapy uniformly gives poorer results.

In experimental tuberculosis the necessity for long treatment has also been shown. In the moving picture made by Ebert and Barclay at the University of Chicago, using the technique of making a window in the rabbit's ear, allowing normal tissue to regrow, inoculating with tuberculosis, and making daily pictures of the reaction obtained, treatment with effective antimicrobials started at 5 days prevented the further spread of infection. It was still necessary for this minute amount of tuberculosis to be treated 40 to 128 days before an appreciable degree of resolution could be obtained.

I think that any treatment must include those concomitant measures which will restore the inherent resistance of the child being treated. This would obviously include hospitalization for the serious form of the disease, and may include hospitalization, or convalescent care, for those whose home conditions are such that proper quantities of food, rest, and relaxation cannot be supplied.

The investigation of the patient must also include examination of all members of his family and household contacts to determine, if possible, the source of his infection. This can be done in any available Public Health Clinic. It is, however, the physician's responsibility to determine that the child is not being further exposed to tuberculous infection during the course of treatment.

In summary then, I believe that any patient with clinically active tuberculosis must be treated. I believe that all patients with a positive tuberculin test and roentgenographic evidence of disease should be treated, and that an increasing number of patients whose only evidence of the presence of living tubercle bacilli in their body is a positive tuberculin test should be treated.

We are not at present treating all children with a positive tuberculin test, but I will immediately qualify that statement by saying that 10 years ago only those patients were treated who had definitely progressive forms of disease. For the past 3 years we have treated those patients who had definite, recognizable disease. Today we are instituting treatment on an increasing number of new tuberculin converters and some whose conversion date is not known.

The proof of the results of this treatment will not be available until the experiments carried on by others have been completed in 10 to 20 years.

It is, however, hard to conceive that a drug as effective as isoniazid in pulmonary tuberculosis in the adult even in its chronic phase, and which works equally well in all experimental animals with primary tuberculosis, might prove to be ineffective in the human.
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