Tuberculosis Prophylaxis Trials in Preview

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SINCE 1952 the drug isoniazid has been used widely and effectively in the treatment of tuberculosis. This demonstrated effectiveness in treatment has led to the idea that isoniazid may be effective as a prophylactic agent.

To say that isoniazid prophylaxis of tuberculosis is controversial is certainly not to exaggerate. Some believe it can prevent tuberculous infection from progressing to clinical disease or can even prevent infection itself. Others just as firmly believe it can prevent neither infection nor disease but instead will interfere with the acquisition of resistance. On the basis of these beliefs, the use of prophylactic isoniazid is either advocated or opposed.

Both these beliefs are based on analogy. Advocates draw support for their view from the results of the treatment of patients. Opponents base their position on animal experiments. No direct evidence of the effectiveness of isoniazid prophylaxis in human beings has yet been produced.

The Public Health Service finds itself unwilling, without direct evidence, to endorse the prophylactic use of isoniazid. It is equally unwilling, without direct evidence, to dismiss the possibility that isoniazid may be an effective prophylactic. In this dilemma, a program of carefully planned control studies involving large numbers of people seems the only solution. Consequently, the Public Health Service, with the cooperation of tuberculosis workers throughout the country, has initiated a series of prophylaxis trials.

The first of these trials was begun in January 1955. Its purpose is to see whether the frequency of complications of primary tuberculosis can be decreased by the prophylactic use of isoniazid. In this study, more than 2,500 children with asymptomatic primary tuberculosis are being observed in 31 pediatric clinics.

A second trial, in which local health departments are participating, is now getting under way. Health departments ordinarily keep under observation persons considered to be at greater than average risk of tuberculosis so that treatment can be started at the first sign of active disease. These persons are of two kinds: those whose risk is considered to be due to unusual exposure, that is, the household contacts of newly discovered cases of tuberculosis, and those who are considered at unusual risk because of suspicious pulmonary pathology observed on X-ray films but whose present condition does not require treatment.

For these "special risk" groups, the Public Health Service is helping health departments add the prophylaxis trial to their already established services. Household contacts make up the larger part of the study population. In addition to the usual "watchful waiting," half the persons in this trial are receiving daily isoniazid and the other half placebo.

Each participating health department tuberculin tests and X-rays the household contacts of each newly discovered case of pulmonary tuberculosis. Any contact with evidence of active tuberculosis is referred to his family physician or a tuberculosis clinic for treatment. The others are asked to enter the study.

The household is given a bottle containing a month's supply of enough pills for each adult member of the family to receive a daily dose of between 3 and 7 mg./kg. of body weight and for each child to receive a daily dose of between 5 and 10 mg./kg. Each month for the next 11 months, a member of the household picks up a new supply of pills at the health

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department and returns the previous month's bottle. The number of pills remaining in the bottle when it is returned is a clue to the regularity with which the family has been taking the pills.

At 3-month intervals during the year, a nurse from the health department visits the family and reports on the health of each family member the regularity with which the family is taking its pills, and the amount of time the member with tuberculosis has spent in the home.

At the end of the 12th month, the household members are reexamined in the clinic with tuberculin tests and X-rays.

The procedure is essentially the same for the tuberculosis suspects, except that the suspect, rather than his family, is the study member.

During the year each health department continues its usual observation of these tuberculosis suspects and household contacts. If one of them develops clinical tuberculosis, he is removed from the assigned medication and referred to his physician or tuberculosis clinic for treatment. The other members of the family continue to receive the assigned medication.

While this scheme is simple for any one household, its application to many households in a number of cities creates administrative problems for the central office in Washington. Most of the difficulties stem from our determination to make the observations as objective as possible. We believe it is critical that neither those who are taking pills nor those who are observing them should know whether a household is receiving isoniazid or placebo. Households receiving placebo must have the same faith in the usefulness of their pills as those taking isoniazid. The public health nurses must watch those who are taking isoniazid with the same concern they feel for those taking placebo. The physician who diagnoses tuberculosis in a household contact must not be influenced by the knowledge that a person has or has not been receiving isoniazid. The only way to make sure that the study is free from bias is to make the two products indistinguishable and to tell no one outside the central office what each bottle contains.

Bottles of pills labeled only with code numbers are sent to the health departments. They are of the various sizes necessary to provide a month's supply of pills for families containing from 1 to 16 persons ranging from 2 months to more than 70 years of age. The health departments assign the initial bottles to the households and thereafter receive from the central office each month a new bottle for each family. The scheme is so arranged that half the households of each size receive isoniazid and the other half placebo.

It will not be known with any precision how faithfully people take their pills. The most we shall know is how many say they do, how many of them return each month for a new supply, and what the returned bottles indicate. If, at the end of the year, the isoniazid households should have as much tuberculosis as the placebo households, we would not know whether this is a failure of isoniazid or a failure to take the pills. But we would know that to distribute isoniazid as a prophylactic in the way it is being done in this study is not a useful tuberculosis control measure. If isoniazid households should have less tuberculosis than placebo households, we would know that this is a minimum difference, that prophylactic isoniazid is at least this effective. The inclusion of both positive and negative tuberculin reactors in the study population should provide a means of learning whether new infection can be prevented among the tuberculin negatives and whether new disease can be prevented among the tuberculin positives while isoniazid is being taken.

Each person will take pills for only 1 year, but he will be observed, at least at 6-month intervals, we hope, for a number of years. From this continued followup, we hope to gain some information as to whether isoniazid has any lasting effect on old infections and whether prophylaxis of the uninfected during exposure interferes with their resistance during subsequent exposure.

We recognize that the task of evaluating isoniazid as a prophylactic agent is formidable. Nevertheless, the consequences for the control of tuberculosis would be so tremendous should the drug prove effective, and the indirect evidence that it will work is so promising, that we feel obliged to try.