Experiments With Isoniazid As a Preventive Measure Against Tuberculosis

ISONIAZID, which has shown remarkable powers in the treatment of tuberculosis, shows promise of being equally potent as a preventive.

At the annual meeting of the National Tuberculosis Association in Milwaukee, May 23–27, 1955, Dr. Carroll E. Palmer and Shirley H. Ferebee, chief and assistant chief, respectively, of the Operational Research Branch, Tuberculosis Program, Division of Special Health Services, Public Health Service, presented their report, entitled "Experimental Studies on Prevention of Tuberculosis," in which they demonstrated the effectiveness of isoniazid as a preventive against tuberculosis in guinea pigs.

Methods and Results

The studies incorporated these basic principles: large numbers of animal subjects, controls, random allocation of animals to treatment groups, and unbiased observations. About 1,250 guinea pigs were first isolated for 3 weeks. The death rate during this period was about 1 percent per week. The 1,224 living pigs were distributed into 5 comparable experimental groups.

In the drinking water of the first 3 groups were placed concentrations of isoniazid in amounts of 0.25, 0.05 and 0.01 milligram per milliliter, respectively. There were two groups of untreated pigs, one held for challenge and one reserved as normal, uninfected controls. By weighing each animal every week and by measuring the amount of water consumed each day, it was found that the pigs drank a fairly constant amount of water every day. The amount of isoniazid taken daily in the 3 drug groups approximated 25, 5, and 1 milligram per kilogram of body weight.

All groups except the "normals" were challenged intraperitoneally with virulent tubercle bacilli. The normal pigs received a placebo challenge. The controls—those that received no isoniazid—died rapidly after the challenge infection, and by the 10th week only 7 percent remained alive. Eighty-eight percent of the normals—those that had not been infected—were still alive in the 10th week. The pigs that received 1 mg./kg. of isoniazid received some protection since they did not die as rapidly as the controls. Thirty-seven percent were still alive by the 10th week. The challenged pigs that received either 5 or 25 mg./kg. of isoniazid did not have a greater death rate than the normal pigs.

For the first 10 weeks after challenge with tubercle bacilli the daily dose of 5 mg./kg. was enough to protect the pigs against an infection that was sufficiently virulent to kill nearly all of the controls.

At this point, the investigators considered the problem of the effect of withdrawal of isoniazid. They withdrew the drug, 10 weeks after infection, from pigs selected at random in each of the three treatment groups. The pigs that had received 1 mg./kg. of isoniazid continued to fare better than the controls. The animals that had received 5 or 25 mg./kg. survived as well as the normal animals over a period of 26 weeks.

At the 26th week, 75 percent of the pigs that received at least 5 mg./kg. for only 10 weeks, 74 percent of those that received 5 or 25 mg./kg. for the entire 26 weeks, and 71 percent of the unchallenged normal controls were still alive. This part of the experiment appears to indicate that as little as 5 mg./kg. of isoniazid per day for only 10 weeks is sufficient to knock out a

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virulent tuberculosis infection in guinea pigs.

Fourteen weeks after the date of the first challenge, randomly selected parts of each group of animals that had received 5 and 25 mg./kg. were rechallenged. Part of the original group of normals were challenged at the same time to obtain a new group of controls.

The new, untreated controls died rapidly, as expected. The animals that survived the first challenge while receiving isoniazid and had then been taken off the drug after the first 10 weeks, when rechallenged, did not die as rapidly as the controls even though they were not receiving the drug. This evidence suggests that a relatively small amount of isoniazid in the drinking water of guinea pigs not only protects them from getting tuberculosis but also allows them to develop a certain amount of resistance to a later untreated infection. This resistance is at least as great as has been produced in guinea pigs by vaccination with BCG.

The pigs that received 5 or 25 mg./kg. of isoniazid continuously during two challenge infections survived as well as the normals that had never been challenged.

Summary

A daily dose of isoniazid of not more than 5 mg./kg. of body weight, given in the drinking water, is apparently sufficient to protect guinea pigs completely from a large intraperitoneal challenge of virulent tubercle bacilli. This dose given for only 10 weeks after a virulent challenge was sufficient to prevent the appearance of disease after the drug was discontinued. Resistance to a later virulent infection, at least equal to that produced by BCG vaccination, develops in guinea pigs during the course of an isoniazid-treated challenge.

Whether isoniazid will be effective as a preventive of human tuberculosis depends on the results of controlled trials in large population groups, which are now being planned. Continuing experiments with laboratory animals will provide additional information essential to trials among human beings. Isoniazid has been used extensively since 1952 in treating tuberculosis, and its effectiveness and harmlessness have been conclusively demonstrated. The drug can be produced easily in large quantities, and its cost is low. Persons who are reactors to tuberculin or persons who exhibit suspicious shadows on X-ray films might be the first to benefit from the preventive and curative properties of isoniazid. These findings may mean that whole populations could be treated for as little as a penny a day per person.

CDC Slide Series

A series of approximately 35 color slides with descriptive notes has been prepared by the Public Health Service Communicable Disease Center. These slides emphasize the importance of communicable disease in the United States today. They outline Federal and State organization for control and show several phases of the center's program activities, such as orientation lectures, training courses, and other public presentations. Latest statistics are interpreted in diagrammatic and flow charts. Actual photographs of program activities are included. The series is available on loan in either 2- by 2-inch or 3¼- by 4-inch size. Requests should be addressed to James A. King, Jr., Special Assistant for Operations, Communicable Disease Center, Public Health Service, Atlanta, Ga.