Chemotherapy of Tuberculosis, Progress and Promise

THE DECLINE in tuberculosis mortality in the United States, which began in 1910, has been sharply accelerated during the past 10 years. Tuberculosis deaths dropped from 40 per 100,000 in 1945 to about 10 in 1955. Although this drop may be due in part to a slight decrease in new cases and perhaps in some measure to earlier detection of the disease, it must be primarily a result of improved treatment. Without question, the greatest single factor in the improvement of treatment has been the development of antimicrobial agents active against the tubercle bacillus.

Adequate assessment of the new drugs required new methods in clinical research. Aside from the knowledge about what could be expected of various antimicrobial agents, the most significant result of the evaluation of tuberculosis chemotherapy was the evolution of the large-scale, centrally coordinated, cooperative control study. The pattern developed for this type of study has elements necessary for evaluation of any treatment, in tuberculosis or in other diseases. A review of the therapy trials of the Public Health Service will not only summarize the present position of the chemotherapy of tuberculosis but will illustrate the scope and possibilities of such studies.

The Public Health Service first became engaged in evaluating tuberculosis treatment in 1947, when it acted as the central office for a control study of streptomycin. Congress had made special funds available for testing this antibiotic, the first to show marked antituberculous activity in the test tube and in animals. To avoid possible repetition of the disappointment and disillusionment that followed the high hopes raised by previous "wonder" treatments, such as gold, it was necessary to test streptomycin in such a way that the great desire to find an effective drug would not influence the appraisal of its efficacy. Therefore, it was decided that the available funds should be spent largely on control studies carried out in a number of hospitals throughout the country.

To date, the Public Health Service cooperative group has undertaken nine studies on tuberculosis therapy. Tuberculosis clinicians in hospitals in all parts of the country have voluntarily pooled their facilities and case material to carry out carefully designed control studies. This cooperative arrangement provides wide geographic representation, which gives a picture of variations in the disease and its response to treatment in different parts of the country. The Public Health Service has organized the studies, provided detailed protocols, assigned treatment regimens, coordinated the work in the participating hospitals, analyzed the data, and provided financial assistance to the hospitals to meet the special study expenses.

Each clinician relinquishes some autonomy in treating patients he places in a study. But he is aware of the exact limits of the restrictions because he himself has helped to plan the study. Knowing that any patient placed in the study may by chance receive any one of the regimens to be investigated, the clinician

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This paper was presented before the American College of Preventive Medicine by Dr. Rufus Payne, Medical College of Georgia, Augusta, one of the clinical investigators in the Public Health Service tuberculosis therapy trials. It was prepared by Shirley H. Ferebee and Dr. Frank W. Mount, Tuberculosis Program, Division of Special Health Services, Public Health Service.

selects only those patients for whom he feels he can ethically accept the alternatives. Once he has decided to include a patient, treatment is assigned in the central office by a system of random numbers, and the patient is treated with the assigned medication for a specified period. This is a critical point in the studies: a system in which treatment is assigned by persons who have no knowledge of the patient. It eliminates any influence, conscious or unconscious, which physicians treating the patient might exert on the assignment of treatment regimens. Not only is this method simpler for the physician responsible for the care of the patient but it is also the only sure way of obtaining groups of patients that are alike at the moment the different chemotherapeutic regimens are started. Thus, any subsequent differences between the groups can be attributed to the effects of chemotherapy.

Only in two exceptional circumstances is treatment altered: if a patient develops an intolerance to one or more of the assigned drugs or if his disease becomes critically worse, threatening his life.

The number of patients in a study ranges from 541 in the first cooperative effort, with 12 participating hospitals, to 1,990 in one of the more recent trials, with 29 hospitals. The size of these studies insures that the results are unlikely to be due to chance variation. In addition, it permits examination of the influence of various factors, such as age, race, and sex of the patient and stage and extent of disease, on the response to treatment.

In this era of bigness the impression is sometimes created that numbers alone are enough. But a definitive study depends only partly on size. These studies have also been carefully designed with these points in mind: What are the critical questions? What observations will provide the most information? How can these observations be made most objective and accurate?

Random allocation of treatment provides treatment groups completely comparable at the beginning of a study. By several other devices we try to obtain objectivity and freedom from bias in measuring the effects of treatment.

In testing for bacterial resistance, for example, sputum cultures are first examined in each hospital laboratory by technicians who are not allowed to know the patient's treatment. All positive cultures from all hospitals are sent to one central laboratory not associated with any of the hospitals. There each culture is tested for drug sensitivity without the bacteriologist's knowing the patient's regimen. In every study, many cultures are tested for sensitivity to drugs that the patient is not even receiving. The results of these cultures provide valuable information on the validity of the other results.

In the interpretation of X-rays, as another example, duplicate X-rays of each patient are taken monthly. One is kept at the hospital and one is sent to the central office. Periodically, the participating clinicians meet in Washington to review all the films. The serial films for each patient are read independently by three readers who do not know the patient or his treatment regimen. Each reader interprets the films for an equal number of patients on each regimen from every hospital except his own.

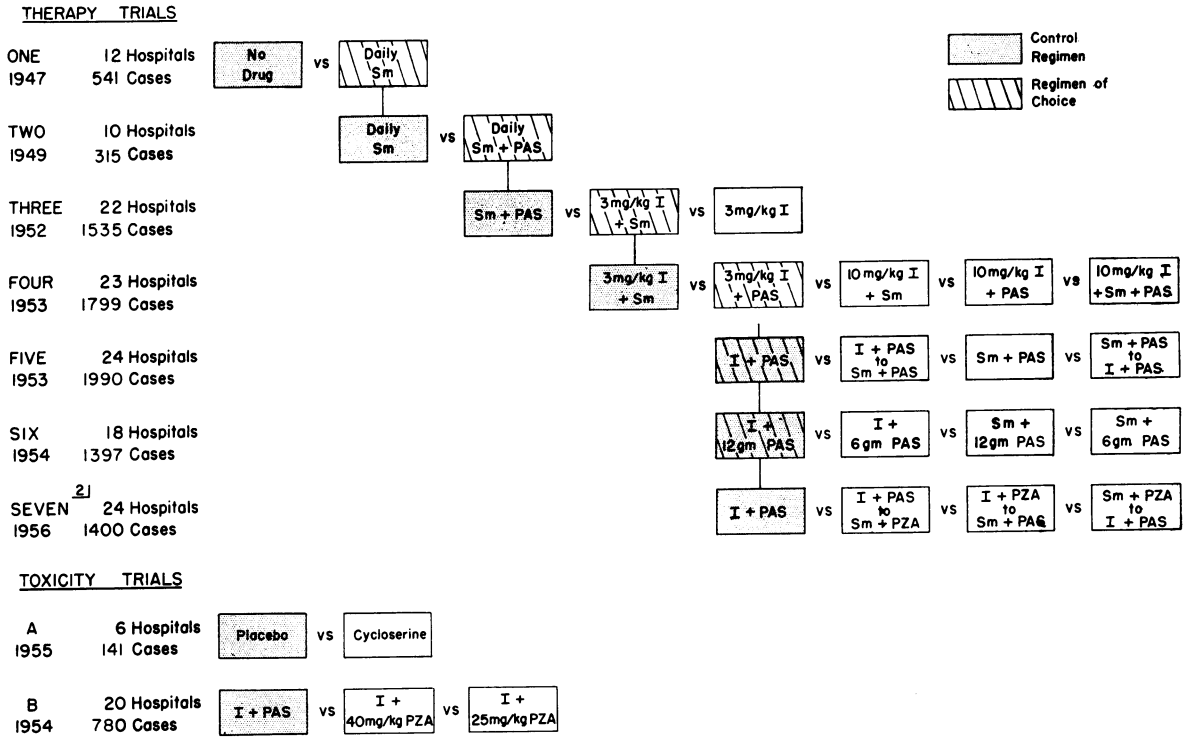
We shall now review briefly the nine cooperative studies carried out since 1947, tracing the evolution of tuberculosis chemotherapy and highlighting the results of the studies. In each subsequent study, new regimens are tested against the regimen which has previously given the best results. A summary of the studies is presented in figure 1.

Streptomycin and PAS

In the first study streptomycin was tested against no chemotherapy. A randomly selected half of the 541 patients received the classic treatment of bed rest, diet, and surgery, while their counterparts in each hospital received, in addition, streptomycin for the first 3 months of a 12-month observation period. Physicians in the 12 hospitals participating in this investigation deserve credit for their courage in carrying through a study in which streptomycin was withheld from half their patients.

By every criterion, patients who received streptomycin for 3 months were in better condition after 12 months than were the controls. Seventy percent of the streptomycin patients showed X-ray improvement, as compared with only 45 percent of the controls. Cultures were

Figure 1. Summary of the Public Health Service tuberculosis therapy trials.[1]



[1] Unless otherwise specified, Sm (streptomycin) was given in doses of 1 gm. 3 times a week; I (isoniazid), 3 to 5 mg./kg. daily; PAS (para-aminosalicylic acid), 12 gm. daily; and PZA (pyrazinamide), 40 mg./kg. daily. Cycloserine was tested in four dosages: 0.5 gm. twice a day, 1.0 gm. every second day, 0.5 gm. once a day, and 0.25 gm. twice a day.

[2] In progress.

negative for 24 percent of the streptomycin patients but for only 16 percent of the controls. The most striking finding in this first study, however, was that streptomycin halved the number of deaths: Only 10 percent of the streptomycin patients, as compared with 20 percent of the controls, died during the year of observation.

Shortly after streptomycin was introduced, PAS (para-aminosalicylic acid) became available in this country. With the usefulness of streptomycin clearly evident, the cooperating group decided its second study should compare streptomycin alone with streptomycin plus PAS. Since PAS showed much less tuberculostatic activity than streptomycin in the test tube and experimental animals, it was not thought necessary to include a group receiving only this drug. Each of 315 patients was randomly assigned to receive either streptomycin or streptomycin plus PAS for 3 months, with observation to continue for another 3 months. The primary purpose was to see whether PAS might prolong the usefulness of streptomycin by delaying the emergence of streptomycin-resistant organisms. It was found that not only did PAS prolong the streptomycin sensitivity of the tubercle bacilli, but it increased the frequency of sputum conversion and resulted in greater X-ray improvement.

By 1952 the price of a gram of streptomycin had fallen from $20 to about 20 cents, and the drug was available in plentiful supply, as was PAS. The two drugs together had become the standard treatment for hospitalized tuberculosis patients throughout the United States. They were indispensable adjuncts to bed rest and surgery in the long-term care necessary for tuberculosis patients. Then in March 1952 isoniazid made its dramatic entrance. In the midst of tremendous enthusiasm for the new drug, the Public Health Service took the posi-

tion that isoniazid must be compared in strict control studies with the best therapy then available, that is, streptomycin plus PAS. Consequently, in that same month, representatives of 22 tuberculosis hospitals met in Washington and adopted a common protocol to evaluate the therapeutic efficacy of isoniazid. Within 5 months 1,535 patients were under observation.

In the course of these investigations, bacteriological change had emerged as the most sensitive index of the effectiveness of antimicrobial agents. In the charts to follow, bacteriological results of various regimens are compared for previously untreated patients who were infectious when they were admitted to the studies.

Isoniazid

Since the second study had shown streptomycin plus PAS to be superior to streptomycin alone, we used streptomycin plus PAS in the third study as the yardstick against which to measure isoniazid alone and isoniazid in combination with streptomycin. For all regimens the decrease in positive cultures was rapid during the early weeks of treatment. By the 40th week, however, cultures were still positive for 39 percent of the patients treated with streptomycin plus PAS and 38 percent with isoniazid alone, but for only 25 percent with isoniazid plus streptomycin (fig. 2).

Having found isoniazid plus streptomycin superior to either streptomycin plus PAS or isoniazid alone, we proceeded to a fourth study, which included 1,799 patients. We used isoniazid plus streptomycin as the basic regimen and compared it with isoniazid plus PAS and with all three drugs together, isoniazid plus streptomycin plus PAS. We also investigated the possibility that better results might be obtained by increasing the daily dose of isoniazid from 3 mg./kg. to 10 mg./kg.

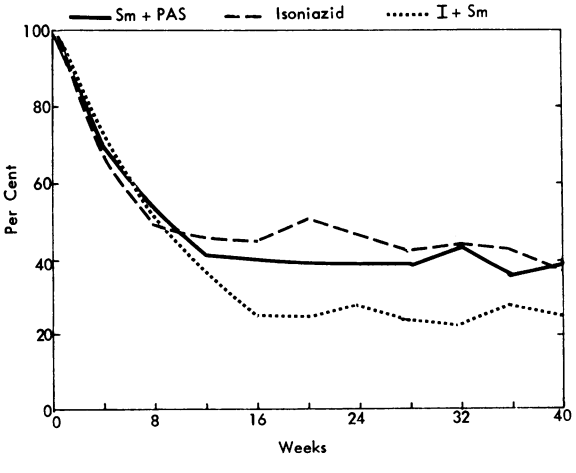
The three regimens with 10 mg./kg. of isoniazid were about equally effective in reversing infectiousness (fig. 3). At the end of 40 weeks of treatment, tubercle bacilli were detected in the cultures of 17 percent of the patients treated with isoniazid plus streptomycin, in 8 percent treated with isoniazid plus PAS, and in 6 percent treated with all three drugs. Although there was no therapeutic advantage when the dose of isoniazid was raised from 3 to 10 mg./kg., the 10 mg./kg. dose was considerably more toxic, producing peripheral neuritis in about 10 percent of the patients. On the basis of these findings, we reasoned that the regimen of choice at that point was isoniazid at 3 mg./kg. plus PAS, which would leave streptomycin to be used later if necessary.

Switching Regimens

In all these studies bacteriological changes were rapid during the early weeks of treatment, but patients still producing positive sputum after the 20th to 24th week seldom became negative. This observation led to the fifth study, in which major drugs were switched after 24 weeks of treatment and different sequences tried. For the first 24 weeks we gave half the patients isoniazid plus PAS and half streptomycin plus PAS. Then we switched half the patients receiving isoniazid plus PAS to streptomycin plus PAS and half those receiving streptomycin plus PAS to isoniazid plus PAS.

During the first 24 weeks, when half the 1,990 patients were receiving isoniazid plus PAS and half streptomycin plus PAS, the decrease in positive cultures was greater with isoniazid plus PAS (fig. 4). By the 24th week cultures

Figure 2. Percentage of patients with positive cultures during 40 weeks of treatment with streptomycin plus PAS, isoniazid, or isoniazid plus streptomycin.



had become negative for all but 26 percent of the patients on streptomycin plus PAS and for all but 8 percent of the patients on isoniazid plus PAS. Patients whose cultures had not become negative may be regarded as treatment failures, and their course during the subsequent 24 weeks is reported here.

The treatment failures included patients who died of tuberculosis or whose chemotherapy was changed because of critical worsening, as well as those who continued to produce tubercle bacilli after 24 weeks on the primary regimen. Of course, for those who died there was no opportunity for the secondary regimen to change the course of their disease, and for those whose treatment was changed earlier the status at the 24th week is not a measure of the effect of 24 weeks of treatment on the assigned regimen.

The left chart in figure 5 deals with the 26 percent of the streptomycin-plus-PAS patients who had failed to become sputum negative, including 4 percent who had died or been removed from the regimen. When treatment with streptomycin plus PAS was continued, the failure group decreased to 20 percent by the 40th week. However, when isoniazid plus PAS was substituted for streptomycin plus PAS, the proportion of bacteriological failures dropped to 10 percent by the 40th week.

Figure 3. Percentage of patients with positive cultures during 40 weeks of treatment with isoniazid plus streptomycin, isoniazid plus PAS, or isoniazid plus streptomycin plus PAS.

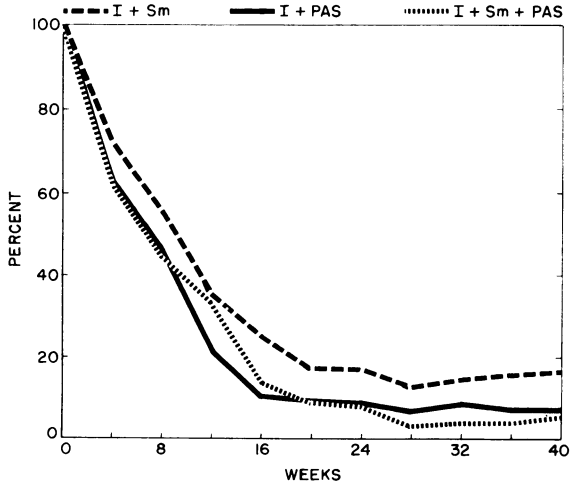
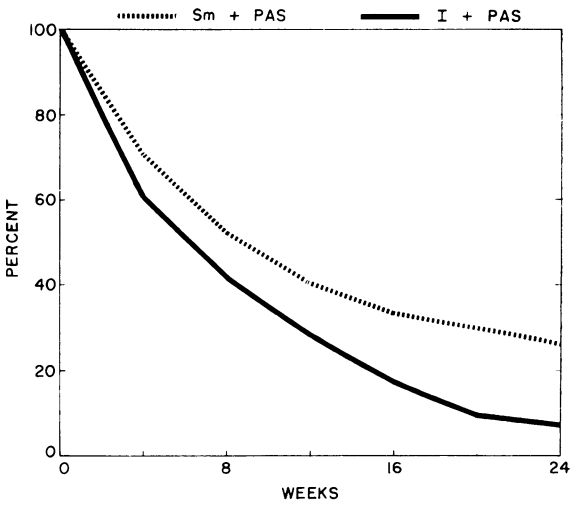


Figure 4. Percentage of patients with positive cultures during 24 weeks of treatment with streptomycin plus PAS or isoniazid plus PAS.



The right chart in figure 5 deals with the 8 percent of the isoniazid-plus-PAS patients whose cultures had not become negative by the 24th week. This group includes 1 percent who had died or had been changed to another treatment regimen. When treatment with isoniazid plus PAS was continued, the percentage of failures dropped to 4 by the 40th week. When treatment was switched to streptomycin plus PAS, the results were no better.

This study showed isoniazid plus PAS to be such an effective regimen that there was little advantage in switching to streptomycin plus PAS after 24 weeks. On the other hand, among patients initially treated with streptomycin plus PAS, a switch to isoniazid plus PAS after 24 weeks was preferable to an additional 16 weeks of streptomycin plus PAS.

Decreased PAS Dosage

Again isoniazid plus PAS appeared to be the regimen of choice both for initial and long-term use. However, it had always had one disadvantage. A number of patients were unable to tolerate the usual large dose of PAS, 12 grams a day. Encouraged by the results of a small pilot study, we decided to see whether decreasing the dose of PAS would reduce toxicity without loss of therapeutic effect. Although we were primarily interested in the use

of PAS with isoniazid, we also used this opportunity to test a lower dose of PAS with streptomycin. We randomly divided the 1,397 patients into 4 groups to receive daily isoniazid with 12 grams of PAS, isoniazid with 6 grams of PAS, streptomycin with 12 grams of PAS, and streptomycin with 6 grams of PAS.

This study demonstrated that PAS toxicity was reduced by decreasing the daily dose. During the 40 weeks of treatment about 11 percent of the patients could not tolerate the 12 gram dose, but only 4 percent could not tolerate 6 grams. Most of the patients who could not tolerate the larger dose were able to continue the drug when the dosage was cut in half.

In combination with either isoniazid or streptomycin the large dose of PAS was slightly more effective than the small dose (fig. 6). Again, the combination of isoniazid plus PAS was superior to streptomycin plus PAS. In fact, even the small dose of PAS with isoniazid was more effective than the large dose with streptomycin.

We concluded that all patients should be placed first on a regimen of isoniazid plus 12 grams of PAS. However, for those unable to tolerate that dose of PAS, the daily dose could be reduced to 6 grams with only a small loss in therapeutic effectiveness.

Figure 5. Percentage of patients with positive cultures from the 24th through the 40th week among patients treated continuously with streptomycin plus PAS or switched from streptomycin plus PAS to isoniazid plus PAS after 24 weeks and among patients treated continuously with isoniazid plus PAS or switched to streptomycin plus PAS after 24 weeks.

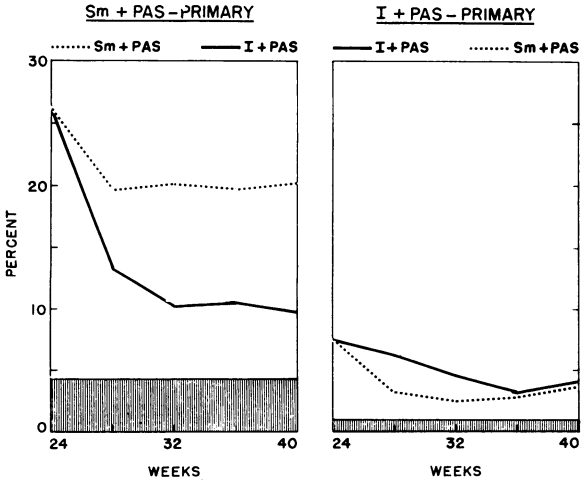
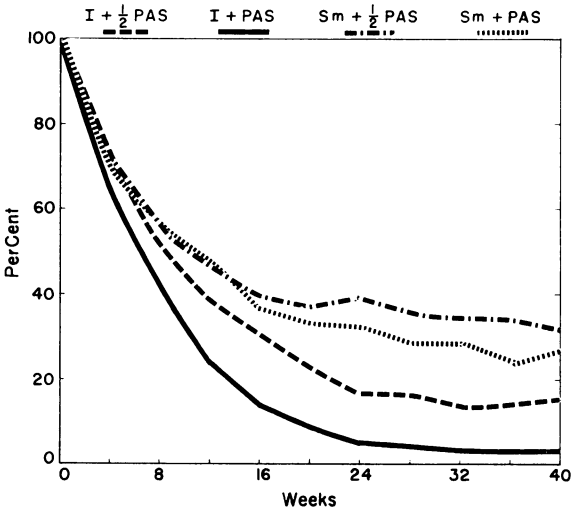


Figure 6. Percentage of patients with positive cultures during 40 weeks of treatment with isoniazid plus 6 gm. PAS, isoniazid plus 12 gm. PAS, streptomycin plus 6 gm. PAS, or streptomycin plus 12 gm. PAS.



Cycloserine and Pyrazinamide

Up to this point, we had been investigating ways of using the three available drugs, isoniazid, streptomycin, and PAS. In the past 2 years we have considered, in addition, two other antimicrobial agents, cycloserine and pyrazinamide. Both drugs had been reported to produce severe toxic reactions. Therefore, before testing their therapeutic efficacy in previously untreated patients, we undertook studies among "hopeless cases" to determine the frequency and severity of the toxic reactions.

In one toxicity study we compared several different doses of cycloserine with a placebo. No significant toxic reactions occurred among the 26 patients receiving placebos, but toxic reactions to cycloserine occurred at all dose levels tested except the lowest, which we found to be below the range of therapeutic effectiveness (see table). Convulsions, the most serious of the toxic effects, were not confined to a single dosage, and we found no evidence that they were limited to patients with certain characteristics. Therefore, in contrast with the safety and effectiveness of isoniazid

Toxic reactions of patients unable to tolerate assigned cycloserine regimens

Cycloserine regimen	Number patients treated	Number with toxic reactions[1]	Number with convulsions
Total	115	18	8
0.5 gm. twice daily	25	11	4
1.0 gm. every second day	39	5	3
0.5 gm. once daily	38	2	1
0.25 gm. twice daily	13	0	0

[1] Includes convulsions.

plus PAS, we concluded that cycloserine was too toxic for us to undertake a large-scale therapeutic trial in patients with a favorable prognosis.

Pyrazinamide had been reported to have a dramatic therapeutic effect when used with isoniazid but to cause acute liver damage in some patients. In a carefully controlled study among 780 treatment failures, we used isoniazid plus PAS as a control and tested 2 doses of pyrazinamide in combination with isoniazid. Liver function tests were carried out in the hospital laboratories by technicians who did not know what drugs the patients were receiving, and the patients were examined for signs and symptoms of hepatitis by physicians who had no knowledge of their treatment.

During the first 12 weeks of treatment, evidence of hepatic toxicity was reported for 0.8 percent of the patients receiving isoniazid plus PAS and for 0.8 and 1.2 percent of the patients receiving, respectively, 40 mg./kg. and 24 mg./kg. of pyrazinamide with isoniazid. During the second 12-week period liver damage appeared among 5.4 percent of those receiving the larger dose of pyrazinamide and among 1.2 percent of those receiving the smaller dose. These findings, plus the fact that the treatment failures had shown considerable therapeutic benefit from the combination of isoniazid and pyrazinamide, made us decide to undertake a large-scale therapeutic trial of pyrazinamide in combination with isoniazid and in combination with streptomycin. However, we are using pyrazinamide for only 16 weeks and are then switching regimens. This study was begun only recently, and it will be some months before results will be available.

Prophylactic Possibilities

For those of us concerned with preventive medicine, interest in the treatment of persons with active pulmonary tuberculosis is not confined to the direct benefits to the patients. We are sensitive to an indirect benefit from improved treatment: the decrease in spread of disease. More infectious persons are willing to accept treatment, and infectiousness is reversed in most of those treated.

Now, isoniazid introduces the possibility of a new method of tuberculosis control: prophylaxis. It is a cheap, orally administered drug that has been demonstrated during the past 4 years to be extremely effective in the treatment of patients with tuberculosis and to be practically nontoxic in therapeutic doses. A drug that can reverse the course of far-advanced cavitary disease might, if given at the right time, prevent the appearance of clinical disease.

Prophylaxis in tuberculosis has become a highly controversial subject. Some enthusiasts advocate immediate widespread use of the drug in highly exposed population groups. Others are equally firm in their conviction that such use of isoniazid would have grave consequences by interfering with the development of natural immunity. But there is also a middle ground, one occupied by many physicians and public health workers. They feel, as does the Public Health Service, that only a series of large, long-term, controlled investigations can provide actual data to replace the present spate of conjecture on the effects of using isoniazid to prevent clinical tuberculosis in human beings.

The Public Health Service and a number of cooperating clinicians and public health workers have begun a series of studies on the prophylactic possibilities of isoniazid. In the first study in human beings, the prophylactic goal is the prevention of meningitis and other complications among children with asymptomatic primary tuberculosis whose present condition does not require treatment. More than 2,000 children are now under observation in 31 pediatric clinics in the continental United

States, San Juan, Mexico City, and Toronto. Each child takes pills for 1 year, and neither the patient, nor his family, nor the physician knows whether the pills contain isoniazid or placebo. By comparing the number, kind, and severity of complications that develop among children taking isoniazid with the complications that develop among children taking placebos, we expect to determine isoniazid's effectiveness.

In the meantime we are accumulating information to answer an even more basic question: How often today do meningitis and other complications of primary tuberculosis occur? In other words, we are collecting precise information on how much there is to prevent, by isoniazid or any other preventive procedure.

The next step in the Public Health Service's investigation is to determine whether isoniazid will prevent infection and the appearance of clinical disease among the highly exposed household contacts of active cases of tuberculosis. A nationwide study is being started in which contact households are randomly assigned to isoniazid or placebo groups and are kept under close observation by their local health departments. Each contact is tuberculin tested and X-rayed at the beginning and at

Clinical Investigators in the Tuberculosis Therapy Trials

The following 53 physicians in 39 hospitals scattered throughout the United States participated in the Public Health Service tuberculosis therapy and toxicity trials conducted from 1947 through 1956. The figures and letters in parentheses are trial designations, as given in figure 1.

Baltimore City Hospital, Baltimore, Md.: Edmund G. Beacham (7).

Battey State Hospital, Rome, Ga.: Rufus Payne (2,3,4) and Raymond Corpe (4,5,6,7,B).

Benjamin Franklin Hospital, Columbus, Ohio: Harold Humphrey (5, 6,7).

Cedarcrest Hospital, Newington, Conn.: R. C. Edson (5,6,7,B).

Channing Home for Tuberculosis, Boston, Mass.: Theodore L. Badger (2).

Firland Sanatorium, Seattle, Wash.: Roberts Davies (3,4,B), Daniel Zahn (6,A), and Thomas Sheehy (7).

Florida State sanatoriums in Lantana, Orlando, and Tampa: Roberts Davies (6,7), W. L. Potts (3,4, 5,B), George H. Hames (6,7), Benjamin L. Brock (3,4,5,6,7,B), Henry C. Sweany (3,4,5,B), A. M. Dietrich (4), and Frank Cline (7).

Freedmen's Hospital, Washington, D. C.: Howard M. Payne (1,2,3,4,5, 6).

Glen Lake Sanatorium, Oak Terrace, Minn.: Sumner S. Cohen (3,4, 5,6,7,A,B).

Herman Kiefer Hospital, Detroit, Mich.: Paul T. Chapman (3,4,5,6,7, A,B).

Maybury Sanatorium, Northville, Mich.: W. J. Steininger (3,4,5,6,7, A,B).

Middlesex County Sanatorium, Waltham, Mass.: Francis P. Dawson (2,3).

Missouri State Sanatorium, Mount Vernon, Mo.: Charles A. Brasher (4, 5,6,7,B).

Municipal Tuberculosis Sanitarium, Chicago, Ill.: LeRoy H. Berard (5,7).

New York State hospitals: H. McLeod Riggins (1,2); Hermann M. Biggs Memorial Hospital, Ithaca: N. Stanley Lincoln (1,2); Homer Folks Tuberculosis Hospital, Oneonta: Ralph Horton (1,2); Mount Morris Tuberculosis Hospital, Mount Morris: Arthur M. Stokes (1,2); Ray Brook Sanatorium, Ray Brook: Harry A. Bray (1) and Frederick Beck (2).

North Carolina State sanatoriums in Black Mountain, McCain, and Wilson: Charles D. Thomas (1,3,4,5,6, 7,B), H. Stuart Willis (1,2,3,4,5,B), W. H. Gentry (3,4,5,B), and Herman F. Easom (1,3,4,B).

Olive View Sanatorium, Olive View, Calif.: Emil Bogen (1).

Ohio Tuberculosis Hospital, Columbus, Ohio: R. H. Browning (7).

Pennsylvania State sanatoriums in Cresson, Hamburg, Philadelphia, and South Mountain: J. L. Wilson (3,4,5), H. W. Weest (3,4), Frederick R. Lang (B), G. M. Eckley (3,4,5,7,B), and H. C. Dooling (3, 4,5).

Pittsburgh Tuberculosis Hospital, Pittsburgh, Pa.: George E. Martin (3,4,5,6,7,B).

Robert Koch Hospital, Koch, Mo.: Alfred Goldman (1,2,3,4,5,7,B) and Mario Pianetto (3,4,5,7,B).

San Antonio State Tuberculosis Hospital, San Antonio, Tex.: E. H. Gist (5,B) and E. H. Roberts (6,7).

Seward Sanatorium, Seward, Alaska: Lawrence M. Lowell (1).

Stanford University Hospital, San Francisco, Calif.: William M. M. Kirby (1).

Sunny Acres Tuberculosis Hospital, Cleveland, Ohio: Harold G. Curtis (3,4,5,6,7,B).

Tennessee State Tuberculosis sanatoriums in Memphis and Oakville: E. P. Bowerman (3,4,5,6,7,A,B) and F. H. Alley (3,4,5,6,7,A,B).

Uncas-on-Thames Sanatorium, Norwich, Conn.: George C. Wilson (3,4,5,7,B).

U. S. Public Health Service Hospital, Brooklyn, N. Y.: Raymond Hofstra (3), J. E. Wilson (4,5), and Erwin Blatter (6,7).

the end of a year of prophylaxis. Included in the study population are both uninfected (tuberculin negative) members of the household and infected (tuberculin positive) members who show no clinical evidence of disease. The study should provide information on the effectiveness of isoniazid in preventing new infections and in preventing development of clinical disease in those already infected. Because this study includes a group that gets only placebos, it will also provide information on just how much tuberculosis is arising today among household contacts of the tuberculous.

In still another branch of this investigation, isoniazid's effect among previously infected persons who are not in highly exposed situations will be studied. An impressive body of evidence is accumulating that much of the new clinical tuberculosis is occurring among previously infected persons whose subclinical infection progresses to active disease under either external stress or decreased general resistance. It seems most important to determine whether the threat of tuberculosis which millions of older persons infected in childhood carry with them can be removed by prophylactic use of isoniazid.

This difficult and costly investigation may show that isoniazid has no prophylactic value, or that its value is offset by interference with natural immunity, or that it is effective only while it is being taken. It may show that it only delays but does not prevent. On the other hand, if it is effective in any one of the areas under investigation, in preventing infection, in preventing new infection from progressing to clinical disease, or in eradicating old subclinical infections which may flare up in endogenous disease, we will have gained an important public health weapon in the fight against tuberculosis.

Cerebral Vascular Disease Program

The first nationwide cooperative research program on cerebral vascular disease was launched in April 1957.

Ten medical research centers in 9 States have joined in the program, and it is expected that 35 to 40 institutions will eventually participate. The program, which is under the auspices of the National Institute of Neurological Diseases and Blindness of the Public Health Service, was made possible by grants from the National Institutes of Health to the various participating organizations. The program is supplemented by 29 current research projects on various aspects of cerebral vascular disease.

Cooperative investigation will make possible the study of thousands of patients who either have suffered a stroke or who show clinical signs indicating that a stroke might be approaching. The program is specifically concerned with patients suffering from cerebral vascular disease involving hemorrhage, blood clots, blood tumors, (aneurysms), and malformations of the arteries or veins of the brain.

Research results may reveal more about the nature and causes of strokes and facilitate more effective treatment methods.

Data collected will be collated and evaluated at the University of Iowa, Iowa City, one of the cooperating institutions.