

# Research Recherche

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## Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial

INTERNATIONAL UNION AGAINST TUBERCULOSIS COMMITTEE ON PROPHYLAXIS<sup>1</sup>

*A total of 28 000 persons with fibrotic pulmonary lesions compatible with tuberculosis were followed for five years after receiving 12, 24, or 52 weeks of preventive treatment with isoniazid or placebo.*

*Compared with placebo, 12 weeks of isoniazid eliminated less than one-third, and 24 weeks eliminated two-thirds of the tuberculosis risk. Where preventive treatment is not currently practised, adopting a 24-week regimen could decrease the incidence of tuberculosis in such populations by 65%.*

*Hepatitis, the only serious side-effect encountered, occurred infrequently but was more common among isoniazid recipients (0.5%) than among placebo recipients (0.1%).*

*Fifty-two weeks of isoniazid prevented the most tuberculosis, but 24 weeks prevented more tuberculosis cases per case of hepatitis caused. Where preventive treatment is currently practised for 52 weeks, adopting a 24-week regimen would decrease hepatitis by one-third and increase tuberculosis by 40%.*

The major public health objective of tuberculosis control is to stop transmission of tubercle bacilli. The most important means of reducing transmission is the treatment of infectious cases with antituberculosis drugs. However, treatment of cases alone will not benefit those persons who have already been infected; therefore, the prevention of disease among infected persons at high risk of becoming infectious is a desirable second step.

Controlled trials in several countries have established that isoniazid therapy for one year is effective in preventing tuberculosis (1–4). However, twelve months of daily pill-taking is difficult to accomplish

both for persons being treated and health workers responsible for supervising treatment. Therefore, the Scientific Committee on Prophylaxis of the International Union Against Tuberculosis developed the trial described in this paper to study the relative efficacy of shorter durations of isoniazid preventive therapy. Persons with fibrotic lesions were selected for the trial population for two reasons: with the exception of recently infected persons such as household contacts, they had the highest risk of developing progressive disease; and in the participating countries they were an already identified group who were under lifetime annual surveillance.

The trial was designed to follow the study population systematically for a period of five years. Passive follow-up of a portion of the population has continued. This report presents the final results at the end of the five years.

<sup>1</sup> The list of participants in this trial is given in Annex I on page 564. This report was prepared by N. J. Thompson, Centers for Disease Control, Atlanta, GA, USA. Requests for reprints should be addressed to: Technical Information Services, Center for Prevention Services, Centers for Disease Control, Atlanta, GA 30333, USA.

## MATERIALS AND METHODS

Tuberculin-positive persons with fibrotic lesions were admitted to the trial from 115 dispensaries in seven European countries: Czechoslovakia, Finland, German Democratic Republic (DDR), Hungary, Poland, Romania, and Yugoslavia. The data were collected in each dispensary, reviewed in each country's national coordinating office (NCO), and transmitted to the central coordinating office (CCO) in the Research Institute for Tuberculosis and Respiratory Disease, Berlin-Buch, DDR, for initial data processing. Final data processing and statistical analyses were conducted at the Centers for Disease Control (CDC) in the United States of America. A more detailed discussion of the materials and methods has been presented in preliminary reports (5-8).

For the purpose of entry to the trial, fibrotic lesions were defined as well-delineated radiographic lesions of probable tuberculous origin, usually in the upper half of the lung, which had been stable during the year prior to entry.

The trial population was originally limited to persons 20-64 years of age; however, a few persons outside these limits were eventually admitted. The principal criteria for exclusion were: less than 6-mm induration to a Mantoux test using 2 TU of RT23 with Tween 80, lesions limited to solitary calcifications or thickening of apical or diaphragmatic pleura, previous treatment with antituberculosis drugs, or a previous record of positive bacteriological findings.

It was left to the discretion of each dispensary, according to local standards, whether to tell a candidate that this was a controlled double-blind trial in which he or she might, by chance, receive either isoniazid or placebo and, by chance, be treated for 12, 24, or 52 weeks.

For randomization of patients into treatment groups, each dispensary was assigned a block of identification numbers (ID numbers) to be assigned in sequence and a matching supply of numbered packs of pills (pill calendars), each containing 35 pills of either placebo or 300 mg of isoniazid. The isoniazid and placebo, contributed by the DDR, were manufactured to look, smell, and taste alike. Only the central coordinating office and the statistical office at CDC knew which ID numbers were associated with each product. In each dispensary, one-third of the participants were to receive pills for 12 weeks, one-third for 24 weeks, and one-third for 52 weeks. Within each duration group, three-quarters were to receive isoniazid and one-quarter placebo. Until a participant approached the 12th week of treatment, dispensary staff did not know how long that patient's

treatment was to be.

All positive cultures detected at the admission examinations and during the trial were to be sent to the bacteriological reference laboratory for classification as tubercle bacilli or other mycobacteria. *Mycobacterium tuberculosis* was identified by its colonial morphology and the production of nicotinic acid. If an admission culture was found to be positive, the dispensary was requested to provide a new specimen for a repeat culture. Participants whose admission cultures showed growth of *M. tuberculosis* or *M. bovis* were considered ineligible, removed from the trial, and recommended for antituberculosis chemotherapy. Participants with cultures positive for any other mycobacteria were retained in the trial.

Arrangements were made for central review of all chest radiographs by a single reader in the DDR. Admission radiographs and radiographs taken at least 11 months earlier were reviewed to determine that there had been no change in the fibrotic lesion during the year. Lesions were classified by size; all shadows appearing on a 35×35 cm film were summed and classified as less than 2 cm<sup>2</sup>, 2 cm<sup>2</sup> or more, and extensive pleural thickening covering more than one-third of one lung.

During each of the first two visits to the dispensary, 48-96 hours apart, sputum specimens were collected and tuberculin tests were given and read for each person whose records indicated eligibility for the trial. A chest radiograph was taken on the first visit. Each candidate was told by the dispensary physician about the risk of progressive tuberculosis associated with fibrotic lesions and the protection provided by isoniazid and told that the length of treatment he or she required would be determined at the end of 12 weeks of treatment. Each participant was given a pill calendar and was told to take one pill a day and to bring the calendar back in four weeks' time, when returning to receive a new supply of pills. Participants were advised to call the dispensary if they had any unexpected reactions. On return visits, they were questioned about their health in general. Dispensary physicians and nurses were informed that most adverse reactions would occur during the first two months of pill-taking. In addition, dispensary staff were told to be particularly alert for symptoms of isoniazid-induced hepatitis.

Urine tests to detect the ingestion of isoniazid were performed once in every three-month period to verify reported pill-taking as described previously (6). Participants were instructed in the performance of the urine test using filter-paper strips prepared at the CCO, according to Nielsch's method (9). The CCO developed the strips, classified them as negative or positive, and forwarded the results to the statistical centre.

The dispensary physician judged the participant's

completion of treatment; most participants who "completed" their regimens received almost all of the calendars allotted for their assigned duration. For participants who stopped collecting new pill calendars before their intended duration was completed, the reason was recorded. Using both the participant's testimony and the returned calendars, dispensary personnel recorded the number of pills "taken" from each calendar. If the number of pills taken from a calendar was sufficient to allow a daily dose on at least 80% of the days covered by that calendar, the participant was defined as "compliant" for that month. Participants who closely adhered to their regimen by both completing the assigned duration and complying during each month are referred to as "completer-compliers" in subsequent discussions.

Five annual health examinations were scheduled on or close to the anniversary of the admission examination. A specimen for culture and a chest radiograph were taken at each annual health examination. If neither culture results nor a radiograph were available for a participant, information was provided by the dispensary as to whether that person was known to be living and in good health. If a participant received antituberculosis drugs in addition to the assigned regimen for any reason, or died, this information was recorded on the annual health examination report.

A total of 27 830 participants remained in the trial after exclusion of persons not meeting the admission criteria. Of those, 6956 (25%) were assigned to take 12 weeks of isoniazid (12-I), 6965 (25%) to take 24 weeks of isoniazid (24-I), and 6919 (24.9%) to take 52 weeks of isoniazid (52-I). The remaining 6990 participants (25.1%) were assigned to placebo (P) regimens: 2350 (8.4%) for 12 weeks (12-P), 2338 (8.4%) for 24 weeks (24-P), and 2302 (8.3%) for 52 weeks (52-P). The compositions of the populations assigned to each product and duration of therapy were very similar to the composition of the entire study population with respect to

each of the characteristics described below.

The median age of the population upon entry to the trial was 50 years. The population was skewed toward older age groups, 38% of the participants being between 55 and 65 years of age. Fifty-three percent of the population were male, 47% were female. Participants had a median induration size to tuberculin of 15 mm (range 6–90 mm).

At the time participants entered the trial, the median length of time for which their lesions had been known to exist was 8 years (range 11 months–58 years). Sixty-seven percent of the participants had lesions that were smaller than 2 cm<sup>2</sup>, 30% had lesions 2 cm<sup>2</sup> or greater, and 3% had pleural thickening that precluded measurement of the size of the lesion.

Participants suspected of developing progressive tuberculosis during the trial were first identified by the dispensary physician. Their records were then reviewed by the NCO and the CCO. A diagnosis of tuberculosis was considered to be confirmed only if tubercle bacilli were grown in culture. These confirmed diagnoses were then classified according to the scheme presented in Table 1. Using these rules, all classifications were re-evaluated independently by two physicians without knowledge of duration or product, and complete agreement was achieved. Only those persons whose diagnoses were classified in the first three categories of Table 1 were counted as cases for these analyses.

The risk of tuberculosis in any segment of the population was determined using rates determined by the life-table method (10). The percentage reduction in risk provided by an isoniazid regimen was determined by comparing the risk of tuberculosis among persons assigned to that regimen with the risk among those on placebo. The relative risk of tuberculosis was determined by comparing persons assigned to one regimen with persons assigned to another (11). Statistical significance was achieved if a *P* value was less

Table 1. Method for classification of cases with positive culture

No. of positive cultures	X-ray status	Therapy started	Additional conditions	Classification	Counted as case
> 1	Irrelevant		—	Confirmed	Yes
1	Progression immediately or later	Yes or refused or contraindicated		Confirmed	Yes
1	No change	Yes	—	Possible	Yes
1	Progression but probably not due to TB	Yes or no	Negative statement by physician	Unlikely	No
1	No change	No	—	Unlikely	No

Table 2. Percentage of participants by regimen and weeks completed and complied

Duration	Product	No. of weeks completed (complied)			
		12	24	36	52
12 weeks	Isoniazid	95 (87)			
	Placebo	97 (91)			
24 weeks	Isoniazid	94 (84)	93 (78)		
	Placebo	96 (87)	95 (82)		
52 weeks	Isoniazid	93 (84)	91 (79)	89 (73)	88 (68)
	Placebo	95 (87)	93 (79)	91 (74)	90 (69)

than 0.05. Tests of significance employed in this study were the chi-square test for linear trends (12) and the chi-square test for proportions (13). The power of these tests ( $100 - B$ ) was calculated according to the method described by Snedecor & Cochran (14).

## RESULTS

The percentages of participants completing 12, 24, and 52 weeks of pill-taking, as well as the percentage of those who both completed and complied (see page 557), is shown by regimen in Table 2. Two percent fewer persons completed each duration of isoniazid than the same duration of placebo. The shorter the regimen, the higher the proportion of patients who completed (and complied with) the assigned therapy.

Few side-effects occurred in the trial. Most of these were mild and transient, e.g., headache, nausea, and dizziness. The only serious side-effect reported was hepatitis, which occurred in a total of 95 (0.5%) of 20 840 persons receiving isoniazid, and 7 (0.1%) of 6990 persons receiving placebo. Three of these cases resulted in death (0.14 per 1000 persons receiving the drug), 2 on the 12-I regimen, and 1 on 52-I. Table 3

shows the risk of hepatitis by three-month period, and the cumulative risk for various durations of therapy. The risk reductions indicate the number of hepatitis cases per 1000 persons that could be avoided by shortening the duration of isoniazid therapy from the standard 52-week regimen.

Of the 27 830 participants entering the trial, the five-year follow-up was complete for 27 049 (97.2%). Persons for whom the follow-up was not completed included 480 (1.7%) for whom one or more of the annual report forms were never received, and 301 (1.1%) who were lost to follow-up. Another 412 participants (1.5%) were removed from the trial at some stage as suspected cases of tuberculosis; 140 of these were confirmed cases with two or more positive cultures, 60 were confirmed cases with one positive culture, and 31 were possible cases with one positive culture (Table 1). The remainder were determined to have disease compatible with progressive pulmonary tuberculosis but not confirmed by culture, extrapulmonary tuberculosis, or only one isolated positive culture with scanty growth. An additional 124 participants (0.5%) were withdrawn from the study because they received isoniazid for reasons not related to the trial (such as corticosteroid therapy or pregnancy). Throughout the five years of the trial, 1124 participants (4.0%) were lost because of death.

The risk of breakdown with tuberculosis disease on each isoniazid regimen and on the placebo regimens combined is presented in Table 4. Three persons developed tuberculosis during the first 6 months of pill-taking, 1 on placebo, 1 on 24-I, and 1 on 52-I. Three cases of tuberculosis resulted in death (0.42 per 1000 persons), all among persons assigned to placebo regimens. As shown in column 4, the risk of tuberculosis was reduced by 21% by 12 weeks of isoniazid, 65% by 24 weeks, and 75% by 52 weeks of isoniazid, when compared with placebo.

The relative risk of developing tuberculosis on each of the shorter isoniazid regimens when compared to the 52-I regimen, is given in column 5. For each case that occurred on the 52-I regimen, 1.4 cases (a 40%

Table 3. Risk of hepatitis by quarter (per 1000 persons)

Weeks	Risk by quarter			Cumulative risk			Risk reduction (cases prevented per 1000 persons)
	Placebo (P)	Isoniazid (I)	Excess (I-P)	Placebo (P)	Isoniazid (I)	Excess (I-P)	
1-12	0.7	3.2	2.5	0.7	3.2	2.5	2.7
13-24	0.5	1.6	1.1	1.2	4.8	3.6	1.6
25-36	0.0	0.8	0.8	1.2	5.6	4.4	0.8
37-52	0.0	0.8	0.8	1.2	6.4	5.2	standard

Table 4. Efficacy of various durations of isoniazid therapy compared with placebo: all assigned participants

Regimen	No. of participants entering regimen	Cumulative no. of cases	5-Year incidence <sup>a</sup>	Percentage reduction	Relative risk
Placebo	6990	97 <sup>b</sup>	14.3	0	4.0
12-I	6956	76	11.3	21	3.1
24-I	6965	34 <sup>b</sup>	5.0	65	1.4
52-I	6919	24 <sup>c</sup>	3.6	75	1.0

<sup>a</sup> Culture-positive tuberculosis per 1000 persons at risk.

<sup>b</sup> Includes 1 case during the first 6 months of pill-taking.

<sup>c</sup> Includes 2 cases during the first 6 months of pill-taking.

increase) occurred on 24-I, 3.1 cases (a 210% increase) occurred on 12-I, and 4 cases (a 300% increase) occurred on placebo. The differences between the 52-I and 24-I regimens and between the 12-I and placebo regimens are not statistically significant ( $0.20 > P > 0.10$ ). The powers of these tests are 35% and 45%, respectively. All other inter-regimen differences are statistically significant.

The rate of breakdown with tuberculosis by year is graphically depicted for each regimen in Fig. 1. The only regimen that showed a trend in risk of tuberculosis over time was the placebo regimen. This regimen showed a significant downward trend ( $P < 0.005$ ) indicating that the risk of tuberculosis decreased as the follow-up period was extended. In the fifth year of

follow-up, the risk of tuberculosis for participants on the 12-I regimen exceeded the risk of those on the placebo regimens.

Table 5 shows the results of 5 years of follow-up with regard to the benefits and risks of each isoniazid regimen. The benefit associated with each regimen is measured in terms of the cumulative number of cases of tuberculosis prevented compared with the placebo regimen. The risk associated with each regimen is measured as the cumulative number of cases of hepatitis incurred that would not have occurred on a placebo regimen. The last column of the table shows the changes in the benefit-to-risk ratio over the five

Table 5. Benefit-to-risk ratio by regimen and year

Year of follow-up	Regimen	Cumulative no. of tuberculosis cases prevented <sup>a</sup>	Cumulative no. of hepatitis cases incurred <sup>b</sup>	Benefit-to-risk ratio
First	12-I	2.6	2.5	1.0
	24-I	3.9	3.6	1.1
	52-I	3.6	5.2	0.7
Second	12-I	2.9	2.5	1.2
	24-I	5.5	3.6	1.5
	52-I	5.3	5.2	1.0
Third	12-I	3.6	2.5	1.4
	24-I	7.6	3.6	2.1
	52-I	8.0	5.2	1.5
Fourth	12-I	3.9	2.5	1.6
	24-I	8.8	3.6	2.4
	52-I	9.3	5.2	1.8
Fifth	12-I	3.0	2.5	1.2
	24-I	9.3	3.6	2.6
	52-I	10.7	5.2	2.1

<sup>a</sup> Reduction in cases over placebo regimen (per 1000 persons).

<sup>b</sup> Excess of cases over placebo regimen (per 1000 persons).

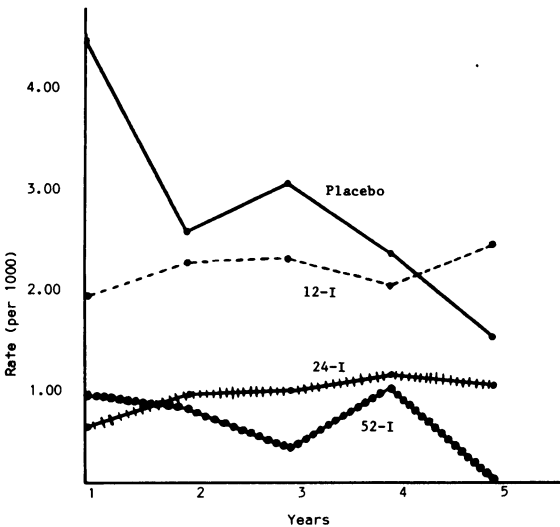


Fig. 1. Annual incidence of culture-positive tuberculosis: all participants, by regimen.

Table 6. Efficacy of various durations of isoniazid therapy compared with placebo for "completer-compliers"

Regimen	No. of participants	No. of cases	Incidence <sup>a</sup>	Percentage reduction	Relative risk
Placebo	5616	83	15.0	0	13.6
12-I	6039	61	10.4	31	9.4
24-I	5437	25	4.7	69	4.3
52-I	4543	5	1.1	93	1.0

<sup>a</sup> Culture-positive tuberculosis per 1000 persons at risk.

years of follow-up. As of the fifth year, the benefit of each isoniazid regimen outweighed its associated risks; the ratio was highest for 24-I, followed by 52-I and 12-I respectively. After the fourth year the ratio of benefit to risk declined for the 12-I regimen.

The efficacy of each isoniazid regimen is increased when only those participants who completed and complied with their assigned regimens are evaluated. This is demonstrated when the data in Table 6 are compared with those in Table 4. All the inter-regimen differences for "completer-compliers" are statistically significant. The rate of breakdown with tuberculosis is depicted by year for "completer-compliers" in Fig. 2. Among these persons, both the placebo and the 24-I regimens showed statistically significant trends over time while the 12-I and 52-I regimens did not. The placebo regimen again showed a significant downward trend ( $P < 0.005$ ). In contrast, the 24-I regimen

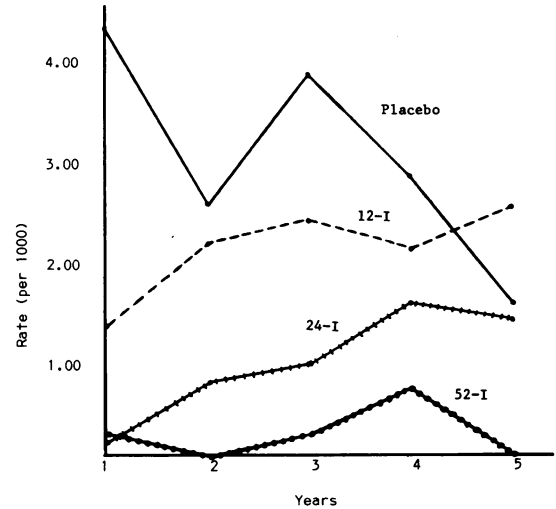


Fig. 2. Annual incidence of culture-positive tuberculosis: "completer-compliers", by regimen.

showed a significant upward trend ( $P = 0.02$ ) indicating that the breakdown rate increased as follow-up was extended. However, the rate in the fifth year for the 24-I regimen was slightly lower than that in the fourth year.

The effectiveness of the various regimens was further analysed by grouping participants according to the size of their fibrotic lesions. The results of these analyses are presented in Table 7. The incidence of tuberculosis among persons assigned to the placebo regimens was only half as great among persons with

Table 7. Efficacy by size of lesion: all assigned participants

Regimen	No. of participants	No. of cases	Incidence <sup>a</sup>	Percentage reduction	Relative risk
Lesions < 2 cm <sup>2</sup>					
Placebo	4701	53 <sup>b</sup>	11.6	0	2.8
12-I	4650	42	9.2	20	2.2
24-I	4677	18 <sup>b</sup>	4.0	66	1.0
52-I	4635	19 <sup>b</sup>	4.2	64	1.0
Lesions > 2 cm <sup>2</sup>					
Placebo	2094	43	21.3	0	8.9
12-I	2129	33	16.2	24	6.8
24-I	2097	14	7.0	67	2.9
52-I	2108	5	2.4	89	1.0

<sup>a</sup> Culture-positive tuberculosis per 1000 persons at risk.

<sup>b</sup> Includes 1 case during the first 6 months of pill-taking.

small lesions (11.58 per 1000) as among persons with large lesions (21.28 per 1000). For both groups (large and small lesions), the differences in rates between the placebo and 12-I regimens are not statistically significant. Neither is the difference between the 24-I and 52-I regimens significant among persons with small lesions, although this difference is significant among persons with large lesions ( $P = 0.04$ ). Otherwise, for both groups, the risk of disease decreases with an increase in the number of months of isoniazid therapy. Persons who developed tuberculosis on the 52-I regimen whose fibrotic lesions were small were significantly less likely to have collected all of their assigned pill calendars than all other groups (47% and  $\geq 80\%$ , respectively;  $P < 0.001$ ). For "completer-compliers", the incidence of tuberculosis in subjects on 52-I was significantly less than in those on 24-I, even among persons with small lesions ( $P = 0.02$ ).

#### DISCUSSION

This trial of various durations of isoniazid preventive therapy was conducted among persons with fibrotic lesions, because it was expected that the high risk of progressive tuberculosis in this population would ensure that results were obtained relatively quickly. In general, they were a highly compliant European population of relatively high average age, with small lesions. Nonetheless, despite the select characteristics of the study population, the results regarding the risks and efficacy associated with isoniazid treatment in this population are similar to those found in earlier trials in other populations (4, 15–18). The similarity suggests that these results may be applicable generally to groups other than those with fibrotic lesions.

The evaluation of each regimen as a preventive measure must balance all the adverse consequences of that regimen against its effectiveness in preventing tuberculosis. Adverse consequences include inability to follow the recommendation (non-compliance or dropping-out) as well as inability to tolerate the drug (adverse reactions). Failures to complete regimens increased with increasing duration at the same rate among isoniazid and placebo takers, indicating that the increased drop-out rate with time was related to the duration rather than to the drug.

As past experience had indicated, isoniazid was found to be a generally acceptable drug. The most serious adverse reaction noted was hepatitis. The occurrence of this complication was highest during the first three months of pill-taking for both the isoniazid and placebo groups, the increased risk on the placebo regimen during this period suggesting that surveillance was not equal throughout the treatment period.

Therefore the risk among placebo recipients was subtracted from the risk among isoniazid recipients to determine the excess risk attributable to isoniazid. Almost half of the excess risk of hepatitis for those taking isoniazid occurred during the first 12 weeks; two-thirds had occurred by 24 weeks. Thus, about one-third of the cases of isoniazid-induced hepatitis could have been prevented by shortening a 52-week standard regimen to 24 weeks. At the time this trial was begun, the potential danger of isoniazid-induced hepatitis was not fully recognized. As a result, the risk of hepatitis and subsequent death seen in this trial might be reduced by the knowledge available today. All three of the participants who died of hepatitis had continued taking isoniazid after liver abnormalities had been recognized. Discontinuing medication at the onset of such abnormalities would probably have prevented these deaths.

Currently, the accepted practice for preventive therapy of tuberculosis varies greatly from country to country. While in some countries a 12-month regimen of isoniazid is commonly used to prevent tuberculosis among persons at high risk, in other countries isoniazid preventive therapy is not used at all. In assessing the benefit of each duration of preventive therapy, consideration must be given to the current policy of the area. The values for the "percentage reduction" (Table 4) indicate how much the current disease rate might be reduced if a programme were introduced in an area which currently does not use preventive therapy. On the other hand, the calculations of "relative risk" are useful for assessing how much the risk to an individual would be increased if shorter regimens were adopted in an area in which 52 weeks of preventive therapy is recommended at present.

Each of the isoniazid regimens studied reduced the risk of tuberculosis for a period of at least 5 years, the protective effect increasing as the duration of isoniazid therapy was increased. However, the efficacy of the isoniazid regimens relative to one another has changed throughout the five years of follow-up and is likely to continue changing for several years.

The reduction in risk of disease produced by isoniazid regimens when compared with placebo was greater during the first 24 weeks of therapy than during the subsequent weeks. The effectiveness of the 52-I regimen was increased when it was assessed only among the highly compliant portion of the study population or among those participants with large fibrotic lesions. Nevertheless, even in these groups, the greatest increase in number of tuberculosis cases prevented occurred when isoniazid therapy was extended from 12 to 24 weeks; this gain in cases prevented exceeded that achieved by replacing placebo with 12 weeks of therapy, or extending 24 weeks of therapy to 52 weeks. These results imply that the monitoring of patient compliance is most critical

between the 12th and 24th weeks of therapy.

How far beyond five years protection attributable to isoniazid will continue can only be estimated from the currently available data. In the fifth year of follow-up, the incidence of tuberculosis in subjects on the 12-I regimen exceeded that in subjects on the placebo regimens. Furthermore, over the course of the five years of follow-up, a significant upward trend was present in the rate of disease among "completer-compliers" who took isoniazid for 24 weeks. This finding is compatible with the hypothesis that 24 weeks of isoniazid defers rather than prevents disease. If the hypothesis is correct, a similar upward trend would not be present among less compliant persons, or persons who took the drug for only 12 weeks, as these persons would not have received sufficient therapy to defer disease significantly. Under this hypothesis, the failure of the upward trend in the 24-week regimen to continue in the fifth year could indicate that the number of cases deferred had been fully exhausted. Since passive follow-up is being conducted for an additional 5 years for a portion of the study population, this hypothesis should be supported or refuted by information obtained during this period. Considerable experience with 52-I indicates that this regimen should afford lasting protection (19).

The benefit-to-risk ratio is one of several useful tools for quantifying the balance between the advantages and disadvantages of the isoniazid regimens. When employing this tool to evaluate the outcome of the study, however, one must be aware of several facts. The ratio calculated in this study is based upon the assumption that a case of tuberculosis is equal to a case of isoniazid-induced hepatitis. This assumption may not be accurate for several reasons: (a) each new case of tuberculosis will probably cause additional cases, whereas isoniazid-induced hepatitis is not transmissible; (b) the mycoplasma in persons who develop tuberculosis after a period of isoniazid therapy may exhibit resistance to isoniazid thereby complicating future treatment for tuberculosis, while the treatment for hepatitis is unaffected by previous isoniazid therapy; (c) liver tissue damaged by hepatitis can in most cases regenerate, whereas lung tissue destroyed by tuberculosis cannot; (d) the hepatitis deaths, and at least some of the cases, that occurred in this trial could possibly have been avoided by employing the knowledge that is now available, whereas the same is not true of the deaths from tuberculosis. Considering these factors, cases of tuberculosis may actually be more serious than cases of isoniazid-induced hepatitis. As a result, the calculated benefit-to-risk ratio may underestimate the value of a tuberculosis case prevented, and thereby be an unfair representation, particularly for the 52-I regimen, which prevents the greatest number of cases of tuberculosis.

One must also recognize that the effectiveness of each regimen, and therefore the benefit it provides, depends in part upon the characteristics of the target population. For example, in this trial in the highly compliant population and the population with large fibrotic lesions, the effectiveness of the 52-I regimen was greater. This alters the benefit-to-risk ratio in favour of the 52-I regimen. Another factor to consider in employing the benefit-to-risk ratio is that it takes no account of the differences in resources required to administer successfully the various regimens, a major consideration if one is concerned with relative efficiency. This particular oversight works to the disadvantage of the shorter regimens which require fewer resources to achieve completion.

Lastly, one must realize that the benefit-to-risk ratio will change over time. The incidence of tuberculosis in those on the placebo regimens will decrease once all the potential cases have developed. If the potential cases among subjects on the isoniazid regimens are also exhausted, then the benefit-to-risk ratios will level off and eventually remain constant. However, if cases in persons on an isoniazid regimen are simply deferred and continue to occur after all the cases in persons on placebo have developed, the cumulative number of tuberculosis cases prevented, i.e., the difference between those occurring on an isoniazid regimen and those occurring on placebo, will decrease and the benefit-to-risk ratio will also decrease. In the fifth year of follow-up in this study, the benefit-to-risk ratio for the 12-I regimen showed a decrease. At the end of five years follow-up, the 24-I regimen had maintained the greatest benefit per unit of risk; however, the ratio for this regimen was beginning to level off more rapidly than that for the 52-I regimen.

In summary, the results of five years of follow-up in this trial have indicated the following:

- (1) The rates of completion of, and compliance with, a regimen are inversely related to its duration.
- (2) More than half of the cases of hepatitis attributable to isoniazid occur during the first 3 months of therapy.
- (3) A 12-week regimen of preventive treatment eliminates, at most, one-third of the cases of tuberculosis that would occur without treatment.
- (4) Two-thirds of the preventive value of isoniazid therapy is achieved after 6 months. Therefore, in areas where preventive therapy is not currently practised, the adoption of a 24-week regimen would result, over a five-year period, in a 65% decrease in the number of cases of tuberculosis among persons treated preventively.
- (5) In areas where a 52-week regimen is currently practised, the adoption of a 24-week regimen would result, over a five year period, in a 40% increase in the number of cases of tuberculosis among persons who



had been treated preventively.

(6) For up to 5 years, a 52-week regimen prevents the greatest number of cases of tuberculosis, but a 24-week regimen prevents the greatest number of cases of tuberculosis per case of hepatitis caused.

(7) In highly compliant populations and populations with large fibrotic lesions, a 52-week regimen is clearly the most effective regimen for prevention of tuberculosis.

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### RÉSUMÉ

#### EFFICACITÉ DE DIFFÉRENTES PÉRIODES DE TRAITEMENT PRÉVENTIF À L'ISONIAZIDE CONTRE LA TUBERCULOSE : SUIVI PENDANT CINQ ANS DANS L'ESSAI DE L'UIC

Des sujets réagissant positivement à la tuberculine et porteurs de lésions pulmonaires fibreuses ont été retenus par le personnel de dispensaires de sept pays d'Europe pour une étude sur l'efficacité de diverses périodes de traitement préventif à l'isoniazide. Les participants ont reçu des paquets de comprimés (paquets calendriers), contenant soit de l'isoniazide soit un placebo, pour l'une des trois périodes suivantes: 12 semaines, 24 semaines, ou 52 semaines. Pour chaque participant, on a noté s'il avait achevé le traitement (retiré tous les paquets calendriers prescrits) et s'y était conformé (pris au moins 80% des comprimés contenus dans chaque paquet calendrier reçu). Les réactions adverses, y compris les hépatites, ont été surveillées pendant toute la période de prise de comprimés. Les signes et symptômes de tuberculose ont aussi été surveillés, et les cas ont été confirmés par des cultures positives. Les participants sont restés sous surveillance pour la tuberculose pendant cinq ans, y compris la période de prise de comprimés.

Les résultats de l'essai après un suivi de cinq ans se résument ainsi:

a) Le pourcentage des traitements terminés et des traitements conformes était en rapport inverse avec la période de traitement prescrite.

b) Plus de la moitié des cas d'hépatite attribuables à l'isoniazide sont survenus au cours des trois premiers mois de traitement.

c) Un traitement préventif à l'isoniazide pendant 12

semaines a éliminé, au plus, un tiers des cas qui se seraient produits en l'absence de traitement.

d) L'effet préventif du traitement à l'isoniazide s'est manifesté aux deux tiers après six mois. C'est pourquoi, dans les régions où l'on n'applique pas couramment la chimiothérapie préventive, l'adoption d'un schéma de traitement de 24 semaines à l'isoniazide aboutirait, sur une période de cinq ans, à une réduction de 65% des cas de tuberculose chez les sujets qui ont été traités préventivement.

e) Dans les régions où un traitement de 52 semaines à l'isoniazide est couramment appliqué, l'adoption d'un schéma de traitement de 24 semaines à l'isoniazide aboutirait, sur une période de cinq ans, à une augmentation de 40% des cas de tuberculose chez les sujets qui ont été traités préventivement.

f) Pour une période allant jusqu'à cinq ans, la prise d'isoniazide pendant 52 semaines permet d'éviter le plus grand nombre de cas de tuberculose, mais la prise d'isoniazide pendant 24 semaines permet d'éviter le plus grand nombre de cas de tuberculose par cas d'hépatite provoquée.

g) Dans les populations qui se conforment étroitement au traitement, et dans celles qui portent de graves lésions fibreuses, la prise d'isoniazide pendant 52 semaines est de toute évidence le schéma de traitement le plus efficace pour la prévention de la tuberculose.

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### Annex 1

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