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# A Controlled Comparison of a Twice-Weekly and Three Once-Weekly Regimens in the Initial Treatment of Pulmonary Tuberculosis

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS [1]

*A previous report from the Tuberculosis Chemotherapy Centre, Madras, demonstrated the value of a fully supervised twice-weekly regimen of high-dosage isoniazid plus streptomycin in the treatment of newly diagnosed tuberculous patients with drug-sensitive cultures. A logical consequence of this finding was an investigation of regimens with a longer interval between successive doses. The present report describes the findings of a controlled study of 3 once-weekly regimens and the twice-weekly regimen. The results confirm that the twice-weekly regimen is highly effective and demonstrate that its efficacy is not influenced by the rate of inactivation of isoniazid or by a reduction (by one-fourth) in the dosage of streptomycin. The results also show that once-weekly chemotherapy from the beginning, whether with high-dosage isoniazid plus streptomycin or high-dosage isoniazid plus streptomycin plus high-dosage pyrazinamide, gives unsatisfactory results. However, when an initial daily phase of 4 weeks with a moderate dosage of isoniazid plus streptomycin preceded the once-weekly phase of high-dosage isoniazid plus streptomycin, the response was highly satisfactory in slow inactivators of isoniazid (as good as with the twice-weekly regimen) but was considerably less satisfactory in rapid inactivators. These findings suggest that if a method of compensating for the insufficiency of this regimen in rapid inactivators of isoniazid can be found, the prospects for evolving a highly satisfactory once-weekly regimen are bright.*

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[1] The Tuberculosis Chemotherapy Centre, Madras-31, India, is under the joint auspices of the Indian Council of Medical Research (ICMR), the Tamil Nadu (Madras State) Government, and the World Health Organization (WHO) in collaboration with the Medical Research Council of Great Britain (BMRC).

The research of the Centre has been guided by a Project Committee consisting of the Adviser in Tuberculosis to the Government of India (Dr N. L. Bordia, Chairman), the Director-General of the ICMR (Dr C. G. Pandit, succeeded by Col. B. L. Taneja in August 1964), the Director of Health Services and Family Planning, Tamil Nadu (Dr A. B. Marikar), the Director of the Centre (Dr N. K. Menon), the WHO Senior Medical Officer of the Centre (Dr Hugh Stott), Dr J. Frimodt-Møller, Dr K. S. Sanjivi, a WHO representative and a BMRC representative. The BMRC, acting through its Tuberculosis and Chest Diseases Unit, is responsible for advising WHO on the research in accordance with plans prepared by the Project Committee. Close contact has been maintained between the Centre and Dr Wallace Fox (BMRC Tuberculosis and Chest Diseases Unit) and Professor D. A. Mitchison (BMRC Unit on Drug Sensitivity in Tuberculosis).

The members of the scientific staff of the Centre with major responsibility for the work reported here are: Dr N. K. Menon, Director: Dr Hugh Stott (WHO), Senior Medical Officer; the late Dr S. Velu, Dr C. V. Ramakrishnan, Dr S. Devadatta, Dr O. Nazareth, Dr S. R. Kamat, Dr J. J. Y. Dawson (WHO) and Dr C. Evans (WHO), Medical Officers; Mrs M. Jeyalakshmi Monga, Senior Public Health Nurse; Dr S. P. Tripathy and Dr. L. Eidus (WHO), Senior Bacteriologists; Dr P. R. J. Gangadharam, Bacteriologist; Mrs S. Subbammal, Assistant Bacteriologist; Dr D. V. Krishnamurthy and Dr K. V. Nageswara Rao, Biochemists; Mr C. V. Jacob, Miss S. Joseph, Mr P. Venkataraman, Mr S. Kailasam, Miss K. Prema and Mr R. Raghunathan, Laboratory Research Assistants; Mr A. G. Beer (WHO), Laboratory Technician; Dr S. Radhakrishna, Senior Statistician; Mr P. R. Somasundaram, Mr K. Ramachandran and Mr N. G. K. Nair, Statisticians; and Mr B. Janardhanam and Mr A. S. L. Narayana, Statistical Assistants.

The report was prepared by Dr S. Radhakrishna, Dr Wallace Fox and Professor D. A. Mitchison, in collaboration with Dr N. K. Menon, Mr P. R. Somasundaram and other scientific staff of the Centre.

The great majority of the patients in the present study were referred to the Centre from the Government Tuberculosis Demonstration and Training Centre (Director: Dr M. A. Hamid) and a Corporation Tuberculosis Clinic (Medical Officer in Charge: Dr V. S. Selvapathy).

## I. INTRODUCTION

One of the major problems in the treatment of tuberculosis is the difficulty experienced in ensuring regularity in the long-term daily self-administration of drugs. This difficulty is encountered both in the developing countries and in the technically advanced countries (see review by Fox, 1962), and is largely due to the fact that patients rapidly become symptom-free after the commencement of chemotherapy. Fully supervised chemotherapy has the advantage that it permits a precise knowledge of, and consequently greater scope for control over, the actual drug-intake of the patients. However, daily supervision on a large scale is impracticable, especially in developing countries. On the other hand, if the drugs could be administered intermittently, supervision might become a more practicable proposition. Studies of fully supervised intermittent regimens were therefore initiated at this Centre in 1961. The rationale, mode of action and advantages of such regimens, together with the literature, have been discussed in detail elsewhere (Tuberculosis Chemotherapy Centre, Madras, 1964; Mitchison, 1965 ; Fox, 1968).

An earlier study from this Centre (Tuberculosis Chemotherapy Centre, Madras, 1964) showed that a completely supervised, twice-weekly regimen of isoniazid (approximately 14 mg/kg body-weight, orally) plus streptomycin (1 g, intramuscularly), both drugs given at the same time, for 1 year, was at least as effective as a standard self-administered daily oral regimen of isoniazid plus PAS [1] in the treatment of newly diagnosed tuberculous patients with drug-sensitive cultures. Regimens with a longer interval between successive doses-for instance, once-weekly regimens-would have the further advantages of being more convenient for the patient and easier to organize. Also, for any given combination of drugs, they would probably be less expensive and less toxic. Thus, the potential advantages of such regimens appear to be substantial, especially if the number of patients involved is large, as in a mass treatment programme. A study was therefore undertaken at the Centre to investigate the efficacies of three once-weekly regimens (one of which included an initial daily phase) in comparison with that of the twice-weekly regimen (SHTW) described above. One of these regimens (SHOW) consisted of isoniazid and streptomycin in the same dosages as in the twice-weekly regimen but administered once weekly. As it was felt that this regimen might prove to be insufficiently effective, two modifications were also studied:

(1) In one modification (SHZOW), pyrazinamide in high dosage was administered at the same time as the isoniazid plus streptomycin, making a once-weekly triple-drug regimen. Preliminary studies had shown that high-dosage pyrazinamide resulted in appreciably high serum concentrations in Madras patients (Subbammal et al., 1968) and, when administered once weekly for up to a year, did not produce acute or chronic toxicity (Ramakrishnan et al., 1968). These findings, together with the fact that pyrazinamide is bactericidal, made it preferable to PAS, thioacetazone, ethionamide and cycloserine, for each of which there is a greater limitation on the size of the individual dose, due to considerations such as acute intolerance or bulk.

(2) In the other modification (SH/SHOW), streptomycin plus moderate-dosage isoniazid was administered daily for the first 4 weeks, followed by streptomycin plus high-dosage isoniazid administered once weekly for the rest of the year. The initial daily phase was introduced because of laboratory and clinical evidence that the intensity of treatment in the first few weeks has a substantial influence on the outcome of chemotherapy (see review by Fox, 1968).

In the earlier study (Tuberculosis Chemotherapy Centre, Madras, 1964), the proportion of patients who became uncooperative and stopped treatment during the year was higher with the twice-weekly regimen of isoniazid plus streptomycin than with the standard daily regimen of isoniazid plus PAS. This finding, together with the fact that the incidence of giddiness was substantially higher with the former regimen, raised the possibility that side-effects due to streptomycin (1 g) might have an influence on the acceptability of the twice-weekly regimen, and possibly also on the acceptability of the once-weekly regimens. In consequence, only half the patients in this study (selected at random) were prescribed the same dosage of streptomycin as in the earlier study–namely, 1 g–and the other half were prescribed a lower dosage–0.75 g. As there is an element of

[1] p-aminosalicylic acid.

subjectivity, and therefore a possibility of bias, in the assessment of streptomycin toxicity, the study was conducted double-blind in respect of streptomycin dosage–that is, neither the physicians nor the patients were aware of the dosage of streptomycin employed for any individual patient.

The findings over a 1-year period are presented in this report.

## II. PLAN AND CONDUCT OF THE STUDY

The great majority of patients came from the poorest sections of the population of Madras city, and had been referred to the Centre from tuberculosis clinics, at which they had attended with symptoms. The criteria for admission were similar to those in previous studies (Tuberculosis Chemotherapy Centre, Madras, 1959, 1960, 19.64, 1966). In brief, the patients were aged 12 years or more, had at least 2 sputum cultures positive for *Mycobacterium tuberculosis* (patients with 2 or more positive smears ware provisionally admitted), had either received no netituberculosis chemotherapy or had received it for not more than 2 weeks, and were judged to be co-operative.

### CHEMOTHERAPEUTIC REGIMENS

Four chemotherapeutic regimens, each of l-year duration, were studied. The details of the regimens are set out below, together with the dosages for a patient weighing 100 lb (45.4 kg) (the detailed dosage schedule is presented in Table 1, together with the mean dosages and ranges on admission).

#### *S H T W*

Streptomycin sulfate by intramuscular injection in a dose equivalent to 1 g (high dosage) or 0.75 g (low dosage) of streptomycin base plus isoniazid in

TABLE 1
DOSAGE SCHEDULE, AND MEAN DOSAGE AND RANGE ON ADMISSION TO TREATMENT

| Drug | Rhythm | Bodt-&weight | Dosage | Dosage in relation to body-weight on admission (mg/kg) | |
|---|---|---|---|---|---|
| | | | | Mean | Range |
| Streptomycin | Daily or intermittent | *Any* | 1 g (high) or<br>0.75 g (low) | 26.7<br>19.8 | 14.5-46.8<br>12.1-36.4 |
| Isoniazid | Daily | Any | 400 mg [b] | **10.5** | **5.8–18.7** |
| | Intermittent | 50-69<br>70-99<br>100 or more | 400 mg [b]<br>600 mg [b]<br>750 mg [b] | 15.4 | 12.1-20.5 |
| Pyrazinamide | Intermittent | 50-69<br>70-79<br>80-89<br>90 or more | 2.5 g<br>3.0 g<br>3.5 g<br>4.0 g | 88.9 | 75.2-97.8 |

[a] 1 lb = 0.45 kg.
[b] Incorporating 6 mg of pyridoxine.

a single oral dose of 750 mg, both drugs being given at the same time, twice weekly (at intervals of 3 and 4 days alternately).

*SHOW*

Streptomycin and isoniazid in the same dosages as in the SHTW regimen, both drugs being given at the same time, once weekly.

*SHZOW*

Streptomycin and isoniazid in the same dosages as in the SHTW regimen, plus pyrazinamide in a dosage of 4 g,[1] all three drugs being given at the same time, once weekly.

*SH/SHOW*

Streptomycin in the same dosage as in the SHTW regimen plus isoniazid in a single oral dose of 400 mg, both drugs being given at the same time, daily (except Sundays) for 4 weeks, followed by streptomycin in the same dosage as in the first 4 weeks plus isoniazid in the same dosage as in the SHTW regimen, both drugs being given at the same time, once weekly for the remaining 48 weeks.

The dosage of streptomycin, whether administered daily or intermittently, and of isoniazid when administered daily, did not depend on the patient's body-weight.

The dosage of pyrazinamide, and of isoniazid when administered intermittently, did depend on body-weight (Table 1). If, at a monthly examination, a patient was found to have gained weight and to have moved into a higher weight category, the dosage was increased; however, the dosage was never reduced for loss in weight.

*Pyridoxine supplement*

All the patients in this study were prescribed 6 mg of pyridoxine, incorporated in the isoniazid tablets, with every dose of isoniazid, in order to prevent isoniazid toxicity (Tuberculosis Chemotherapy Centre, Madras, 1963b).

[1] The safety of pyrazinamide in high dosage (that is, 3 g for a 100-lb patient), when given once weekly for up to one year? had already been established in Madras patients by Ramakrishnan et al. (1968). Also, Subbammal et al. (1968) had shown that increasing the dosage from 3 g to 4 g resulted in appreciably higher serum concentrations, but no acute hepatic toxicity. It was therefore decided to employ 4 g in the present study, but with safeguards (see pages 147 and 148).

## ALLOCATION OF CHEMOTHERAPY AND DOUBLE-BLIND NATURE OF THE STUDY

The regimen and streptomycin dosage were allocated at random by the statisticians from one of four series of sealed envelopes, according to whether the smear result of the first overnight collection specimen of sputum was 3-plus, 2-plus, 1-plus or negative.

The study was conducted double-blind in respect of streptomycin dosage. Immediately after the allocation of chemotherapy, a treatment record sheet was prepared for each patient by the statisticians, and the streptomycin dosage was entered on it. This sheet was then kept in a confidential file in the treatment room, and every dose of streptomycin received by the patient was recorded on it by the nurses in the injection room. Apart from the statisticians and these nurses, no staff member of the Centre had access to the register or knew the dosage of streptomycin received by any individual patient; the dosage was also unknown to the patients themselves.

## EVOLUTION OF THE STUDY

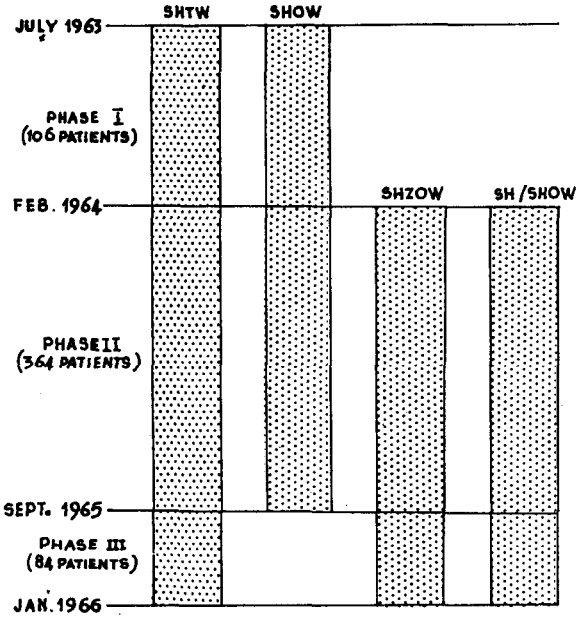
The intake to the study was in three phases (Fig. 1). It began in July 1963, with patients being allocated in equal proportions to the SHTW and SHOW regimens only (Phase I). From February 1964, when the Centre was fully organized to undertake the study of two additional regimens (SHZOW and SH/SHOW), patients were allocated in equal proportions to each of the four regimens (Phase II). By September 1965, it became clear that the SHOW regimen was unsatisfactory. The intake of patients to this regimen was therefore stopped and, subsequently, patients were allocated in equal proportions to the other three regimens only (Phase III) until January 1966, when the intake to the study was completed. In each phase, half the patients on each regimen were allocated to receive 1 g of streptomycin and the other half to receive 0.75 g of streptomycin.

## PRETREATMENT INVESTIGATIONS

The pretreatment investigations included the following :

(1) A clinical examination and assessment of the general clinical condition, the weight (lb), an intracutaneous tuberculin (Mantoux) test (5 TU of PPD,

FIG. 1
INTAKE OF PATIENTS TO THE STUDY




Batch RT 22 without Tween), and examination of urine for albumin and sugar.

(2) A full-plate postero-anterior chest radiograph.

(3) The examination by direct smear and culture of a minimum of 4 sputum specimens. Two were produced overnight in the home (collection specimens) and 2 were expectorated (after the patient had had his throat tickled with a swab) under the direct supervision of a health visitor at the Centre (supervised spot specimens).

(4) Tests of sensitivity to streptomycin and isoniazid on 2 positive cultures.

(5) Identification tests on the 2 cultures tested for drug sensitivity.

(6) Rotating-chair test for vestibular function.

The following additional investigations were undertaken for patients in phases II and III:

*(a)* Urine test for urobilinogen (Harrison, 1957) for all patients.

*(b)* For SHZOW and, as a control, SHOW patients, determinations of the serum L-aspartate: 2-oxoglutarate aminotransferase [1] (glutamic-oxaloacetic transaminase, SGOT) activity and serum L-alanine: 2-oxoglutarate aminotransferase 1 (glutamic-pyruvic transaminase, SGPT) activity.

*(c)* For SHZOW and, as a control, SHOW patients, tests of sensitivity to pyrazinamide on 2 cultures.

[1] Terminology recommended by the Commission on Enzymes of the International Union of Biochemistry (Florkin & Stotz, 1965).

### GENERAL MANAGEMENT

All patients were treated as out-patients from the start, and their progress was assessed at monthly intervals. At each scheduled attendance (daily, twice weekly or once weekly), the patient took a dose of the oral medicament(s) under the careful supervision of a nurse, and immediately afterwards received the injection of streptomycin. If the patient failed to attend on an appointed day, a visit to the home was made by a health visitor the next day as a reminder; if this and further visits by her were unsuccessful, special efforts (including home visits) were made by the social workers and the physicians.

Towards the end of each month of treatment, a health visitor made a *routine* visit to the patient's home to collect a bottle of sputum and to deliver another for collecting sputum.

Very ill patients were asked to restrict their activities, and were brought to the Centre by ambulance or had their chemotherapy administered at home. However, this occurred very infrequently (see page 190).

It was the policy to avoid, as far as possible, collapse therapy and resection; no patient in this study had either measure.

### INVESTIGATIONS DURING TREATMENT

Assessments made at monthly intervals after the start of chemotherapy included (1) the weight (lb), (2) the examination of 2 collection specimens and 1 supervised spot specimen of sputum by smear and by culture, (3) tests of sensitivity to streptomycin and isoniazid on 1 positive culture from the 3rd month onwards, (4) identification tests on the culture tested for drug sensitivity, and (5) the regularity of attendance for the allocated chemotherapy. Further, a routine postero-anterior chest radiograph was taken at 1,2,3,6 and 12 months, and at other months only if at least one sputum smear was positive. A rotating-chair test for vestibular function was undertaken at 1 year for all patients unless their allocated chemotherapy had been terminated in the meantime; extra tests were undertaken in specific situations, namely-after a second complaint of giddiness

or just prior to a reduction in dosage or the withdrawal of streptomycin on account of toxicity.

The following additional investigations were undertaken for patients in phases II and III:

*(a)* Determination of the rate of inactivation of isoniazid, at 1 month. (When it was found that the inactivation rate had prognostic importance in phases II and III, it was decided to perform the test for patients who had been admitted in phase I also; the tests were undertaken between 24 and 36 months after admission.)

*(b)* Estimations of the serum concentrations of isoniazid and streptomycin for all patients, and of serum pyrazinamide concentrations also for the SHZOW patients, at 1, 2, 3 and 6 hours after the *first* supervised dose of chemotherapy; however, for the SH/SHOW patients, the isoniazid dosage appropriate to the once-weekly rhythm (not the daily rhythm) was administered, as the object of the investigation was to determine the serum drug concentrations attained during intermittent chemotherapy.

The *total* amount of urine passed during the 6-hour period was collected, and the isoniazid, acetylisoniazid and isonicotinic acid contents were estimated.

*(c)* Determinations of the SGOT and SGPT activity at 1 and at 12 months for the SHZOW patients and, as a control, for the SHOW patients.

*(d)* A test for urobilinogen on a specimen of urine collected at each weekly attendance, prior to the administration of drugs, for the SHZOW patients and, as a control, for the SHOW patients. If 2 successive results were positive, the SGOT and SGPT activities were determined.

*(e)* A pyrazinamide sensitivity test on 1 positive culture each month from the third month onwards for the SHZOW patients and, as a control, on 1 positive culture at 6 months and at 12 months for the SHOW patients.

### URINE TESTS FOR INGESTION OF ISONIAZID

Since it is known that tablets are not always swallowed even when given under direct supervision (Gilroy, 1952), it was desirable to obtain confirmation of drug ingestion. For this purpose, *surprise visits* to the patients' homes were made from 2 to 24 hours after the supervised administration of chemotherapy, and specimens of urine were collected and tested for a metabolite of isoniazid. Up to July 1964 (that is, in the first year of the intake), the practice was to collect 1 specimen per patient per month. As interim analyses showed the proportion of specimens with a positive result to be very high-namely, 92% of 645–this practice was thereafter modified (to lessen the work-load) to testing about 25 specimens per month from the same number of patients, selected at random.

It was also important to ensure that the patients in this study, approximately two-thirds of whom received once-weekly regimens, did not supplement their chemotherapy from other sources. Therefore, during the year of treatment, a specimen of urine was collected once weekly from all patients immediately prior to the administration of the drugs (i.e., 3-7 days after the previous dose of drugs) and was tested for a metabolite of isoniazid.

The isonicotinic acid test (Kasik et al., 1962) was employed in the first 8 months of the study, and the acetylisoniazid test (Eidus & Hamilton, 1964) thereafter; the two tests have been found to be of similar sensitivity (Venkataraman et al., 1965).

## III. BACTERIOLOGICAL AND ASSAY PROCEDURES

### SMEARS AND CULTURES

Sputum specimens were examined by methods similar to those described previously (Tuberculosis Chemotherapy Centre, Madras, 1959). In brief, smears were examined by fluorescence microscopy (Holst et al., 1959), and graded as 3-plus, 2-plus, 1-plus or negative. Sputum specimens were cultured, after treatment with 4% sodium hydroxide, *on* Löwenstein-Jensen medium (Cruickshank, 1965). The cultures were incubated at 37°C, examined weekly for growth (or presence of contamination), and reported as negative if no growth was present by 8-9 weeks.

### SENSITIVITY TESTS

Sensitivity tests were performed on slopes of Löwenstein-Jensen medium, employing the minimal inhibitory concentration (MIC) and proportion methods for isoniazid, the resistance-ratio (RR) method for streptomycin, and the proportion method

for dihydrostreptomycin (Canetti et al., 1963). For pyrazinamide, sensitivity tests were performed on slopes of acidsed Löwenstein-Jensen medium, with a pre-inspissation pH of 4.85, by the MIC and proportion methods (Tripathy, 1966; Tripathy et al., in press).

The inoculum suspension for the sensitivity tests was made by adding 4 mg (moist weight) of bacilli, as judged by eye, to a previously sterilized " bijou " bottle containing glass beads and 0.2 ml of sterile distilled water. The bottle was shaken mechanically for 1 minute, and 0.8 ml of sterile distilled water was added to give a standard suspension. From this suspension, 4 serial 10-fold dilutions were made. Slopes of the medium, containing the range of drug concentrations indicated in Table 2, were each inoculated with a standard (approximately 3-mm) loopful of the appropriate suspension.

With each batch of streptomycin sensitivity tests, the standard sensitive strain, H37Rv, was also set up, using the same range of drug concentrations. Although this was not done for isoniazid, dihydrostreptomycin and pyrazinamide, every batch of medium was tested, as soon as it was prepared, with the H37Rv strain, using the proportion method and the same range of drug concentrations as for the test strains.

The results of sensitivity tests by the MIC and RR methods were read at the end of 28 days of incubation at 37°C, and those by the proportion method at the end of 40 days. The main measures of sensitivity used in this report are as follows:

*Isoniazid :* MIC–the minimum concentration inhibiting growth (defined as 20 colonies or more) on the slopes inoculated with the standard suspension.

*Streptomycin* : RR–the ratio of the MIC of the test strain to the MIC of strain H37Rv, both MICs being based on the findings on the slopes inoculated with the standard suspension.

*Pyrazinamide :* The proportion resistant to 100 µg/ml, i.e., the bacterial population growing on 100 µg/ml expressed as a proportion of the total bacterial population, the latter being assessed from the counts on the *acidified* drug-free slopes.

The MIC and RR results were accepted only if more than 100 colonies grew on the drug-free slope. If the MIC of isoniazid was 0.4 µg/ml or 1 µg/ml, or if the RR for streptomycin was 4, the test was repeated.

### DEFINITIONS OF DRUG RESISTANCE

*Isoniazid*

*Pretreatment:*

*(a)* growth on 1 µg/ml on at least 1 of the 2 cultures; or

*(b)* growth on 0.2 µg/ml but not on 1 µg/ml on 1 of the 2 cultures, followed by growth on 0.2 µg/ml in the repeat test on the same culture; or

*(c)* growth on 0.2 µg/ml but not on 1 µg/ml, on both cultures.

*During treatment:* growth on 0.2 µg/ml.

*Streptomycin*

*Pretreatment:*

*(a)* an RR of 8 or more on at least 1 of the 2 cultures;

TABLE 2

INOCULUM SUSPENSIONS AND DRUG CONCENTRATIONS µg/ml) [a] EMPLOYED IN SENSITIVITY TESTS

| Suspension | Löwenstein-Jensen medium | | | | | | | | | | | | | | Acidified [b] Löwenstein-Jensen medium | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control (drug-free) | | Streptomycin | | | | | Dihydro-streptomycin | | | | Isoniazid | | | | | | Control (drug-free) | | Pyrazinamide | | | |
| | | | 2 | 4 | 8 | 16 | 32 | 2 | 4 | 8 | 16 | 0.05 | 0.1 | 0.2 | 0.4 | 1.0 | 5.0 | | | 12.5 | 25 | 50 | 100 |
| Standard | + | | + | + | + | + | + | + | + | + | + | | + | + | + | + | + | + | | + | + | + | + |
| 1 in 10 | + | | | | | | | + | + | + | | | + | + | + | + | | + | | + | + | + | + |
| 1 in $10^2$ | + | + | | | | | | + | + | + | | + | + | + | + | + | | + | + | + | + | + | + |
| 1 in $10^3$ | + | + | | | | | | + | + | + | | + | + | + | + | + | | + | + | + | + | + | + |
| 1 in $10^4$ | + | + | | | | | | | | | | | | | | | | + | + | | | | |

[a] Expressed as the amounts added before inspissation.
[b] With a pre-inspissation pH of 4.85.

*(b)* an RR of 4 on 1 of the 2 cultures, followed by an RR of 4 or more in the repeat test on the same culture; or

*(c)* an RR of 4 on both cultures.

*During treatment:*

*(a)* an RR of 8 or more; or

*(b)* an RR of 4 followed by an RR of 4 or more in the repeat test.

*Pyrazinamide*

*Pretreatment and during* treatment: growth on 100 µg/ml of at least 1% of the bacterial population (Tripathy, 1966; Tripathy et al., in press).

### IDENTIFICATION TESTS

The following tests were employed for identifying cultures as *Mycobacterium tuberculosis.*

*Pretreatment* : growth at 25°C, pigment production, catalase activity (qualitative test) and niacin production.

*During treatment* : catalase activity (qualitative test) and niacin production.

### RATE! OF INACTIVATION OF ISONIAZID

The rate of inactivation of isoniazid was determined after verifying that a urine specimen obtained immediately before was negative for acetylisoniazid (Eidus & Hamilton, 1964). A test dose of 3 mg/kg body-weight of isoniazid was given intramuscularly, and a specimen of blood was collected 4½ hours later. The concentration of isoniazid in the serum was estimated by microbiological assay, using a vertical diffusion technique similar to that reported by Lloyd & Mitchison (1964). Fig. 2 illustrates the tidings in 529 patients in this study. On the basis of this histogram, patients with concentrations of 0.63 µg/ml or more were classified as slow inactivators of isoniazid, and those with concentrations below 0.63 µg/ml as rapid inactivators.

### SERIAL ESTIMATIONS OF DRUG CONCENTRATIONS IN SERUM

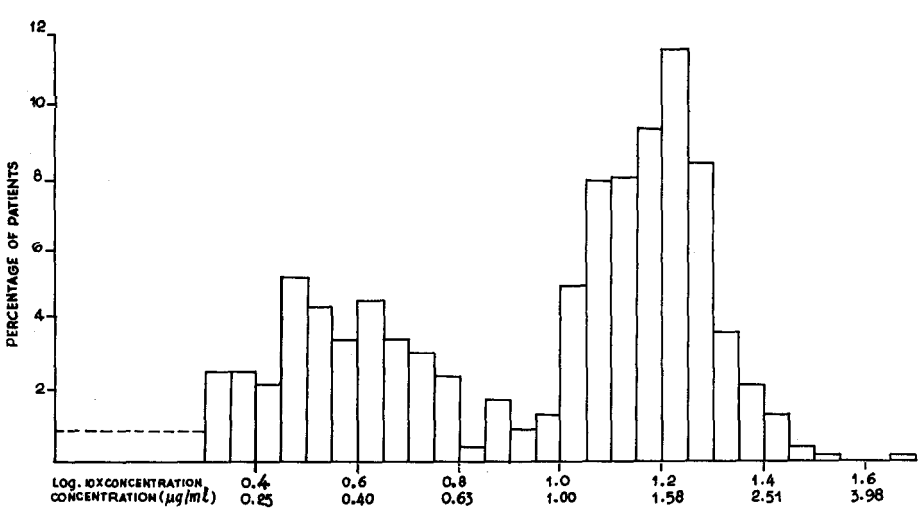
The serum concentration of streptomycin was estimated by microbiological assay with *Staphylococcus aureus* (Mitchison & Spicer, 1949) and using horse serum for the standards, that of isoniazid was estimated by the vertical diffusion technique mentioned above (after diluting the serum 4-fold with 4% bovine albumen solution) and using water for the standards, and that of pyrazinamide by a chemical procedure (Subbammal et al., 1968).

### DETERMINATIONS OF THE SGOT AND SGPT ACTIVITY

The SGOT and SGPT activities were determined by the procedures described by the Sigma Chemical Company (1961), and the activities are expressed in Karmen units.

FIG. 2

DISTRIBUTION OF 529 PATIENTS ACCORDING TO THE LOG. SERUM ISONIAZID CONCENTRATION 4% HOURS AFTER AN INTRAMUSCULAR DOSE OF 3 mg/kg BODY-WEIGHT



## IV. PATIENTS IN ANALYSES AND PLAN OF THE REPORT

### NUMBERS IN MAIN AND SUBSIDIARY ANALYSES

In all, 554 patients were admitted to the study. It was subsequently found that 7 patients failed to conform to the criteria for admission; 3 had received previous chemotherapy for more than 2 weeks and 4 did not have 2 positive cultures on admission. These 7 patients and 5 who had unclassified mycobacterial infections, together with 2 who refused further treatment after just 1 dose of drugs, have not been considered further in this report.

Cultures resistant to isoniazid or streptomycin or to both drugs were isolated from 56 patients on admission. These patients have been excluded from the main analyses, but their progress is described in Section XI. No patient has been excluded for initial resistance to pyrazinamide, since the drug had scarcely been used in Madras city.

There were 14 patients with no isoniazid inactivation test result, 8 in phase I, 5 in phase II and 1 in phase III of the intake. However, for the 6 patients in phases II and III, the inactivation rate could be determined from the serum concentrations obtained after an oral dose of high-dosage isoniazid (page 148). For the remaining 8 patients, this was not possible as such investigations had not been undertaken for patients in phase I. These patients have had to be excluded from the main analyses, as only statistically standardized percentages (for isoniazid inactivation rate and streptomycin dosage) have been employed in this report when comparing the efficacies of the various regimens (the reasons for this are given on page 152); however, their progress is reported on page 160).

After all these exclusions, 476 patients remained in the main analyses. All of them had cultures sensitive to isoniazid and streptomycin on admission, and had received, as far as is known, no previous chemotherapy, apart from 34 patients who had received up to 2 weeks of chemotherapy. The findings in these 476 patients are presented in Sections V to X of this paper.

### PLAN OF THE REPORT

Comparisons between the SHTW and SHOW regimens in phases I and II combined are described in Section V of this report (Fig. l), and this is followed by Section VI that describes comparisons between the SHTW, SH/SHOW, SHZOW and SHOW regimens in phases II and III combined. The comparisons between the SHTW, SH/SHOW and SHZOW regimens are concurrent. However, those between the SHOW regimen and the above three regimens are not fully concurrent, since, as stated earlier, there was no intake to the SHOW regimen in phase III. Nevertheless, *all* the comparisons have been undertaken in phases II and III combined (thereby greatly simplifying the presentation), as the number of patients in the main analysis was relatively small in phase III (75 as compared with 319 in phase II) and, furthermore, the condition of the patients on admission (not tabulated here) was similar in the two phases.

In Sections VII to X the patients from all three phases are considered together. Section VII deals in detail with laboratory findings, especially (1) the influence of streptomycin dosage and isoniazid inactivation rate on the pattern of drug-sensitivity test results, (2) pyrazinamide sensitivity test results, and (3) the influence of serum drug concentrations on response to treatment and drug toxicity. Sections VIII, IX and X, respectively, describe the prognostic importance of various factors on admission to treatment, the drug toxicity, and the regularity of administration of chemotherapy.

The progress of the 56 patients with initial drug resistance to isoniazid or to streptomycin or both is described in Section XI and this is followed by a discussion of the findings (Section XII) and the conclusions (Section XIII).

## V. COMPARISON OF THE SHTW AND SHOW SERIES

### CONDITION ON ADMISSION TO TREATMENT

The comparisons in this section are based on 240 patients (123 SHTW, 117 SHOW), of whom 63 % were males. The distributions by age and weight for all 240 patients are presented in Table 3; the average age was 32 years and the mean weight 85 lb (38.6 kg). Further analyses, not tabulated here, showed that the SHTW and SHOW series were similar in respect of sex, age and weight.

TABLE 3

DISTRIBUTIONS OF PATIENTS ACCORDING TO AGE AND WEIGHT ON ADMISSION TO TREATMENT

| Category | Patients | |
|---|---|---|
| | No. | % |
| **Age (years)** | | |
| **12–24** | **57** | **24** |
| **25–34** | **81** | **34** |
| **35–44** | **61** | **25** |
| **45–54** | **30** | **12** |
| **⩾ 55** | **11** | **5** |
| Weight (lb) [a] | | |
| <70 | 40 | 17 |
| 70-79 | 39 | 16 |
| 80-89 | 71 | 30 |
| 90-99 | 49 | 20 |
| 100-109 | 23 | 10 |
| ≥ 110 | 18 | 8 |
| Total | 240 | 100 |

[a] 1 lb = 0.45 kg.

The extent of cavitation and the total extent of disease were assessed, as described previously (Tuberculosis Chemotherapy Centre, Madras, 1960), from a single full-plate postero-anterior radiograph by an independent assessor, Dr K. V. Krishnaswamy.[1] Moderate or extensive cavitation was reported in 80% of the 123 SHTW patients and in 79 % of the 117 SHOW patients (Table 4, Part A), while the total extent of disease was moderate, extensive or gross in 71% of the SHTW and 72% of the SHOW patients. Direct smear examination of the first collection specimen of sputum yielded a positive result in 89 % of the SHTW and 90 % of the SHOW patients, including 50% and 56%, respectively, in whom it was 3-plus or 2-plus. Among the SHTW patients 32% were rapid inactivators of isoniazid as compared with 47% of the SHOW patients, an unusually large difference (P=0.02). Apart from this finding, it is clear that the two series were similar on admission. Furthermore, within each series, the condition on admission was broadly similar for patients receiving the high dosage of streptomycin and those receiving the low dosage (Table 4, Part B), and for the slow and the rapid inactivators of isoniazid (Table 4, Part C).

[1] Professor of Tuberculosis, Stanley Medical College; and Physician and Medical Superintendent, Government Tuberculosis Sanatorium, Madras, India.

## STATISTICAL STANDARDIZATION

In view of the dissimilarity between the two series in the proportions of rapid inactivators of isoniazid, and the finding that the slow inactivators in the SHOW series responded appreciably better than the rapid inactivators (page 160), the results of treatment needed some adjustment before precise comparisons could be undertaken. Further, there was a suggestion that the difference in streptomycin dosage might have had a slight effect in the SHOW series (page 158). Consequently, statistical standardization of the results was undertaken using the " indirect " method (Hill, 1961), and percentages standardized for isoniazid inactivation rate and streptomycin dosage have been employed throughout for comparing the response to treatment in the two series (except in Table 8, where standardization was not undertaken as the numbers were too small). Similarly, for the comparisons between the streptomycin high-dosage and the low-dosage groups, percentages standardized for isoniazid inactivation rate were employed, while for the comparisons between the slow and the rapid inactivators of isoniazid, percentages standardized for streptomycin dosage were employed.

## DEATHS [2]

Four patients (1 SHTW, 3 SHOW) died of pulmonary tuberculosis, all with a positive sputum. Of these, 2 died while on their allocated chemotherapy, 1 (SHTW, high, rapid) on the 4th day and the other (SHOW, high, slow) on the 39th day. The other 2 (1 SHOW, high, slow; 1 SHOW, low, rapid) had their chemotherapy changed (to a daily regimen of streptomycin plus isoniazid) because of serious clinical deterioration on the 15th and 25th days, respectively, but died 17 days and 3 days later.

One patient (SHOW, low, slow), all of whose smears and cultures were negative from the 1st month onwards, died of an acute respiratory infection, believed to be pneumonia, in the 4th month. An autopsy was not performed.

[2] The numbers of patients are set out in Table 9.

TABLE 4
CONDITION ON ADMISSION TO TREATMENT

| Condition on admission | Percentage of patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Part A (by regimen) | | Part B (by streptomycin dosage) | | | | Part C (by isoniazid inactivation rate) | | | |
| | SHTW | SHOW | SHTW | | SHOW | | SHTW | | SHOW | |
| | | | High | Low | High | Low | Slow | Rapid | Slow | Rapid |
| *Extent of cavitation:* | | | | | | | | | | |
| Nil | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 2 | 0 |
| Slight | 20 | 21 | 22 | 18 | 22 | 19 | 24 | 13 | 18 | 24 |
| Moderate | 49 | 54 | 47 | 51 | 52 | 56 | 50 | 46 | 53 | 55 |
| Extensive | 31 | 25 | 31 | 31 | 24 | 25 | 26 | 41 | 27 | 22 |
| *Total extent of disease:* | | | | | | | | | | |
| Slight | 4 | 3 | 3 | 5 | 3 | 3 | 6 | 0 | 3 | 4 |
| Limited | 25 | 25 | 31 | 20 | 29 | 20 | 26 | 23 | 24 | 25 |
| Moderate | 45 | 42 | 34 | 54 | 33 | 51 | 46 | 41 | 37 | 47 |
| **Extensive** | 17 | 21 | 19 | 15 | 26 | 15 | 13 | 26 | 26 | 15 |
| *Gross* | 9 | 9 | 12 | 6 | 9 | 10 | 8 | 10 | 10 | 9 |
| *Direct smear result of first collection specimen:* | | | | | | | | | | |
| Negative | 11 | 10 | 12 | 11 | 9 | 12 | 14 | 5 | 11 | 9 |
| Positive: | | | | | | | | | | |
| 1-plus (scanty) | 38 | 34 | 40 | 37 | 34 | 34 | 37 | 41 | 34 | 35 |
| 2-plus(moderate) | 33 | 38 | 34 | 32 | 40 | 37 | 31 | 38 | 40 | 36 |
| 3-plus (heavy) | 17 | 17 | 14 | 20 | 17 | 17 | 18 | 15 | 15 | 20 |
| *Isoniazid inactivation rate:* | | | | | | | | | | |
| Slow | 68 | 53 | 69 | 68 | 48 | 58 | | | | |
| Rapid | 32 | 47 | 31 | 32 | 52 | 42 | | | | |
| Total no. of patients | 123 | 117 | 58 | 65 | 58 | 59 | 84 | 39 | 62 | 55 |

TERMINATION OF THE ALLOCATED CHEMOTHERAPY[1]

*Because of radiographic or serious clinical deterioration in the presence of a positive sputum*

If a patient was considered by the Centre's physicians to have a definite radiographic extension of the disease (after the 1st month) in the presence of a positive sputum, a 10-day course of penicillin was given. If the lesion persisted or spread, the complete radiographic series was shown to an independent assessor (Dr K. S. Sanjivi) [2] who decided whether a change of chemotherapy was necessary. In all, 5 patients (all SHOW) had their allocated chemotherapy terminated on account of radiographic deterioration, 1 (low, rapid) in the 5th month, 1 (low, rapid) in the 6th month, 1 (high, rapid) in the 7th month and 2 (1 high, rapid; 1 low, slow) in the 11 th month.

Serious clinical deterioration in the presence of a

[1] The numbers of patients are set out in Table 9.

[2] Emeritus Professor of Medicine, Madras Medical College; and Director of Projects, Voluntary Health Services, Madras, India.

TABLE 5
RADIOGRAPHIC PROGRESS DURING THE 12-MONTH PERIOD [a]

| Assessment of progress | Standardized percentage of patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Part A (by regimen) | | Part B (by streptomycin dosage) | | | | Part C (by isoniazid inactivation rate) | | | |
| | SHTW | SHOW | SHTW | | SHOW | | SHTW | | SHOW | |
| | | | High | Low | High | Low | Slow | Rapid | Slow | Rapid |
| Radiographic improvement (all grades) | 96 | 89 | 94 | 97 | 89 | 88 | 98 | 94 | **93** | 82 |
| Considerable or exceptional radiographic improvement | 76 | 60 | 76 | 77 | 63 | 58 | 76 | 80 | 63 | 56 |
| Cavitation less or disappeared | 96 | 91 | 94 | 98 | 92 | 90 | 98 | 94 | 93 | 87 |
| Cavitation disappeared | 48 | 43 | 48 | 49 | 43 | 39 | 51 | 43 | 44 | 42 |
| Total no. of patients [b] | 117 | 115[c] | 56 | 61 | 58[c] | 57 | 82 | 35 | 60[c] | 55 |

[a] Assessment on standard radiographs taken on admission to treatment and at 12 months.
[b] Excluding patients who died of non-tuberculous causes, who dischargedthemselves against medical advice or who had their allocated chemotherapy terminated on account of toxicity.
[c] Including 1 patient who had no cavitation initially; she had no cavitation at 12 months either.

positive sputum was regarded as a reason for terminating the allocated chemotherapy without recourse to an independent assessor. In addition to the 2 patients who died after having their chemotherapy changed (see above), 2 SHTW patients (1 high, slow; 1 low, rapid) and 3 SHOW patients (1 high, slow; 2 low, rapid) had their allocated chemotherapy terminated for this reason in the 1st and 8th months and in the 1st, 3rd and 8th months, respectively.

*Because of toxicity*

The allocated chemotherapy was terminated in the 5th month for 1 patient (SHTW, low, rapid) on account of cutaneous hypersensitivity to isoniazid and streptomycin.

## DISCHARGE AGAINST MEDICAL ADVICE [1]

Three patients (all SHTW) became uncooperative and stopped treatment, 1 (low, rapid) in the 3rd month, 1 (high, slow) in the 6th month and 1 (high, rapid) in the 11th month; streptomycin toxicity (giddiness) was a contributory factor in the latter 2 patients.

Three patients, although co-operative, left Madras for domestic reasons, 1 (SHTW, low, slow) in the 2nd month, 1 (SHOW, low, slow) in the 9th month and 1 (SHTW, low, rapid) in the 12th month.

[1]The numbers of patients are set out in Table 9.

## RADIOGRAPHIC PROGRESS

Radiographic changes during the 12-month period were assessed by an independent assessor (Dr K. V. Krishnaswamy), who was unaware of the treatment or bacteriological results of any individual patient. Over-all improvement was shown by 96 % of the SHTW patients and 89 % of the SHOW patients (Table 5, Part A), a significant difference (P=0.03). It was considerable or exceptional in 76 % and 60 %, respectively ($P < 0.01$). Further, cavitation became less or disappeared in 96 % of the SHTW and 91% of the SHOW patients (P=0.09).

There was no evidence that the difference in streptomycin dosage influenced the radiographic response in either series (Table 5, Part B), all the contrasts between the high-dosage and the low-dosage patients being clearly non-significant ($P \geq 0.3$). For example, in the SHTW series, over-all improvement was shown by 94 % of the high-dosage patients and 97 % of the low-dosage patients, while cavitation became less or disappeared in 94% and 98 %, respectively. In the SHOW series, the corresponding proportions were 89 % and 88 %, and 92 % and 90 %, respectively.

The rate of inactivation of isoniazid had no effect on the radiographic response in the SHTW series (Table 5, Part C), all the contrasts between the slow and the rapid inactivators being clearly non-significant ($P \geq 0.4$). In the SHOW series, the proportion with over-all radiographic improvement was appreciably higher in the slow (93%) than in the rapid inactivators (82 %), the difference bordering on significance (P=0.06); however, all the other contrasts were clearly non-significant ($P \geq 0.3$).

In summary, the radiographic response to treatment was highly satisfactory in the SHTW series and less satisfactory in the SHOW series. In both the series, the radiographic response was not influenced by the difference in streptomycin dosage and, in the SHTW series, it was not influenced by the isoniazid inactivation rate. However, in the SHOW series, there was some evidence that the over-all radiographic progress was slightly more satisfactory in the slow inactivators.

## CULTURE RESULTS

Table 6 sets out the percentages of patients with a negative culture from a single collection specimen of sputum at monthly intervals. Considering first the over-all comparisons between the SHTW and the SHOW series (Part A of Table 6, and Fig. 3), the percentages with a negative culture were similar in the two series, both at 1 and at 2 months. However, at 3 months, a clear difference emerged between the two series, the proportions with a negative culture being 80% for the SHTW and 69% for the SHOW series (P=0.06). The proportions increased to 88% and 76%, respectively, at 4 months, a significant difference (P=0.01), and were 90% and 74%,

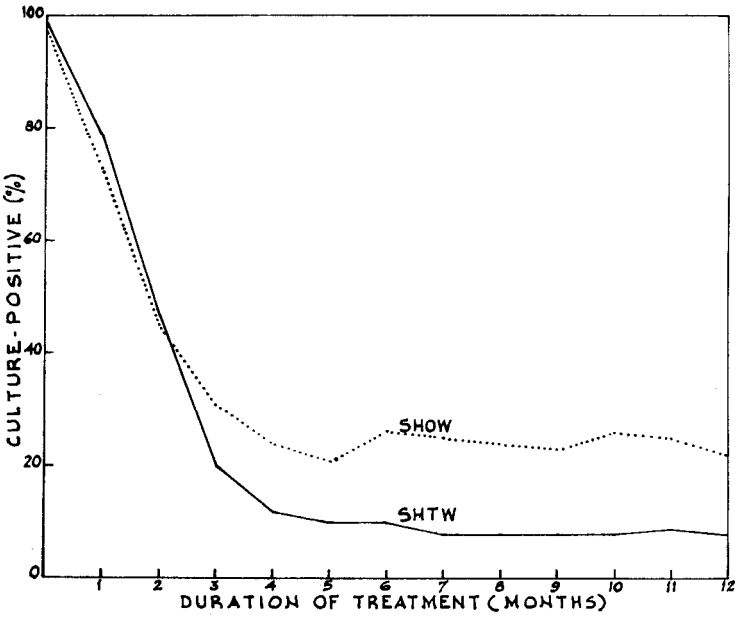
TABLE 6

STANDARDIZED PERCENTAGES OF PATIENTS WITH A NEGATIVE CULTURE FROM A SINGLE COLLECTION SPECIMEN OF SPUTUM

| Months after start of chemotherapy | Part A (by regimen) | | Part B (by streptomycin dosage) | | | | Part C (by isoniazid inactivation rate) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SHTW | SHOW | SHTW | | SHOW | | SHTW | | SHOW | |
| | | | High | Low | High | Low | Slow | Rapid | Slow | Rapid |
| **0** | 1 | 2 | 2 | 1 | 0 | 4 | 2 | 0 | 3 | 0 |
| **1** | 21 | 27 | 16 | 25 | 26 | 27 | 21 | 20 | 27 | 26 |
| **2** | 53 | 55 | 49 | 58 | 58 | 52 | 51 | 58 | 53 | 58 |
| **3** | 80 | 69 | 70 | 88 | 78 | 60 | 78 | 84 | 73 | 65 |
| **4** | 88 | 76 | 84 | 92 | 83 | 69 | 88 | 90 | 80 | 70 |
| **5** | 90 | 79 | 84 | 96 | 83 | 74 | 93 | 86 | 80 | 76 |
| **6** | 90 | 74 | 88 | 90 | 81 | 68 | 93 | 86 | 80 | 66 |
| **7** | 92 | 75 | 90 | 94 | 82 | 68 | 93 | 95 | 81 | 66 |
| **8** | 92 | 76 | 90 | 94 | 34 | 68 | 93 | 95 | 82 | 67 |
| **9** | 92 | 77 | 90 | 94 | 82 | 73 | 93 | 94 | 84 | 68 |
| **10** | 92 | 74 | 90 | 94 | 77 | 71 | 92 | 94 | 81 | 65 |
| **11** | 91 | 75 | 88 | 94 | 81 | 70 | 92 | 92 | 83 | 65 |
| **12** | 92 | 78 | 90 | 94 | 81 | 75 | 92 | 94 | 85 | 69 |
| 7-12 (mean) | 92 | 78 | 90 | 94 | 81 | 71 | 93 | 94 | 82 | 67 |
| No. of patients in analysis (range) [a] | 123-113 | 117-111 | 58-54 | 85-59 | 53-58 | 59-55 | 84-77 | 39-35 | 82-57 | 55-52 |

[a] The highest and the lowest number of patients In the analysis at any of the months. Patients who died of non-tuberculous causes, who discharged themselves against medical advice or who had their allocated chemotherapy terminated on account of toxicity are excludedthereafter. Patients who died oftuberculosis or who had theirallocated chemotherapy terminated on accountof radiographic or clinical deterioration are included throughout.

FIG. 3
STANDARDIZED PERCENTAGES OF PATIENTS WITH A POSITIVE CULTURE FROM A SINGLE COLLECTION SPECIMEN OF SPUTUM




respectively, at 6 months ($P < 0.01$); thereafter, they showed little change, the mean for the period from month 7 to month 12 being 92% for the SHTW patients and 76% for the SHOW patients, a highly significant difference ($P < 0.001$).

There was no evidence that the difference in streptomycin dosage affected the culture results in the SHTW series, the mean culture negativity during the period from month 7 to month 12 being 90% for the high-dosage patients and 94% for the low-dosage patients (Table 6, Part B). In the SHOW series, however, there was a suggestion that the high-dosage patients responded slightly better than the low-dosage patients; thus, the proportions with a negative culture at 6 months were 81% and 68 %, respectively ($P=0.1$), and the values for mean culture negativity during the period from month 7 to month 12 were 81% and 71%, respectively ($P=0.2$).

The rate of inactivation of isoniazid did not influence the culture results in the SHTW series, the mean culture negativity during the period from month 7 to month 12 being 93% for the slow and 94% for the rapid inactivators (Table 6, Part C). In contrast, in the SHOW series, the slow inactivators responded more satisfactorily than the rapid inactivators; thus, 80 % and 66 %, respectively, were culture-negative at 6 months ($P=0.09$), while the mean culture negativity during the period from month 7 to month 12 was 82% and 67%, respectively, a significant difference ($P=0.04$).

In summary, culture negativity was attained considerably more frequently in the SHTW series than in the SHOW series. The difference in streptomycin dosage hardly affected the culture results in the SHTW series but appeared to have had some effect in the SHOW series. The isoniazid inactivation rate had no effect in the SHTW series, but the slow inactivators in the SHOW series responded more satisfactorily than the rapid inactivators.

## SENSITIVITY TEST RESULTS

The findings of tests of sensitivity to isoniazid and streptomycin, at monthly intervals from the 3rd month onwards, are presented in Tables 7 and 8 (isoniazid sensitivity test results were not available for 5.1% of the cultures and streptomycin sensitivity test results for 6.6 %). The comparisons between the streptomycin high-dosage and the low-dosage groups

TABLE 7

STANDARDIZED PERCENTAGES OF PATIENTS WITH DRUG-RESISTANT CULTURES

| Months after start of chemotherapy | Isoniazid-resistant | | Streptomycin-resistant | |
|---|---|---|---|---|
| | SHTW | SHOW | SHTW | SHOW |
| 3 | 4 | 17 | 0 | 3 |
| 4 | 5 | 16 | 2 | 6 |
| 5 | 4 | 18 | 2 | 13 |
| 6 | 6 | 16 | 8 | 10 |
| 7 | 6 | 19 | 5 | 17 |
| 8 | 6 | 21 | 5 | 16 |
| 9 | 8 | 19 | 7 | 16 |
| 10 | 7 | 19 | 7 | 16 |
| 11 | 7 | 20 | 7 | 16 |
| 12 | 8 | 19 | 7 | 18 |
| No. of patients in analysis (range) [a] | 113-115 | 111-107 | 118-115 | 110-104 |

[a] The highest and the lowest number of patients In the analysis at any of the months. Patients who died, who discharged themselves against medical advice or who had their allocated chemotherapy terminated on account of toxicity are excluded thereafter. The policy for patients who had their allocated chemotherapy terminated on account of radiographic or clinical deterioration Is described below.

in each series, and between the slow and the rapid inactivators of isoniazid, are presented in Section VII (pages 173 *et seq.).*

Of the 10 patients who had the allocated chemotherapy terminated on account of radiographic or serious clinical deterioration, 3 had the termination within 3 months and do not therefore appear in Tables 7 and 8. In the remaining 7, the last 2 sensitivity test results prior to the termination showed isoniazid resistance for all and streptomycin resistance for 5. Since the removal of these patients from the analyses after the termination would result in underestimates of resistance, it has been assumed (in Tables 7 and 8) that all 7 patients would have continued to yield isoniazid-resistant cultures and 5 would have continued to yield streptomycin-resistant cultures for the rest of the year; for streptomycin-sensitivity analyses, the remaining 2 patients have been excluded from the time of the termination.

*Percentages of patients with resistant cultures*

*Isoniazid.* Resistance to isoniazid occurred more frequently in the SHOW series, even in the early months of treatment (Table 7). Thus, at 3 months, 4% of the SHTW patients had a resistant culture as compared with 17% of the SHOW patients, a

TABLE 8

PERCENTAGES (UNSTANDARDIZED) OF POSITIVE CULTURES WITH DRUG-RESISTANT BACILLI [a]

| Months after chemotherapy | Isoniazid | | | | | | Streptomycin | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SHTW patients | | | SHOW patients | | | SHTW patients | | | SHOW patients | | |
| | Culture-positive | Resistant | | Culture-positive | Resistant | | Culture-positive | Resistant | | Culture-positive | Resistant | |
| | | No. | %[b] | | No. | % | | No. | %[b] | | No. | % |
| 3 | 30 | 4 | 13 | 33 | 19 | 50 | 30 | 0 | 0 | 38 | 4 | 11 |
| 4 | 16 | 6 | (38) | 31 | 18 | 58 | 16 | 2 | (12) | 31 | 8 | 26 |
| 5 | 11 | 5 | (45) | 30 | 20 | 67 | 11 | 2 | (18) | 30 | 16 | 53 |
| 6 | 12 | 7 | (58) | 28 | 18 | 64 | 12 | 6 | (50) | 25 | 12 | 48 |
| 7 | 8 | 7 | | 27 | | | 8 | 5 | | 25 | 20 | |
| 8 | 8 | 7 | 88 | 27 | 24 | 86 | 8 | 5 | 69 | 26 | 19 | 77 |
| 9 | 10 | 9 | | 24 | 21 | | 10 | 8 | | 23 | 18 | |
| 10 | 9 | 8 | | 28 | | | 9 | 7 | | 27 | 18 | |
| 11 | 11 | 8 | 38 | 27 | 23 | 82 | 11 | 8 | 79 | 24 | 18 | 78 |
| 12 | 8 | 8 | | 27 | 23 | | a | 7 | | 24 | 21 | |

[a] Patients whose allocated chemotherapy was terminated for deterioration are included subsequently also (and regarded as having resistant cultures) provided the last 2 sensitivity test results prior to the termination were resistant (see above).

[b] Parentheses indicate that the percentage is based on fewer than 25 observations.

highly significant difference (P <0.001). Subsequently, the proportions increased slightly, the figures at 12 months being 8 % and 19 %, respectively (P <0.01).

*Streptomycin.* Resistance to streptomycin had not emerged in any of the SHTW patients by 3 months but had done so in 3% of the SHOW patients (Table 7). At 6 months, the proportions with a resistant culture were 6% in the SHTW series and 10% in the SHOW series; the corresponding proportions were 7 % and 16 % at 9 months (P=0.04), and 7 % and 18 % at 12 months (P<0.01).

*Percentages of positive cultures with resistant bacilli*

Table 8 presents *unstandardized* percentages of positive cultures with resistant bacilli, at monthly intervals from the 3rd month onwards (statistical standardization of the results was not undertaken on account of the small numbers of positive cultures obtained in the SHTW series, especially in the later months of treatment).

*Isoniazid.* Resistance to isoniazid emerged more rapidly in the SHOW series; thus, at 3 months, 13 % of 30 positive cultures in the SHTW series were resistant as compared with 50% of 38 in the SHOW series, a significant difference (P <0.01). By 6 months, however, the proportions in the two series were very similar, being 58% for the SHTW and 64% for the SHOW series. The similarity was maintained at subsequent months.

*Streptomycin.* Resistance to streptomycin emerged more rapidly in the SHOW series. Thus, the proportions resistant were 0% for the SHTW and 11% for the SHOW series at 3 months, 12 % and 26 % at 4 months, and 18 % and 53 % at 5 months; these proportions, however, are based on small numbers and none of the differences was statistically significant. At 6 months and subsequently, the findings were similar in the two series.

Summarizing the findings in Tables 7 and 8, resistance to isoniazid and to streptomycin occurred more frequently and more rapidly in the SHOW series than in the SHTW series.

## CLASSIFICATION OF PATIENTS AT 1 YEAR ACCORDING TO THEIR RESPONSE TO TREATMENT

Table 9 presents a classification of all the patients at 1 year, based primarily on the bacteriological response to treatment.

*Over-all efficacies of the two regimens*

Of 117 SHTW patients, 100 had bacteriologically quiescent disease at 1 year, as compared with 75 of 115 SHOW patients (Table 9, Part A). There were 14 patients (7 SHTW, 7 SHOW) who had disease of bacteriologically doubtful status at 1 year. In view of the high frequency with which sputum specimens are collected at the Centre (see page 147), and previous experience with similar groups of patients (Dawson et al., 1966; Evans et al., 1969; Ramakrishnan et al., 1969), these patients also have been regarded as having a favourable response to treatment; moreover, a follow-up of the 14 patients (9 of whom received maintenancechemotherapy in the second year) showed that all of them had produced only negative cultures in the 6 months following the single positive culture. Thus, 91% of the 117 SHTW and 71% of the 115 SHOW patients had a favourable response; the corresponding proportions after standardization for isoniazid inactivation rate and streptomycin dosage were 90 % and 72 %, respectively, the difference being highly significant (P <0.001) (unstandardized percentages are presented in Table 9 in addition to the standardized percentages in order to illustrate the size of the changes resulting from statistical standardization).

In the patients with *bacteriologically quiescent disease at 1 year,* there was no evidence (analyses not tabulated here) that persisting culture negativity had commenced earlier in the SHTW series. Thus, in each of the two series, it was attained within 3 months in 64 % of the patients, and within 6 months in 90 %.

An unfavourable response to treatment occurred in 10 SHTW and 33 SHOW patients (Table 9). It should be noted that 8 of 10 patients who had their allocated chemotherapy terminated for radiographic or serious clinical deterioration and 3 of 4 who died of tuberculosis had received the SHOW regimen.

In summary, the response to treatment was substantially better in the SHTW series.

*Influence of streptomycin dosage on the response to treatment*

The difference in streptomycin dosage had no effect on the response to treatment in the SHTW series, but appears to have had a slight effect in the SHOW series (Table 9, Part B). Thus, the standardized proportions with a favourable response were 90% in both the high-dosage and the low-dosage

TABLE 9

CLASSIFICATION OF ALL PATIENTS AT 1 YEAR ACCORDING TO THEIR RESPONSE TO TREATMENT

| Classification at 1 year | | Part A (by regimen) | | Part B (by streptomycin dosage) | | | | Part C (by isoniazid inactivation rate) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SHTW | SHOW | SHTW | | SHOW | | SHTW | | SHOW | |
| | | | | High | Low | High | Low | Slow | Rapid | Slow | Rapid |
| *Bacteriologically quiescent disease:* that is, all cultures negative at the last 3 monthly examinations, i.e., at 10, 11 and 12 months | | 100 | 75 | 48 | 52 | 40 | 35 | 72 | 28 | 45 | 30 |
| *Disease of bacteriologically doubtful status:* that is, ail cultures negative at 3 or more consecutive monthly examinations but a single positive culture at 10, 11 or 12 months | | 7 | 7 | 3 | 4 | 4 | 3 | 3 | 4 | 4 | 3 |
| Total patients with a favourable response | No. | 107 | 82 | 51 | 56 | 44 | 38 | 75 | 32 | 49 | 33 |
| | % | 91 | 71 | 91 | 92 | 76 | 67 | 91 | 91 | 82 | 60 |
| | Standardized % | 90 | 72 | 90 | 90 | 78 | 67 | 92 | 91 | 82 | 60 |
| *Bacteriologically relapsed disease:* that is, ail cultures negative at 3 or more consecutive monthly examinations but a *total* of 2 or more positive cultures at IO, 11 and 12 months | | 2 | 5 | 1 | 1 | 4 | 1 | 2 | 0 | 0 | 5 |
| *Bacteriologically active disease:* that is (1) cultures never ail negative at 3 consecutive monthly examinations | | **5** | 17 | 2 | 3 | 5 | 12 | 4 | 1 | 7 | 10 |
| *or* (2) termination of allocated chemotherapy on account of | | | | | | | | | | | |
| *(a)* radiographic deterioration | | **0** | 5 | 0 | 0 | 2 | 3 | 0 | 0 | 1 | 4 |
| *(b)* serious clinical deterioration | | **2** | 3 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 2 |
| Tuberculous death | | 1 | 3 | 1 | 0 | 2 | 1 | 0 | 1 | 2 | 1 |
| Total no. of patients with an unfavourable response | | 10 | 33 | 5 | 5 | 14 | 19 | 7 | 3 | 11 | 22 |
| Total no. of patients | | 117 | 115 | 56 | 61 | 58 | 57 | 82 | 35 | 60 | 55 |
| Termination of allocated chemotherapy on account of toxicity | | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Discharge against medical advice | | 5 | 1 | 2 | 3 | 0 | 1 | 2 | 3 | 1 | 0 |
| Non-tubercuious death | | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Grand total of patients | | 123 | 117 | 58 | 65 | 58 | 59 | 84 | 39 | 62 | 55 |

patients in the SHTW series; the corresponding proportions in the SHOW series were 78 % and 67 %, respectively, a non-significant difference (P =0.2).

In the patients with *bacteriologically quiescent disease at 1 year,* there was no evidence (analyses not tabulated here) that persisting culture negativity had commenced earlier in the high-dosage patients; thus, the proportion in whom it was attained within 3 months was 56% for the high-dosage and 71% for the low-dosage patients in the SHTW series, and 68 % and 60%, respectively, in the SHOW series.

*Influence of isoniazid inactivation rate on the response to treatment*

The rate of inactivation of isoniazid had no effect on the outcome of treatment in the SHTW series, the standardized percentages with a favourable response being 92% for the slow and 91% for the rapid inactivators (Table 9, Part C). In the SHOW series, however, the slow inactivators responded much more satisfactorily, 82% having a favourable response as compared with 60% of the rapid inactivators, a highly significant difference (P <0.01).

In the patients with *bacteriologically quiescent disease at 1 year,* there has no evidence (analyses not tabulated here) that persisting culture negativity had commenced earlier in the slow inactivators. Thus, it was attained within 3 months in 64% of the slow and 64% of the rapid inactivators in the SHTW series, and in 67 % and 60%, respectively, in the SHOW series.

*Conclusion*

The SHTW regimen was highly effective and was not influenced by differences in isoniazid inactivation rate and streptomycin dosage. In contrast, the SHOW regimen was much less effective, and was considerably influenced by the isoniazid inactivation rate, and possibly influenced by the streptomycin dosage. Finally, there was no evidence that persisting culture negativity commenced earlier in the SHTW patients, the streptoniycin high-dosage patients or the slow inactivators of isoniazid.

## DISEASE STATUS AT 1 YEAR IN PATIENTS WHO TOOK THEIR DISCHARGE AGAINST MEDICAL ADVICE

In all, 6 patients (5 SHTW, 1 SHOW) took their discharge against medical advice (Table 9, Part A); they have been excluded from the above comparisons. However, attempts were made to obtain sputum specimens from these patients at 12 months, in order to classify their disease status at 1 year.

Of the 6 patients, 1 (SHTW) died of tuberculosis in the 8th month, 2 (1 SHTW, 1 SHOW) had bacteriologically active disease at 1 year, and 1 (SHTW) had 2 positive cultures at 6 months (no specimens were collected subsequently in the first year, but 7 of 8 cultures obtained at 15, 16 and 17 months were positive). These 4 patients, who stopped treatment in the 3rd, 6th, 9th and 2nd month, respectively, may be regarded as having an unfavourable disease status at 1 year. Two patients (both SHTW), who had stopped treatment in the 11th and 12th month, respectively, had all of 5 cultures negative during the period from month 10 to month 12; neither had had a history of treatment subsequent to the discharge and both may be regarded as having a favourable disease status at 1 year.

If the 6 patients are included in the comparison of the therapeutic efficacies of the regimens, the proportion with a favourable disease status at 1 year becomes 89 % for the SHTW series and 71% for the SHOW series, the corresponding standardized proportions being 88 % and 72 %, respectively.

## RESPONSE TO TREATMENT OF PATIENTS WHOSE RATE OF INACTIVATION OF ISONIAZID WAS NOT KNOWN

As mentioned on page 151, the rate of inactivation of isoniazid was not known for 8 patients (1 SHTW, 7 SHOW), all of whom were therefore excluded from the main analyses. Of these, 7 (all SHOW) had died by the time the decision was made to undertake isoniazid inactivation tests in phase I patients (see page 148), and 1 patient (SHTW) refused the test. The response of these patients to the allocated chemotherapy is considered below.

The SHTW patient (high) had bacteriologically quiescent disease at 1 year. Of the 7 SHOW patients, 1 (low) died of tuberculosis on the 16th day, 4 (2 high, 2 low) had bacteriologically active or relapsed disease and 1 (high) had bacteriologically quiescent disease at 1 year; the 7th patient (low) died of a non-tuberculous cause, believed to be agranulocytosis, in the 3rd month, having had all smears and cultures negative at 2 months. If the 7 patients (1 SHTW, 6 SHOW) with an assessable response (that is, the non-tuberculous death apart) are amalgamated with those in the main analyses, the *unstandardized* proportions with a favourable re-

sponse become 92 % of 118 in the SHTW series and 69% of 121 in the SHOW series; the corresponding unstandardized proportions are 91% of 57 in the high-dosage patients and 92% of 61 in the low-dosage patients in the SHTW series, and 74% of 61 and 63% of 60, respectively, in the SHOW series.

## VI. COMPARISONS BETWEEN THE SHTW, SH/SHOW, SHZOW AND SHOW SERIES

### CONDITION ON ADMISSION TO TREATMENT

The comparisons in this section are based on 394 patients (104 SHTW, 106 SH/SHOW, 105 SHZOW, 79 SHOW), of whom 66% were males. The distributions by age and by weight were closely similar to those in Table 2, the average age of the patients being 33 years and the mean weight 86 lb (39.1 kg). Analyses, not tabulated here, showed that the four individual series were similar in respect of sex, age and weight.

Considering the radiographic and bacteriological condition on admission in the four series (Table 10, Part A), moderate or extensive cavitation was present in 80% of the 104 SHTW, 89 % of the 106 SH/SHOW, 87 % of the 105 SHZOW and 80 % of the 79 SHOW patients, while the total extent of disease was moderate, extensive or gross in 75%, 75 %, 70% and 76%, respectively. Direct smear examination of the first collection specimen of sputum yielded a positive result in 88% of the SHTW, 90 % of the SH/SHOW, 90 % of the SHZOW and 90% of the SHOW patients, including 62%, 67 %, 64% and 67 %, respectively, in whom it was 3-plus or 2-plus. Lastly, 37% of the SHTW, 37% of the SH/SHOW, 33% of the SHZOW, and 49% of the SHOW patients were rapid inactivators of isoniazid; the difference between the SHZOW and the SHOW series is unusually large (P=0.04). Apart from this finding, it is clear that the four series of patients were similar on admission.

Within each of the four series, the condition on admission of the streptomycin high-dosage patients was broadly similar to that of the streptomycin low-dosage patients (Table 10, Part B), apart from one exception; this was in the SHOW series, where 62% of the high-dosage patients were rapid inactivators of isoniazid as compared with 38% of the low-dosage patients (P = 0.06). Considering next the comparisons between the slow and the rapid inactivators of isoniazid in each series (Table 10, Part C), all the differences were non-signficant in the SHTW, SH/SHOW and the SHOW series. However, in the SHZOW series, there was some evidence that rapid inactivators had a larger bacterial content in the sputum; [1] thus, 86% had a 2-plus or 3-plus smear result from the first collection specimen as compared with 53% of the slow inactivators (P <0.01). [2]

### STATISTICAL STANDARDIZATION

In view of the dissimilarities between the series in the proportions of rapid inactivators of isoniazid, and the finding that the slow inactivators in the SH/SHOW, SHZOW and SHOW series responded appreciably better than the rapid inactivators (page 172), the results of treatment needed some adjustment before precise comparisons between the series could be undertaken. Further, there was a suggestion that the difference in streptomycin dosage might have had a slight effect in the SH/SHOW and the SHOW series (page 169). Consequently, statistical standardization of the results was undertaken using the " indirect " method (Hill, 1961), and percentages standardized for isoniazid inactivation rate and streptomycin dosage have been employed throughout for comparing the response to treatment in the four series (except in Table 14, where standardization was not undertaken as the numbers were too small). Similarly, for the comparisons between the streptomycin high-dosage and the low-dosage groups, percentages standardized for isoniazid inactivation rate were employed, while for those between the slow and the rapid inactivators of isoniazid, percentages standardized for streptomycin dosage were employed.

### DEATHS [3]

Six patients (1 SHTW, 2 SHZOW, 3 SHOW) died of pulmonary tuberculosis, all with a positive

[1] For the implications of this difference on the classification at 1 year according to the response to treatment, see footnote on page 172.

[2] Analyses of the results of the second collection specimen confirmed this finding, the corresponding proportions being 83 % for the rapid and 59 % for the slow inactivators (P = 0.02).

[3] The numbers of patients are set out in Table 15.

TABLE 10

CONDITION ON ADMISSION TO TREATMENT

| Condition on admission | Percentage of patients | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Part A (by regimen) | | | | Part B (by streptomycin dosage) | | | | | | | | Part C (by isoniazid inactivation rate) | | | | | |
| | | | | | SHTW | | SH/SHOW | | SHZOW | | SHOW | | SHTW | | SH/SHOW | | SHZOW | | SHOW | |
| | SHTW | SH/SHOW | SHZOW | SHOW | High | Low | High | Low | High | Low | High | Low | Slow | Rapid | Slow | Rapid | Slow | Rapid | Slow | Rapid |
| *Extent of cavitation:* | | | | | | | | | | | | | | | | | | | | |
| *Nil* | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Slight | 20 | 11 | 12 | 20 | 22 | 19 | 8 | 15 | 10 | 15 | 26 | 15 | 24 | 13 | 12 | 10 | 14 | 9 | 18 | 23 |
| Moderate | 50 | 51 | 51 | 53 | 53 | 47 | 52 | 50 | 49 | 54 | 49 | 58 | 48 | 53 | 51 | 51 | 51 | 51 | 52 | 54 |
| Extensive | 30 | 38 | 35 | 27 | 25 | 34 | 40 | 35 | 39 | 31 | 26 | 28 | 27 | 34 | 37 | 38 | 33 | 40 | 30 | 23 |
| *Total extent of disease:* | | | | | | | | | | | | | | | | | | | | |
| Slight | 5 | **1** | 4 | 1 | 6 | 4 | 0 | 2 | 2 | 6 | 0 | 2 | 8 | 0 | 1 | 0 | 6 | 0 | 2 | 0 |
| Limited | 20 | **24** | 27 | 23 | 24 | 17 | 19 | 28 | 25 | 28 | 28 | 18 | 23 | 16 | 27 | 18 | 26 | 29 | 15 | 31 |
| Moderate | 55 | **38** | 38 | 44 | 45 | 64 | 44 | 31 | 35 | 41 | 36 | 52 | 55 | 55 | 36 | 41 | 36 | 43 | 42 | 46 |
| Extensive | 12 | **31** | 28 | 22 | 14 | 9 | 27 | 35 | 33 | 22 | 23 | 20 | 8 | 18 | 30 | 33 | 30 | 23 | 30 | 13 |
| Gross | 9 | **7** | 4 | 10 | 12 | 6 | 10 | 4 | 4 | 4 | 13 | 8 | 8 | 11 | 6 | 8 | 3 | a | IO | IO |
| *Direct smear result of first collection specimen:* | | | | | | | | | | | | | | | | | | | | |
| Negative | 12 | **10** | 10 | 10 | 12 | 11 | 10 | 11 | 10 | 11 | 8 | 12 | 14 | 8 | 10 | 10 | 16 | 0 | 15 | 5 |
| Positive: | | | | | | | | | | | | | | | | | | | | |
| 1-plus (scanty) | 26 | **23** | 26 | 23 | 27 | 25 | 21 | 24 | 25 | 26 | 23 | 22 | 24 | 29 | 19 | 28 | 31 | 14 | 20 | 25 |
| 2-plus (moderate) | 40 | **42** | 39 | 43 | 39 | 42 | 44 | 41 | 41 | 37 | 44 | 42 | 38 | 45 | 48 | 33 | 29 | 60 | 42 | 44 |
| 3-plus (heavy) | 22 | **25** | 25 | 24 | 22 | 23 | 25 | 24 | 24 | 26 | 26 | 22 | 24 | 18 | 22 | 28 | 24 | 26 | 22 | 26 |
| *Isoniazid inactivation rate.* | | | | | | | | | | | | | | | | | | | | |
| Slow | 63 | 63 | 67 | 51 | 65 | 62 | 63 | 63 | 71 | 63 | 38 | 62 | | | | | | | | |
| Rapid | 37 | 37 | 33 | 49 | 35 | 38 | 37 | 37 | 29 | 37 | 62 | 38 | | | | | | | | |
| Total no. of patients | 104 | 105 | 105 | 79 | 51 | 53 | 52 | 54 | 51 | 54 | 39 | 40 | 66 | 38 | 67 | 39 | 70 | 35 | 40 | 39 |

sputum: Of these, 4 (1 SHTW, high, rapid; 1 SHZOW, high, rapid; 1 SHZOW, low, slow; 1 SHOW, high, slow) died while on their allocated chemotherapy, the deaths occurring on the 4th, 6th, 12th and 39th days, respectively. The other 2 (1 SHOW, high, slow; 1 SHOW, low, rapid) had their chemotherapy changed (to daily streptomycin plus isoniazid) for serious clinical deterioration on the 15th and 25th days, respectively, but died 17 and 3 days later.

Three patients (1 SHTW, 1 SH/SHOW, 1 SHOW) died of non-tuberculous causes. The SHTW patient (high, slow) committed suicide (following a domestic quarrel) in the 8th month, the SH/SHOW patient (low, rapid) died of intestinal obstruction in the 6th month, and the SHOW patient (low, slow) died of an acute respiratory infection, believed to be pneumonia, in the 4th month. These patients had all smears and cultures negative from the 2nd, 2nd and 1st month onwards, respectively. An autopsy was not performed on any of the patients.

### TERMINATION OF THE ALLOCATED CHEMOTHERAPY [1]

*Because of radiographic or serious clinical deterioration in the presence of a positive sputum*

Eleven patients (6 SHZOW, 5 SHOW) had their allocated chemotherapy terminated on account of radiographic deterioration. For the 6 SHZOW patients, this was in the 6th month in 1 (high, slow), 8th month in 1 (high, slow), 9th month in 2 (both low, rapid), 10th month in 1 (low, slow), and 12th month in 1 patient (high, slow). For the 5 SHOW patients, the month of termination was the 5th in 1 (low, rapid), 6th in 1 (low, rapid), 7th in 1 (high, rapid) and 11th in 2 patients (1 high, rapid; 1 low, slow).

In addition to the 2 patients who died after having their chemotherapy changed (see above), there were 2 patients who had their allocated chemotherapy terminated on account of serious clinical deterioration, one (SHZOW, low, rapid) in the 8th month, and the other (SHOW, high, slow) in the 1st month.

*Because of toxicity*

Three patients had their allocated chemotherapy terminated on account of toxicity, 1 (SHTW, low, rapid) in the 5th month for cutaneous hypersensitivity to isoniazid and streptomycin, and the other 2 (1 SHTW, high, rapid; 1 SH/SHOW, high, slow) in the 11th and 9th month, respectively, for vestibular toxicity.

### DISCHARGE AGAINST MEDICAL ADVICE [1]

Nine patients (3 SHTW, 2 SH/SHOW, 4 SHZOW) became uncooperative and stopped treatment, 2 (1 SHTW, low, rapid; 1 SHZOW, low, slow) in the 3rd month, 3 (1 SH/SHOW, low, rapid; 1 SHZOW, low, slow; 1 SHZOW, low, rapid) in the 4th month, 1 (SHTW, high, slow) in the 6th month, 1 (SH/SHOW, low, slow) in the 10th month and 2 (1 SHTW, high, rapid; 1 SHZOW, high, slow) in the 11th month; streptomycin toxicity (giddiness) was a contributory factor in 2 of these patients (1 SHTW, high, slow; 1 SHTW, high, rapid).

Four patients, although co-operative, left Madras for domestic reasons, 1 (SHTW, low, slow) in the 2nd month, 1 (SH/SHOW, high, slow) in the 8th, 1 (SHOW, low, slow) in the 9th, and 1 (SHTW, low, rapid) in the 12th month.

### RADIOGRAPHIC PROGRESS

Radiographic changes during the 12-month period, as reported by the independent assessor, are set out in Table 11. Over-all improvement was shown by 99 % of 96 SHTW patients, 100% of 101 SH/SHOW, 90 % of 101 SHZOW and 86 % of 77 SHOW patients (Part A). It was considerable or exceptional in 79 %, 73 %, 65 % and 57%, respectively; three of the contrasts were statistically significant-namely, those between the SHTW and SHZOW ($P=0.02$), the SHTW and SHOW ($P<0.01$), and the SH/SHOW and SHOW regimens ($P=0.02$). Cavitation became less or disappeared in 99% of the SHTW, 100% of the SH/SHOW, 91% of the SHZOW and 88 % of the SHOW patients; the differences between the SHTW or the SH/SHOW series on the one hand and the SHZOW or the SHOW series on the other hand were all statistically significant ($P <0.01$). Thus, the radiographic response to treatment was similar and highly satisfactory in the SHTW and the SH/SHOW series, and less satisfactory but similar in the SHZOW and the SHOW series.

Considering differences in streptomycin dosage and isoniazid inactivation rate, there was little evidence that these influenced the radiographic response in any of the four series (Table 10, Parts B and C). Combining the findings in the four series, over-all radiographic improvement was observed in 94% of 186 high-dosage patients and 95 % of 189 low-dosage patients, including 71% and 68 %,

[1] The numbers of patients are set out in Table 15.

TABLE 11

RADIOGRAPHIC PROGRESS DURING THE 12-MONTH PERIOD [a]

| Assessment of progress | Standardized percentage of patients | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Part A (by regimen) | | | | Part B (by streptomycin dosage) | | | | | | | | Part C (by isoniazid inactivation rate) | | | | | | | |
| | SHTW | SH/SHOW | SHZOW | SHOW | SHTW | | SH/SHOW | | SHZOW | | SHOW | | SHTW | | SH/SHOW | | SHZOW | | SHOW | |
| | | | | | High | Low | High | Low | High | Low | High | Low | Slow | Rapid | Slow | Rapid | Slow | Rapid | Slow | Rapid |
| Radiographic improvement (all grades) | 99 | 100 | 90 | 86 | 98 | 100 | 100 | 100 | 90 | 90 | 85 | 87 | 100 | 97 | 100 | 100 | 91 | 88 | 89 | 82 |
| Considerable or exceptional radiographic improvement | 79 | 73 | 65 | 57 | 83 | 75 | 78 | 69 | 62 | 69 | 59 | 55 | 79 | 79 | 73 | 73 | 64 | 68 | 58 | 56 |
| Cavitation less or disappeared | 99 | 100 | 91 | 88 | 98 | 100 | 100 | 100 | 92 | 90 | 88 | 90 | 100 | 97 | 100 | 100 | 92 | 88 | 89 | 87 |
| Cavitation disappeared | 48 | 43 | 29 | 45 | 53 | 43 | 38 | 49 | 26 | 31 | 51 | 40 | 52 | 39 | 48 | 35 | 30 | 26 | 45 | 44 |
| Total patients [b] | 96 | 101 | 101 [c] | 77 | 47 | 49 | 50 | 51 | 50 [c] | 51 | 39 | 38 | 63 | 33 | 64 | 37 | 67 [c] | 34 | 38 | 39 |

[a] Assessment on standard radiographs taken on admission to treatment and at 12 months.
[b] Excluding patients who died of non-tuberculous causes, who discharged themselves against medical advice or who had their allocated chemotherapy terminated on account of toxicity.
[c] Including 1 patient who had no cavitation initially; she had no cavitation at 12 months either.

respectively, in whom it was classified as considerable or exceptional; further, in both the groups, cavitation became less or disappeared in 95% of the patients. (These proportions were obtained by standardizing for isoniazid inactivation rate, and by weighting appropriately (Snedecor, 1956) on the basis of the numbers of high-dosage and low-dosage patients in each of the four series.) The radiographic response was also similar in the slow and the rapid inactivators of isoniazid. Thus, 95% of 232 slow inactivators showed over-all improvement as compared with 92 % of 143 rapid inactivators, including 69 % in each group with considerable or exceptional improvement ; cavitation became less or disappeared in 96 % and 93 %, respectively. (These proportions were obtained by standardizing for streptomycin dosage, and by weighting appropriately on the basis of the numbers of slow and rapid inactivators in each of the four series.)

In summary, the radiographic response to treatment was highly satisfactory in the SHTW and the SH/SHOW series, and less satisfactory in the SHZOW and the SHOW series. There was little evidence that it was influenced by differences in streptomycin dosage or isoniazid inactivation rate.

## CULTURE RESULTS

Table 12 sets out the percentages of patients with a negative culture from a single collection specimen of sputum at monthly intervals. Considering first the over-all comparisons between the four series (Part A of Table 12, and Fig. 4) the percentages with a negative culture were broadly similar in the four series, both at 1 and at 2 months. However, at 3 months, a clear difference emerged between the SHTW or the SH/SHOW series on the one hand, and the SHZOW or the SHOW series on the other hand. Thus, 84% of the SHTW and 86% of the SH/SHOW patients were culturenegative, as compared with 73 % of the SHZOW and 65 % of the SHOW patients, the 'difference between each of the former two and each of the latter two regimens being statistically significant ($P<0.05$). The proportions increased to 94 %, 89 %, 81% and 71%, respectively, at 6 months, and showed little change thereafter. Thus, the mean value for the period from month 7 to month 12 was 95 % for the SHTW, 91% for the SH/SHOW, 80 % for the SHZOW and 72 % for the SHOW series. The difference between the SHTW and the SH/SHOW series was neither large nor significant ($P = 0.1$), and this was also the case with the difference between the

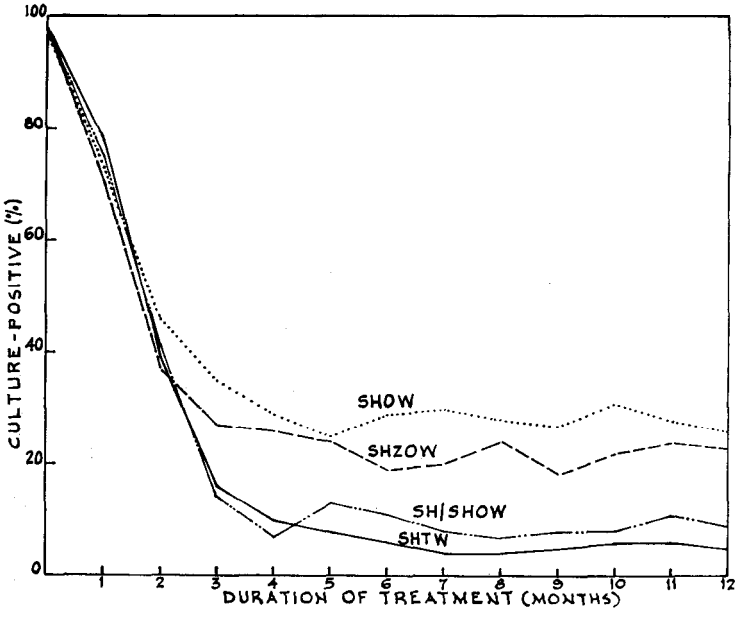
TABLE 12

STANDARDIZED PERCENTAGES OF PATIENTS WITH A NEGATIVE CULTURE FROM A SINGLE COLLECTION SPECIMEN OF SPUTUM

| Months after chemotherapy | Part A (by regimen) | | | | Part B (by streptomycin dosage) | | | | | | | | Part C (by isoniazid inactivation rate) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SHTW | SH/SHOW | SHZOW | SHOW | SHTW | | SH/SHOW | | SHZOW | | SHOW | | SHTW | | SH/SHOW | | SHZOW | | SHOW | |
| | | | | | High | Low | High | Low | High | Low | High | Low | Slow | Rapid | Slow | Rapid | Slow | Rapid | Slow | Rapid |
| | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 5 | 3 | 0 | 1 | 3 | 1 | 3 | 5 | 0 |
| 1 | 22 | 25 | 29 | 27 | 18 | 25 | 29 | 20 | 20 | 37 | 26 | 27 | 20 | 24 | 19 | 33 | 38 | 11 | 27 | 26 |
| 2 | 61 | 59 | 63 | 54 | 59 | 63 | 54 | 63 | 62 | 63 | 54 | 54 | 55 | 70 | 61 | 55 | 70 | 48 | 50 | 59 |
| 3 | 84 | 86 | 73 | 65 | 78 | 90 | 86 | 87 | 68 | 77 | 71 | 60 | 83 | 86 | 88 | 84 | 81 | 57 | 67 | 62 |
| 4 | 90 | 93 | 74 | 71 | 86 | 94 | 94 | 92 | 73 | 75 | 76 | 67 | 92 | 86 | 97 | 87 | 86 | 53 | 71 | 68 |
| 5 | 92 | 87 | 76 | 75 | 86 | 98 | 90 | 85 | 73 | 78 | 79 | 72 | 94 | 89 | 91 | 82 | 86 | 56 | 74 | 74 |
| 6 | 94 | 89 | 81 | 71 | 91 | 96 | 90 | 88 | 79 | 82 | 79 | 64 | 94 | 94 | 93 | 84 | 88 | 68 | 76 | 65 |
| 7 | 96 | 92 | 80 | 70 | 93 | 98 | 92 | 91 | 76 | 84 | 76 | 66 | 97 | 94 | 95 | 86 | 87 | 68 | 76 | 63 |
| 8 | 96 | 93 | 76 | 72 | 93 | 98 | 94 | 91 | 75 | 78 | 80 | 64 | 97 | 94 | 95 | 89 | 88 | 55 | 77 | 64 |
| 9 | 95 | 92 | 82 | 73 | 93 | 97 | 96 | 88 | 79 | 84 | 76 | 70 | 97 | 94 | 95 | 86 | 88 | 71 | 77 | 67 |
| 10 | 94 | 92 | 78 | 69 | 93 | 95 | 94 | 90 | 77 | 80 | 74 | 64 | 97 | 91 | 95 | 86 | 88 | 62 | 74 | 61 |
| 11 | 94 | 89 | 76 | 72 | 90 | 98 | 92 | 85 | 76 | 76 | 76 | 68 | 97 | 91 | 95 | 78 | 88 | 56 | 78 | 61 |
| 12 | 95 | 91 | 77 | 74 | 93 | 97 | 92 | 89 | 76 | 78 | 75 | 73 | 97 | 94 | 95 | 83 | 86 | 62 | 81 | 63 |
| 7-12 (mean) | 95 | 91 | 80 | 72 | 93 | 97 | 92 | 89 | 77 | 82 | 77 | 67 | 97 | 94 | 94 | 85 | 89 | 63 | 77 | 64 |
| No. of patients in analysis (range) [a] | 104-93 | 106-99 | 105-96 | 79-74 | 51-46 | 53-47 | 52-48 | 54-49 | 51-47 | 54-47 | 39-37 | 40-36 | 66-59 | 39-33 | 67-62 | 39-35 | 70-63 | 35-32 | 40-35 | 39-36 |

[a] The highest and the lowest number of patients in the analysis at any of the months. Patients who died of non-tuberculous causes, who discharged themselves against medical advice or who had their allocated chemotherapyterminated on accountof toxicity are excluded thereafter. Patients who died of tuberculosis or who had their allocated chemotherapy terminated on account of radiographic or clinical deterioration are included throughout.

FIG. 4
STANDARDIZED PERCENTAGES OF PATIENTS WITH A POSITIVE CULTURE FROM A SINGLE COLLECTION SPECIMEN OF SPUTUM




SHZOW and the SHOW series (P=0.2); however, the response in both the SHTW and the SH/SHOW series was significantly superior to that in the SHZOW and the SHOW series (SHTW-SHZOW, P <0.0001 ; SHTW-SHOW,P <0.00001 ; SH/SHOW-SHZOW, P=0.01 ; SH/SHOW-SHOW, P <0.001).

There was no evidence that the difference in streptomycin dosage affected the culture results in the SHTW, SH/SHOW or the SHZOW series (Table 12, Part B). Thus, the mean culture negativity during the period from month 7 to month 12 was 93 % for the high-dosage patients and 97 % for the low-dosage patients in the SHTW series, the corresponding proportions being 92% and 89 % in the SH/SHOW series, and 77 % and 82 % in the SHZOW series. In the SHOW series, however, there was a slight suggestion that the high-dosage patients responded slightly better than the low-dosage patients, the percentages with a negative culture at 6 months being 79% and 64%, respectively (P=0.2), and the mean culture negativity from month 7 to month 12 being 77 % and 67 %, respectively (P=0.4).

There was no evidence that the rate of inactivation of isoniazid influenced the culture results in the SHTW series (Table 12, Part C), the mean culture negativity between month 7 and month 12 being 97 % for the slow inactivators and 94 % for the rapid inactivators (P=0.5). In contrast, in all the other series, there was some evidence that the slow inactivators responded better than the rapid inactivators. Thus, the mean culture negativity between month 7 and month 12 was 94% for the slow inactivators and 85% for the rapid inactivators in the SH/SHOW series (P=0.1), 89% and 63%, respectively, in the SHZOW series (P=0.001), and 77% and 64%, respectively, in the SHOW series (P=0.2).

In summary, culture negativity was attained most frequently in the SHTW series, only slightly less frequently in the SH/SHOW series, and appreciably less frequently in the SHZOW and the SHOW series. The difference in streptomycin dosage hardly affected the culture results in the SHTW, SH/SHOW and the SHZOW series, but may have had a slight effect in the SHOW series. The rate of inactivation of isoniazid had little effect in the SHTW series, but

there was some evidence that the slow inactivators in the SH/SHOW, SHZOW and the SHOW series responded better than the rapid inactivators.

### SENSITIVITY TEST RESULTS

The findings of tests of sensitivity to isoniazid and streptomycin, at monthly intervals from the 3rd month onwards, are presented in Tables 13 and 14 (isoniazid sensitivity test results were not available for 3.7 % of the cultures and streptomycin sensitivity test results for 5.8 %). The comparisons between the high-dosage and the low-dosage groups in each series, and between the slow and the rapid inactivators, are described in Section VII (page 173 et *seq.),* as also are all the findings of pyrazinamide sensitivity tests.

Of the 13 patients who had the allocated chemotherapy terminated on account of radiographic or serious clinical deterioration, 1 had the termination within 3 months and does not therefore appear in Tables 13 and 14. In the remaining 12, the last 2 sensitivity test results prior to the termination showed isoniazid-resistance for all and streptomycin-resistance for 7. Consequently, for the reason stated earlier (page 157), it has been assumed in Tables 13 and 14 that all 12 patients would have continued to yield isoniazid-resistant cultures and that 7 would have continued to yield streptomycin-resistant cultures for the rest of the year; for streptomycin-sensitivity analyses, the remaining 5 patients have been excluded from the time of the termination.

#### *Percentage of patients with resistant cultures*

*Isoniazid.* Resistance to isoniazid occurred more frequently in the SHZOW and the SHOW series than in the SHTW and the SH/SHOW series, even in the early months of treatment. Thus, at 3 months, 2% of the SHTW and 3 % of the SH/SHOW patients yielded a resistant culture, as compared with 11% of the SHZOW and 19% of the SHOW patients (Table 13), the differences between each of the former two and each of the latter two series being statistically significant ($P \leq 0.02$). Thereafter, the proportions increased slightly in all four series, the figures at 12 months being 5% for the SHTW,

TABLE 13

STANDARDIZED PERCENTAGES OF PATIENTS WITH DRUG-RESISTANT CULTURES

| Months after start of chemotherapy | Isoniazid-resistant | | | | Streptomycin-resistant | | | |
|---|---|---|---|---|---|---|---|---|
| | SHTW | SW SHOW | SHZOW | SHOW | SHTW | SW SHOW | SHZOW | SHOW |
| 3 | 2 | 3 | 11 | 19 | 0 | 2 | 6 | 5 |
| 4 | 3 | 3 | 13 | 20 | 2 | 1 | 11 | 9 |
| 5 | 4 | 4 | 13 | 21 | 2 | 4 | 10 | 12 |
| 6 | 5 | 5 | 12 | 20 | 4 | 2 | 10 | 11 |
| 7 | 4 | 5 | 14 | 23 | 4 | 4 | 12 | 17 |
| 8 | 4 | 5 | 15 | 24 | 4 | 5 | 13 | 18 |
| 9 | 5 | 6 | 14 | 23 | 4 | 8 | 15 | 17 |
| 10 | 5 | 7 | 14 | 19 | 4 | 5 | 14 | 16 |
| 11 | 5 | 7 | 16 | 23 | 6 | 6 | 10 | 16 |
| 12 | 5 | 9 | 16 | 22 | 4 | 8 | 15 | 19 |
| No. of patients in analysis (range) [a] | 100-95 | 105-99 | 102-97 | 74-70 | 100-95 | 105-98 | 102-93 | 74-67 |

[a] The highest and the lowest number of patients in the analysis at any of the months. Patients who died, who discharged themselves against medical advice or who had their allocated chemotherapy terminated on account of toxicity are excluded thereafter. The policy for patients who had their allocated chemotherapy terminated on account of radiographic or clinical deterioration is described above.

TABLE 14

PERCENTAGES (UNSTANDARDIZED) OF POSITIVE CULTURES WITH DRUG-RESISTANT BACILLI [a]

| Months after start of chemotherapy | Isoniazid | | | | | | | | | Streptomycin | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SHTW patients | | | SH/SHOW patients | | SHZOW patients | | SHOW patients | | SHTW patients | | | SH/SHOW patients | | SHZOW patients | | SHOW patients | |
| | Culture-positive | Resistant | | Culture-positive | Resistant | Culture-positive | Resistant | Culture-positive | Resistant | Culture-positive | Resistant | | Culture-positive | Resistant | Culture-positive | Resistant | Culture-positive | Resistant |
| | | No. | %[b] | | No. %[b] | | No. % | | No. % | | No. | %[b] | | No. %[b] | | No. % | | No. % |
| 3 | 21 | 2 | (10) | 19 | 3 (16) | 31 | 11 35 | 30 | 14 47 | 21 | 0 | (0) | 19 | 2 (11) | 31 | 6 19 | 30 | 4 13 |
| 4 | 10 | 3 | | 13 | 3 | 28 | 13 | 26 | 14 | 10 | 2 | | 13 | 1 | 28 | 10 | 26 | 8 |
| 5 | 8 | 4 | 48 | 14 | 4 31 | 25 | 13 54 | 23 | 16 64 | 8 | 2 | 32 | 14 | 4 19 | 24 | 9 41 | 23 | 11 42 |
| 6 | 7 | 5 | | 12 | 5 | 17 | 12 | 20 | 14 | 7 | 4 | | 10 | 2 | 16 | 9 | 18 | 9 |
| 7 | 5 | 4 | | 8 | 5 | 21 | 14 | 21 | 18 | 5 | 4 | | 7 | 4 | 20 | 11 | 19 | 14 |
| 8 | 5 | 4 | (87) | 11 | 5 52 | 21 | 14 67 | 21 | 19 89 | 5 | 4 | (80) | 10 | 5 59 | 18 | 11 63 | 20 | 15 75 |
| 9 | 5 | 5 | | 12 | 6 | 21 | 14 | 19 | 17 | 5 | 4 | | 12 | 8 | 19 | 14 | 18 | 14 |
| 10 | 6 | 6 | | 10 | 7 | 22 | 13 | 19 | 15 | 6 | 4 | | 10 | 5 | 19 | 13 | 18 | 13 |
| 11 | 6 | 5 | (94) | 11 | 7 72 | 22 | 15 65 | 20 | 18 85 | 6 | 5 | (76) | 10 | 6 61 | 18 | 9 64 | 17 | 13 79 |
| 12 | 5 | 5 | | 11 | 9 | 22 | 15 | 21 | 18 | 5 | 4 | | 11 | 8 | 19 | 14 | 18 | 16 |

[a] Patients whose allocated chemotherapy was terminated for deterioration are included subsequently also (and regarded as having resistant cultures), provided the last 2 sensitivity test results prior to the termination were resistant (see page 167).
[b] Parentheses indicate that the percentage is based on fewer than 25 observations.

9% for the SH/SHOW, 16% for the SHZOW and 22% for the SHOW patients; the differences were significant in three of the comparisons–namely those between SHTW and SHZOW (P=0.02), SHTW and SHOW (P <0.001), and SH/SHOW and SHOW (P=0.01).

*Streptomycin.* Resistance to streptomycin occurred more frequently in the SHZOW and the SHOW series than in the SHTW and the SH/SHOW series, especially from the 4th month onwards, at which time the proportion of patients with a resistant culture was 2% for the SHTW, 1% for the SH/SHOW, 11% for the SHZOW and 9% for the SHOW series (Table 13); the differences between each of the former two and each of the latter two regimens were significant ($P \leq 0.03$). The corresponding proportions at 12 months were 4 %, 8 %, 16 % and 19 %, respectively; three of the differences were significant –namely, those between SHTW and SHZOW (P<0.01), SHTW and SHOW (P=0.001), and SH/SHOW and SHOW (P=0.02).

*Percentage of positive cultures with resistant bacilli*

Table 14 presents *unstandardized* percentages of positive cultures with resistant bacilli, at monthly intervals from the 3rd month onwards (statistical standardization of the results was not undertaken on account of the small number of positive cultures obtained in the SHTW and the SH/SHOW series, especially in the later months of treatment).

*Isoniazid.* Resistance to isoniazid emerged more rapidly in the SHZOW and the SHOW series than in the SHTW and the SH/SHOW series. Thus, at 3 months, 10% of 21 positive cultures in the SHTW series and 16% of 19 in the SH/SHOW series were resistant, as compared with 35% of 31 in the SHZOW and 47% of 30 in the SHOW series. Subsequently, the increase was substantial in the SHTW series, less substantial in the SH/SHOW series, and even smaller in the SHZOW and the SHOW series. For months 10, 11 and 12, combined the proportions resistant were 94% in the SHTW series, 72% in the SH/SHOW series, 65% in the SHZOW series and 85% in the SHOW series.

*Streptomycin.* At 3 months, none of 21 positive cultures in the SHTW series was streptomycin-resistant as compared with 11% of 19 in the SH/SHOW, 19 % of 31 in the SHZOW and 13 % of 30 in the SHOW series; the corresponding proportions for months 4, 5 and 6 combined were 32%, 19%, 41% and 42 %, respectively. These findings indicate

that resistance to streptomycin emerged more rapidly in the SHZOW and the SHOW series than in the SHTW and the SH/SHOW series. For months 10, 11 and 12 combined, the proportions resistant were 76% in the SHTW series, 61% in the SH/SHOW, 64% in the SHZOW and 79% in the SHOW series.

Summarizing the findings in Tables 13 and 14, resistance to isoniazid and streptomycin occurred more frequently and more rapidly in the SHZOW and the SHOW series than in the SHTW and the SH/SHOW series.

### CLASSIFICATION OF PATIENTS AT 1 YEAR ACCORDING TO THEIR RESPONSE TO TREATMENT

Table 15 presents a classification of all the patients at 1 year, based primarily on the bacteriological response to treatment.

*Over-all efficacies of the four regimens*

Of 96 SHTW patients, 86 had bacteriologically quiescent disease at 1 year, as compared with 86 of 101 SH/SHOW, 73 of 101 SHZOW and 49 of 77 SHOW patients (Table 15, Part A). There were 13 patients (5 SHTW, 3 SH/SHOW, 3 SHZOW, 2 SHOW) who had disease of bacteriologically doubtful status at 1 year; these also have been regarded as having a favourable response to treatment, for reasons stated earlier (page 158). [A follow-up of these 13 patients (9 of whom received maintenance chemotherapy in the second year) showed that 12 had produced only negative cultures in the 6 months following the single positive culture; in the remaining patient, the single positive culture occurred at 12 months and proved to be the commencement of a bacteriological relapse.] In all, therefore, 91 (95 %) of the SHTW patients, 89 (88 %) of the SH/SHOW, 76 (75 %) of the SHZOW and 51(66 %) of the SHOW patients had a favourable response. The corresponding percentages, after standardization for isoniazid inactivation rate and streptomycin dosage, were 94 % for the SHTW, 88 % for the SH/SHOW, 74 % for the SHZOW and 68 % for the SHOW series. The difference between the SHTW and the SH/SHOW series was small and not significant (P=0,1), as was the difference between the SHZOW and the SHOW series (P=0.4). However, the response in both the SHTW series and the SH/SHOW series was significantly superior to that in the SHZOW series and the SHOW series (SHTW-SHZOW, P =0.00001 ; SHTW-SHOW, P = 0.00001; SH/SHOW-SHZOW, *P<0.01 ; SH/SHOW-SHOW, P < 0.01).*

Considering next the speed of sputum conversion in patients with bacteriologically quiescent disease at 1 year (analyses not tabulated here), persisting culture negativity was attained within 6 months in 93 % of the SHTW patients, 91% of the SH/SHOW, 97 % of the SHZOW and 95 % of the SHOW patients, including 69 %, 75 %, 76 % and 60 %, respectively, in whom it was attained within 3 months; none of the differences was statistically significant. Thus, in patients with *bacteriologically quiescent disease at 1 year*, there was no evidence that sputum conversion had occurred earlier with the more effective regimens.

An unfavourable response to treatment occurred in 5 SHTW, 12 SH/SHOW, 25 SHZOW and 26 SHOW patients (Table 15). It should be noted that all 13 patients who had their allocated chemotherapy terminated for radiographic or serious clinical deterioration, and 5 of 6 who died of tuberculosis, had received either the SHZOW or the SHOW regimen, that is once-weekly chemotherapy from the very beginning. Next, it is of interest that of the 12 SH/SHOW patients who had an unfavourable response, 6 (50%) had had a sputum conversion followed by a bacteriological relapse in the first year; the corresponding proportions were 0 of 5 in the SHTW, 2 of 25 in the SHZOW and 4 of 26 in the SHOW series.

In summary, the response to treatment was similar and highly satisfactory in the SHTW and the SH/SHOW series, and appreciably less satisfactory but similar in the SHZOW and the SHOW series.

*Influence of streptomycin dosage on the response to treatment*

Amalgamating all four series, 153 (82 %) of 186 high-dosage patients had a favourable response to treatment, as compared with 154 (81%) of 189 low-dosage patients. The corresponding percentages, standardized for isoniazid inactivation rate and weighted appropriately on the basis of the numbers of high-dosage and low-dosage patients in each of the four series, were also similar-namely, 83 % and 81%, respectively.

Considering the findings (standardized percentages) in the individual series (Table 15, Part B), 93 % of the high-dosage patients in the SHTW series had a favourable response as compared with 95 % of the low-dosage patients; the corresponding proportions were 92% and 84% in the SH/SHOW series, *70* % and 78 % in the SHZOW series, and 74 % and 63 % in the SHOW series. Thus, the proportion was higher in the high-dosage patients in two *of the*

TABLE

CLASSIFICATION OF ALL PATIENTS AT 1 YEAR

| Classification at 1 year | | Part A (by regimen) | | | | Part (by streptomycin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | SHTW | SH/SHOW | SHZOW | SHOW | SHTW | | SH/SHOW | |
| | | | | | | High | Low | High | Low |
| *Bacteriologically quiescent disease:* that is, all cultures negative at the last 3 monthly examinations, i.e., at 10, 11 and 12 months | | 86 | 86 | 73 | 49 | 43 | 43 | 46 | 40 |
| *Disease of bacteriologically doubtful status:* that is, all cultures negative at 3 or more consecutive monthly examinations but a single positive culture at 10, 11 or 12 months | | 5 | 3 | 3 | 2 | 1 | 4 | 0 | 3 |
| Total patients with a favourable response | No. | 91 | 89 | 76 | 51 | 44 | 47 | 46 | 43 |
| | % | 95 | 88 | 75 | 66 | 94 | 96 | 92 | 84 |
| | Standardized % | 94 | 88 | 74 | 68 | 93 | 95 | 92 | 84 |
| *Bacteriologically relapsed disease:* that is, all cultures negative at 3 or more consecutive monthly examinations but a *total* of 2 of more positive cultures at 10, 11 and 12 months | | 0 | 6 | 2 | 4 | 0 | 0 | 1 | 5 |
| *Bacteriologically active disease:* | | | | | | | | | |
| that is, (1) cultures never all negative at 3 consecutive monthly examinations | | 4 | 6 | 14 | 13 | 2 | 2 | 3 | 3 |
| or (2) termination of allocated chemotherapy on account of | | | | | | | | | |
| *(a)* radiographic deterioration | | 0 | 0 | 6 | 5 | 0 | 0 | 0 | 0 |
| *(b)* serious clinical deterioration | | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Tuberculous death | | 1 | 0 | 2 | 3 | 1 | 0 | 0 | 0 |
| Total no. of patients with an unfavourable response | | 5 | 12 | 25 | 26 | 3 | 2 | 4 | 8 |
| Total patients | | 96 | 101 | 101 | 77 | 47 | 49 | 50 | 51 |
| Termination of allocated chemotherapy on account of toxicity | | 2 | 1 | 0 | 0 | 1 | 1 | | |
| Discharge against medical advice | | 5 | 3 | 4 | 1 | 2 | 3 | 1 | 2 |
| Non-tuberculous death | | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 |
| Grand total of patients | | 104 | 106 | 105 | 79 | 51 | 53 | 52 | 54 |

[a] See footnote on page 172.

**15**

ACCORDING TO THEIR RESPONSE TO TREATMENT

| **B dosage)** | | | | Part C (by Isoniazid inactivation rate) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SHZOW | | SHOW | | SHTW | | SH/SHOW | | SHZOW | | SHOW | |
| High | Low | High | Low | Slow | Rapid | Slow | Rapid | Slow | Rapid | Slow | Rapid |
| 36 | 37 | 25 | 24 | 60 | 26 | 59 | 27 | 56 | 17 | 29 | 20 |
| 0 | 3 | 2 | 0 | 1 | 4 | 2 | 1 | 2 | 1 | 0 | 2 |
| 36 | 40 | 27 | 24 | 61 | 30 | 61 | 28 | 58 | 18 | 29 | 22 |
| 72 | 78 | 69 | 63 | 97 | 91 | 95 | 76 | 87 | 53 | 76 | 56 |
| 70 | 78 | 74 | 63 | 97 | 91 | 95 | 76 | 87 [a] | 53 [a] | 76 | 56 |
| 1 | 1 | 3 | 1 | 0 | 0 | 2 | 4 | 0 | 2 | 0 | 4 |
| 9 | 5 | 4 | 9 | 2 | 2 | 1 | 5 | 4 | 10 | 5 | 8 |
| 3 | 3 | 2 | 3 | 0 | 0 | 0 | 0 | 4 | 2 | 1 | 4 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| 1 | 1 | 2 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 2 | 1 |
| 14 | 11 | 12 | 14 | 2 | 3 | 3 | 9 | 9 | 16 | 9 | 17 |
| 50 | 51 | 39 | 38 | 63 | 33 | 64 | 37 | 67 | 34 | 38 | 39 |
| 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 |
| 1 | 3 | 0 | 1 | 2 | 3 | 2 | 1 | 3 | 1 | 1 | 0 |
| 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| 51 | 54 | 39 | 40 | 66 | 38 | 67 | 39 | 70 | 35 | 40 | 39 |

series but lower in the other two; further, the difference was not statistically significant in any of the four series ($P \geq 0.2$). Also, the variation between the four series in the difference in response between the high-dosage and the low-dosage patients (that is the interaction between streptomycin dosage and chemotherapeutic regimen) was non-significant (P=0.2).

In patients with *bacteriologically quiescent disease at 1 year*, there was no evidence (analyses not tabulated here) that persisting culture negativity had commenced earlier in the high-dosage patients. Thus, combining all four series, it was attained within 6 months in 93% of the high-dosage patients and 94% of the low-dosage patients, including 71% and 71%, respectively, in whom it was attained within 3 months (these proportions are standardized and weighted, as above). Considering the findings in the individual series, the corresponding proportions with sputum conversion by 3 months were 68 % and 70 % in the SHTW series, 68 % and 82 % in the SH/SHOW series, 82% and 70% in the SHZOW series (P=0.2), and 65 % and 54 % in the SHOW series (P=0.4).

In summary, the difference in streptomycin dosage appears to have had little effect on the response to treatment. However, the possibility cannot be excluded that it had a slight effect in the SH/SHOW and the SHOW series (see also page 173 *et seq.*).

*Influence of the rate of inactivation of isoniazid on the response to treatment*

Amalgamating all four series, 209 (90%) of 232 slow inactivators of isoniazid had a favourable response as compared with 98 (69%) of 143 rapid inactivators. The corresponding percentages, standardized for streptomycin dosage and weighted appropriately on the basis of the numbers of slow and rapid inactivators in each of the four series, were 89 % and 69 %, respectively, the difference being highly significant ($P < 0.00001$).

Considering the findings (standardized percentages) in the individual series (Table 15, Part C), the response was favourable in 97% of the slow inactivators and 91 % of the rapid inactivators in the SHTW series, a non-significant difference (P=0.3). The corresponding figures were 95 % and 76 % in the SH/SHOW series ($P < 0.01$), 87 % and 53 % in the SHZOW series [1] ($P < 0.001$), and 76 % and 56 % in the SHOW series (P=0.05).

In patients with *bacteriologically quiescent disease at 1 year*, there was no evidence (analyses not tabulated here) that 'persisting culture negativity had commenced earlier in the slow inactivators. Thus, combining all four series, it was attained within 6 months in 94 % of the slow inactivators and 92 % of the rapid inactivators, including 71% and 67%, respectively, in whom it was attained within 3 months (these proportions are standardized and weighted, as above). Considering the findings in the individual series, the corresponding proportions with sputum conversion by 3 months were 70 % and 65 % in the SHTW series (P=0.7), 71% and 81% in the SH/SHOW series, 82% and 59% in the SHZOW series (P=0.06), and 62% and 55% in the SHOW series (P=0.6).

In summary, the rate of inactivation of isoniazid had a considerable influence on the response to treatment in the SH/SHOW, SHZOW and the SHOW series, but had little effect in the SHTW series.

*Conclusion*

The SHTW regimen was highly effective and, furthermore, unaffected by differences in isoniazid inactivation rate and streptomycin dosage. Although the SH/SHOW regimen achieved highly satisfactory over-all results, its efficacy was considerably affected by the rate of inactivation of isoniazid, and possibly affected by the streptomycin dosage as well. Both the SHZOW and the SHOW regimens were markedly inferior to the SHTW and the SH/SHOW regimens, their efficacies being considerably influenced by the rate of inactivation of isoniazid and, in the case of the SHOW regimen, possibly influenced by the streptomycin dosage as well. Finally, there was no evidence that persisting culture negativity commenced earlier with the more effective regimens or in the streptomycin high-dosage patients or in the slow inactivators of isoniazid.

### DISEASE STATUS AT 1 YEAR IN PATIENTS WHO TOOK THEIR DISCHARGE AGAINST MEDICAL ADVICE

In all, 13 patients (5 SHTW, 3 SH/SHOW, 4 SHZOW, 1 SHOW) took their discharge against medical advice (Table 15, Part A); they have been excluded from the above comparisons. However, attempts were made to obtain sputum specimens

[1] Since the rapid inactivators in this series had, by chance, a larger bacterial content in the sputum than the slow inactivators (see page 161), and since the bacterial content affected significantly the response to the SHZOW regimen (see page 185), statistical standardization was undertaken to allow for the difference in bacterial content. The standardized percentages were 85 % for the slow inactivators and 60 % for the rapid inactivators, the difference being highly significant ($P < 0.01$).

from these patients at 12 months, in order to classify their disease status at 1 year.

Of the 13 patients, 1 (SHTW) died of tuberculosis in the 8th month, and 1 (SHZOW) restarted treatment in the 9th month (after a break of 6 month%) but developed tuberculous meningitis in the 11th month and was prescribed daily chemotherapy; 3 (1 SHTW, 1 SHZOW, 1 SHOW) had bacteriologically active disease at 1 year, 1 (SH/SHOW) had 1 positive culture at 12 months (followed by positive cultures at 14 and 15 months), and 1 (SHTW) had 2 positive cultures at 6 months (no specimens were obtained subsequently in the first year, but 7 of 8 cultures obtained at 15, 16 and 17 months were positive); these 7 patients, who stopped treatment in the 3rd, 3rd, 6th, 4th, 9th, 10th and 2nd month, respectively, may be regarded as having had an unfavourable disease status at 1 year. Four patients (2 SHTW, 1 SH/SHOW, 1 SHZOW) had all cultures negative between month 10 and month 12 (the numbers varying from 2 to 5), and a fifth (SH/SHOW) had all cultures negative from month 2 to month 7 (and, subsequently, at 18 months). These patients had taken their discharge in the 11 th, 12th, 4th, 11th and 8th month, respectively, and none had a history of treatment subsequent to the discharge. All 5 may be regarded as having a favourable disease status at 1 year. The 13th patient (SHZOW) took his discharge in the 4th month, at which time his sputum was smear-negative but culture-positive; no specimens were obtained from him subsequently, so that the disease status at 1 year is not assessable.

If the 12 patients with an assessable disease status are included in the comparison of the therapeutic efficacies of the regimens, the proportion with a favourable disease status at 1 year becomes 92% for the SHTW, 88 % for the SH/SHOW, 74% for the SHZOW and 65 % for the SHOW series, the corresponding standardized proportions being 92 %, 87 %, 73 % and 67 %, respectively.

## VII. OTHER LABORATORY FINDINGS

### STREPTOMYCIN AND ISONIAZID SENSITIVITY TEST RESULTS

*Influence of regimen on the findings*

As stated earlier (page 169), resistance to isoniazid and to streptomycin occurred more frequently (Table 13) and more rapidly (Table 14) with the less effective SHOW and SHZOW regimens than with the more effective SH/SHOW and SHTW regimens.

Table 16 sets out for the various regimens the standardized percentages of patients with (1) an isoniazid-sensitive culture, and (2) a streptomycin-sensitive culture. The findings suggest that the decline during treatment in the proportion of patients with a sensitive culture was more gradual with the SHOW and the SHZOW regimens than with the SH/SHOW and the SHTW regimens. In other words, the less effective regimens appear to have eliminated drug-sensitive organisms more slowly than the more effective regimens.

*Influence of streptomycin dosage and isoniazid inactivation rate on the findings within each series*

Patients in all three phases of intake have been considered together in the analyses below. The comparisons are *within* each of the four series, that is, between streptomycin high-dosage and low-dosage patients, and between slow and rapid inactivators of isoniazid in each series. Since slow inactivators have higher serum isoniazid concentrations than rapid inactivators (Table 26), the contrasts between these two groups of patients may be regarded as analogous, in pharmacological terms, to comparisons between a higher and a lower dosage of isoniazid.

*SHOW series.* Table 17 sets out the results of streptomycin and isoniazid sensitivity tests in SHOW patients, according to (1) the streptomycin dosage (low or high) and (2) the isoniazid inactivation rate (rapid or slow). Considering first the influence of streptomycin dosage (left half of table), streptomycin-sensitive cultures were obtained more frequently from the low-dosage patients in the first 6 months–for instance, the proportion with a sensitive culture was 40% for the low-dosage patients at 3 months as compared with 22% for the high-dosage patients, the corresponding proportions at 6 months being 17 % and 7 %, respectively. However, the proportions with streptomycin resistance were usually similar in the two groups, being 4% and 3% at 3 months, and 12% and 7% at 6 months. Thus, in the first 6 months, the administration of the low dosage of streptomycin resulted

TABLE 15

STANDARDIZED PERCENTAGES OF PATIENTS WITH DRUG-SENSITIVE CULTURES

| Months after start of chemotherapy | Isoniazid-sensitive | | | | | | Streptomycin-sensitive | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Phases I and II | | Phases II and III | | | | Phases I and II | | Phases II and III | | | |
| | SHTW | SHOW | SHTW | SH/SHOW | SHZOW | SHOW | SHTW | SHOW | SHTW | SH/SHOW | SHZOW | SHOW |
| 0 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 3 | 22 | 18 | 19 | 15 | 20 | 22 | 28 | 32 | 21 | 16 | 25 | 36 |
| 4 | 9 | 11 | 7 | 10 | 15 | 14 | 12 | 22 | 5 | 12 | 18 | 24 |
| 5 | 6 | 8 | 4 | 10 | 13 | 8 | 8 | 12 | 6 | 10 | 16 | 15 |
| 6 | 5 | 5 | 2 | 7 | 6 | | 5 | 12 | 3 | 8 | 7 | 12 |
| 9 | 1 | 2 | 0 | 5 | 8 | 2 | 2 | 5 | 1 | 4 | 5 | 6 |
| 12 | 0 | 3 | 0 | 2 | 8 | 3 | 1 | 2 | 1 | 3 | 5 | 3 |
| Total patients in analysis (range) [a] | 118-114 | 111-107 | 100-95 | 105-99 | 102-97 | 74-90 | 118-114 | 110-104 | 100-95 | 105-98 | 102-93 | 74-87 |

[a] The highest and the lowest number of patients in the analysis at any of the months. Patients who died, who discharged themselves against medical advice or who had theirallocated chemotherapy terminated on account of toxicity are excluded thereafter. The policy for patients who had their allocated chemotherapy terminated on account of radiographic or clinical deterioration is described on pages 157 and 167.

TABLE 17

SHOW SERIES: RESULTS OF STREPTOMYCIN AND ISONIAZID SENSITIVITY TESTS, RELATED TO STREPTOMYCIN DOSAGE AND ISONIAZID INACTIVATION RATE

| Months after start of chemotherapy | Standardized percentage of patients [a] | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Contrast between streptomycin high-dosage and low-dosage patients | | | | | | | | Contrast between slow and rapid inactivators of isoniazid | | | | | | | |
| | Streptomycin sensitivity | | | | Isoniazid sensitivity | | | | Isoniazid sensitivity | | | | Streptomycin sensitivity | | | |
| | Sensitive | | Resistant | | Sensitive | | Resistant | | Sensitive | | Resistant | | Sensitive | | Resistant | |
| | Low | High | Low | High | Low | High | Low | High | Rapid | Slow | Rapid | Slow | Rapid | Slow | Rapid | Slow |
| 3 | 40 | 22 | 4 | 3 | 16 | 18 | 27 | 7 | 22 | 14 | 17 | 18 | 33 | 31 | 6 | 2 |
| 4 | 34 | 7 | 2 | 10 | 9 | 12 | 27 | 5 | 19 | 5 | 18 | 16 | 21 | 21 | 14 | 0 |
| 5 | 16 | 8 | 14 | 12 | 2 | 13 | 28 | 7 | 13 | 5 | 19 | 17 | 10 | 15 | 22 | 7 |
| 6 | 17 | 7 | 12 | 7 | 3 | 11 | 29 | 3 | 15 | 4 | 18 | 16 | 12 | 13 | 18 | 5 |
| 7 | 9 | 0 | 23 | 11 | 5 | 3 | 28 | 10 | 8 | 2 | 25 | 15 | 6 | 3 | 24 | 14 |
| 8 | 11 | 2 | 21 | 10 | 2 | 3 | 31 | 10 | 5 | 0 | 29 | 15 | 8 | 5 | 25 | 10 |
| 9 | 7 | 2 | 19 | 12 | 0 | 4 | 28 | 10 | 6 | 0 | 27 | 13 | 8 | 2 | 23 | 11 |
| 10 | 9 | 6 | 18 | 13 | 2 | 8 | 27 | 10 | 9 | 4 | 24 | 15 | 6 | 10 | 26 | 9 |
| 11 | 9 | 2 | 19 | 13 | 2 | 4 | 29 | 11 | 6 | 2 | 30 | 14 | 7 | 5 | 25 | 11 |
| 12 | 4 | 1 | 22 | 14 | 2 | 4 | 25 | 14 | 8 | 0 | 31 | 12 | 7 | 0 | 28 | 12 |
| Total patients in analysis (range) [b] | 56-51 | 55-53 | 56-51 | 55-53 | 56-52 | 55-53 | 56-52 | 55-53 | 53-49 | 59-54 | 53-49 | 59-54 | **53–48** | **59–54** | 53-48 | 59-54 |

[a] The figures in bold type show contrasts that are statistically significant at the 5% level.

[b] The highest and the lowest number of patients in the analysis at any of the months. Patients who died, who discharged themselves against medical advice or who had their allocated chemotherapy terminated on account of toxicity are excluded thereafter. The policy for patients who had their allocated chemotherapy terminated on account of radiographic or clinical deterioration is described on pages 157 and 167.

in a slower elimination of streptomycin-sensitive organisms (but not in an increased emergence of streptomycin resistance). It resulted also in an increased emergence of *isoniazid resistance,* the proportions resistant being 27 % for the low-dosage patients and 7 % for the high-dosage patients at 3 months, 29 % and 3 % at 6 months, and 25 % and 14 % at 12 months. Finally, from the 7th month onwards, *streptomycin resistance* occurred more frequently in the low-dosage patients (unlike in the first 6 months), the proportions resistant being 19 % at 9 months and 22% at 12 months as compared with 12 % and 14 %, respectively, for the high-dosage patients. This excess in the low-dosage group is presumably due to the emergence of secondary streptomycin resistance in patients whose cultures were already resistant to isoniazid, of whom there was an excess in the low-dosage group in the first 6 months.

An analogous pattern was found when the contrasts between the slow and the rapid inactivators of isoniazid (Table 17, right half) were considered. During the first 6 months of treatment, isoniazid-sensitive cultures were obtained more frequently from the rapid inactivators, the proportions being 22% for the rapid inactivators and 14 % for the slow inactivators at 3 months, and 15 % and 4 %, respectively, at 6 months. Isoniazid-resistant cultures, however, were obtained from similar proportions in the two groups-for instance, 17% and 18% at 3 months, and 18 % and 16% at 6 months. Thus, in the first 6 months, rapid inactivation of isoniazid resulted in a slower elimination of isoniazid-sensitive organisms (but not in an increased emergence of isoniazid resistance). It led also to an increased emergence of streptomycin resistance, the proportions resistant being 14% for the rapid inactivators and 0% for the slow inactivators at 4 months, 18 % and 5 % at 6 months, and 28 % and 12% at 12 months. In the second 6 months, isoniazid-resistant cultures were obtained more frequently from rapid inactivators (presumably secondary resistance), the proportion ranging from 24% to 31% as compared with 12% to 15 % in slow inactivators.

In summary, in the patients who received the low dosage of streptomycin, a streptomycin deficiency was indicated by a slower elimination of streptomycin-sensitive organisms, and a relative failure to prevent the emergence of isoniazid resistance and, subsequently, of secondary streptomycin resistance. Similarly, in the rapid inactivators of isoniazid, an isoniazid deficiency was indicated by a slower elimination of isoniazid-sensitive organisms, and a relative failure to prevent the emergence of streptomycin resistance and, subsequently, of secondary isoniazid resistance.

*SHZOW series.* The mode of interpretation of the findings for this series is the same as that employed for the SHOW series. Considering first the influence of streptomycin dosage (Table 18, left half), the proportions with a streptomycin-sensitive culture were similar for the high-dosage and the low-dosage patients (apart from minor and inconsistent differences in the second 6 months). Next, there was no evidence, either in the first 6 months or in the second 6 months of treatment, that streptomycin resistance or isoniazid resistance had occurred more frequently in the low-dosage patients. These findings, when considered with the experience in the SHOW series (see above), suggest that the pyrazinamide in the SHZOW regimen compensated for the streptomycin deficiency in the low-dosage patients by assisting in (1) the elimination of streptomycin-sensitive bacilli, (2) the prevention of isoniazid resistance, and (3) the prevention of secondary streptomycin resistance.

Considering next the influence of the rate of inactivation of isoniazid (Table 18, right half), (1) isoniazid-sensitive cultures were produced more frequently by the rapid inactivators, especially in the early months of treatment; thus, at 3 months, 39% of the rapid inactivators had an isoniazid-sensitive culture as compared with 10% of the slow inactivators, the corresponding proportions being 32% and 7 % at 4 months, 28 % and 4 % at 5 months, 16 % and 0% at 6 months, and 18 % and 2% at 12 months; (2) appreciably higher proportions of rapid inactivators produced streptomycin-resistant cultures from 4 months onwards; thus, the proportions resistant were 23% for the rapid inactivators and 4% for the slow inactivators at 4 months, 22% and 3 % at 6 months, and 28 % and 8 % at 12 months; and (3) isoniazid-resistant cultures were produced more frequently by the rapid inactivators, the proportion resistant being 14%-21 % between month 3 and month 6 as compared with 9%-11% in the slow inactivators, and 18 %-27 % and 9 %-12 %, respectively, between month 7 and month 12. These findings, when considered together with those in the SHOW series, suggest that the pyrazinamide in the SHZOW regimen was unable to compensate for the isoniazid deficiency in the rapid inactivators of isoniazid. (Other findings in the table, for which there are no ready explanations, have not been described here.)

TABLE 18

SHZOW SERIES: RESULTS OF STREPTOMYCIN AND ISONIAZID SENSITIVITY TESTS. RELATED TO STREPTOMYCIN DOSAGE AND ISONIAZID INACTIVATION RATE

| Months after start of chemotherapy | Standardized percentage of patients [a] | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Contrast between streptomycin high-dosage and low-dosage patients | | | | | | | | Contrast between slow and rapid inactivators of isoniazid | | | | | | | |
| | Streptomycin sensitivity | | | | Isoniazid sensitivity | | | | Isoniazid sensitivity | | | | **Streptomycin sensitivity** | | | |
| | Sensitive | | Resistant | | Sensitive | | Resistant | | Sensitive | | Resistant | | Sensitive | | Resistant | |
| | Low | High | Low | High | Low | High | Low | High | rapid | Slow | Rapid | Slow | Rapid | Slow | Rapid | Slow |
| 3 | 25 | 24 | 2 | 11 | 19 | 20 | 8 | 14 | 39 | 10 | 14 | 9 | 41 | 16 | 12 | 3 |
| 4 | 20 | 17 | 6 | 16 | 14 | 18 | 12 | 14 | 32 | 7 | 21 | 9 | 30 | 12 | 23 | 4 |
| 5 | 18 | 13 | 6 | 14 | 12 | 14 | 12 | 14 | 28 | 4 | 18 | 11 | 27 | 9 | 19 | 4 |
| 6 | 8 | 7 | 8 | 12 | 4 | 8 | 12 | 13 | 16 | 0 | 15 | 11 | 9 | 6 | 22 | 3 |
| 7 | 10 | 8 | 10 | 13 | 6 | 10 | 14 | 15 | 18 | 2 | 18 | 12 | 11 | 8 | 24 | 5 |
| 8 | 11 | 5 | 6 | 19 | 4 | 13 | 14 | 15 | 19 | 1 | 21 | 11 | 10 | 6 | 27 | 5 |
| 9 | 4 | 7 | 14 | 16 | 8 | 7 | 12 | 17 | 18 | 2 | 21 | 11 | 9 | 3 | 28 | 8 |
| 10 | 2 | 11 | 14 | 14 | 6 | 15 | 14 | 13 | 25 | 1 | 18 | 11 | 16 | 2 | 25 | 8 |
| 11 | 9 | 12 | 7 | 14 | 6 | 10 | 15 | 18 | 19 | 2 | 27 | 9 | 22 | 3 | 23 | 3 |
| 12 | 8 | 2 | 8 | 23 | 6 | 10 | 14 | 18 | 18 | 2 | 24 | 11 | 12 | 2 | 28 | 8 |
| Total patients n analysis (range) [b] | 52-45 | 50-47 | 52-45 | 50-47 | 52-48 | 56-48 | 52-48 | 50-48 | 34-32 | 66-65 | 34-32 | 68-65 | 34-30 | 68-62 | 34-36 | 68-62 |

[a] The figures in bold type show contrasts that are statistically significant at the 5% level.

[b] The highest and the lowest number of patients In the analysis at any of the months. Patients who died, who discharged themselves against medical advice or who had their allocated chemotherapy terminated on account of toxicity are excluded thereafter. The policy for patients who had their allocated chemotherapy terminated on account of radiographic or clinical deterioration is described on page 167.

*SH/SHOW series. The* mode of interpretation of the tidings for this series is the same as that employed for the SHOW and the SHZOW series. The dosage of streptomycin had little effect on the findings of streptomycin and isoniazid sensitivity tests (Table 19, left half).

Considering the influence of the rate of inactivation of isoniazid (Table 19, right half), (1) the rapid inactivators produced isoniazid-sensitive cultures more frequently than the slow inactivators, the proportions being 18 % and 5 % at 4 months, 19 % and 0 % at 6 months, 14 % and 2 % at 9 months, and 5 % and 0 % at 12 months; (2) there was some evidence that resistance to streptomycin developed more frequently in the rapid inactivators in the later months, the proportions resistant being 14 % for the rapid and 5 % for the slow inactivators at 9 months, and 13 % and 5 %, respectively, at 12 months; and (3) isoniazid-resistant cultures were produced by similar proportions in the two groups up to 9 months; thereafter, they occurred more frequently in the rapid inactivators, the proportion resistant at 12 months being 14% as compared with 6% in the slow inactivators. These findings suggest that, despite the 4 weeks of initial daily chemotherapy, the rapid inactivators of isoniazid had an isoniazid deficiency. However, the effect of this deficiency occurred later in treatment than in the SHOW series.

*SHTW series.* Neither the speed of elimination of sensitive organisms nor the emergence of resistance appeared to be influenced by the dosage of streptomycin (Table 20, left half) or the rate of inactivation of isoniazid (Table 20, right half).

*Occurrence of drug-sensitive cultures at 10, 11 and 12 months*

An interesting feature of this study (evident from the percentages in Tables 16-20) is the occurrence of drug-sensitive cultures in the later months of treatment. Thus, among patients who produced at least

TABLE 19

SH/SHOW SERIES: RESULTS OF STREPTOMYCIN AND ISONIAZID SENSITIVITY TESTS, RELATED TO STREPTOMYCIN DOSAGE AND ISONIAZID INACTIVATION RATE

| Months after start of chemotherapy | Standardized percentage of patients [a] | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Contrast between streptomycin high-dosage and low-dosage patients | | | | | | | | Contrast between slow and rapid inactivators of isoniazid | | | | | | | |
| | Streptomycin sensitivity | | | | Isoniazid sensitivity | | | | Isoniazid sensitivity | | | | **Streptomycin sensitivity** | | | |
| | Sensitive | | Resistant | | Sensitive | | Resistant | | Sensitive | | Resistant | | Sensitive | | Resistant | |
| | Low | High | Low | High | Low | High | Low | High | Rapid | Slow | Rapid | Slow | Rapid | Slow | Rapid | Slow |
| 3 | 15 | 18 | 2 | 2 | 13 | 18 | 4 | 2 | 16 | 15 | 3 | 3 | 16 | 17 | 3 | 2 |
| 4 | 10 | 13 | 0 | 2 | 8 | 12 | 2 | 4 | 18 | 5 | 0 | 5 | 18 | 8 | 0 | 2 |
| 5 | 13 | 6 | 2 | 6 | 13 | 6 | 2 | 6 | 16 | 6 | 3 | 4 | 11 | 9 | 8 | 1 |
| 6 | 8 | 8 | 4 | 0 | 10 | 4 | 4 | 6 | 19 | 0 | 3 | 6 | 17 | 3 | 3 | 2 |
| 7 | 4 | 2 | 4 | 4 | 4 | 2 | 4 | 6 | 8 | 0 | 5 | 5 | 6 | 2 | 6 | 3 |
| 8 | 6 | 4 | 4 | 6 | 6 | 6 | 4 | 6 | 16 | 0 | 8 | 3 | 14 | 0 | 8 | 3 |
| 9 | 6 | 2 | 8 | 8 | 8 | 4 | 6 | 6 | 14 | 2 | 5 | 6 | 5 | 3 | 14 | 5 |
| 10 | 8 | 2 | 4 | 6 | 6 | 0 | 6 | 8 | 8 | 0 | 11 | 5 | 11 | 2 | 8 | 3 |
| 11 | 8 | 0 | 4 | 8 | 6 | 2 | 8 | 6 | 11 | 0 | 14 | 3 | 11 | 0 | 11 | 3 |
| 12 | 6 | 0 | 6 | 8 | 4 | 0 | 10 | 6 | 5 | 0 | 14 | 6 | 6 | 2 | 13 | 5 |
| Total patients in analysis (range) [b] | 54-48 | 52-49 | 54-46 | 52-49 | 54-49 | 52-49 | **54–49** | **52–49** | 38-36 | 67-62 | 38-36 | 67-62 | 38-35 | 67-62 | 38-35 | 67-62 |

[a] The figures In bold type show contrasts that are statistically significant at the 5% level.

[b] The highest and the lowest number of patients in the analysis at any of the months. Patients who died, who discharged themselves against medical advice or who had their allocated chemotherapy terminated on account of toxicity are excluded thereafter. The policy for patients who had their allocated chemotherapy terminated on account of radiographic or clinical deterioration is described on page 167.

1 positive culture at 10, 11 or 12 months, 36% had at least 1 isoniazid-sensitive culture and 46 % had at least 1 streptomycin-sensitive culture (including 25 % with at least 1 culture sensitive to both the drugs). Table 21 sets out the corresponding proportions (together with the total numbers of sensitive cultures) according to regimen, streptomycin dosage and isoniazid inactivation rate.

There was little evidence that the proportion of patients with a sensitive culture was influenced by the regimen, all the differences being clearly non-significant, both for isoniazid ($P \geq 0.3$) and for streptomycin ($P \geq 0.3$). However, there was some evidence that the proportion with an isoniazid-sensitive culture was higher in the rapid inactivators of isoniazid (45 % of 56) than in the slow inactivators (21% of 34), a significant difference (P=0.04). Similarly, there was a suggestion that the proportion with a streptomycin-sensitive culture was higher in the streptomycin low-dosage patients (52% of 48 than in the high-dosage patients (39% of 36); however, this difference was non-significant (P=0.3). The difference between the streptomycin high-dosage and the low-dosage patients in the proportion with an isoniazid-sensitive culture was non-significant (P=0.1), as also was the difference between the slow and the rapid inactivators of isoniazid in the proportion with a streptomycin-sensitive culture (P=0.4).

Considering next the findings in patients who had positive cultures at almost all the months, *(a)* 5 (1 SH/SHOW, 4 SHZOW) had an isoniazid-sensitive culture at 10 months, 11 months and 12 months; a sixth patient (SHZOW) had an isoniazid-sensitive culture at 10 months and at 12 months, all the cultures at 11 months being negative; *(b)* 3 patients (2 SHZOW, 1 SHOW) had a streptomycin-sensitive culture at 10 months, 11 months and 12 months; a fourth (SHOW) had a streptomycin-sensitive culture at 10 months and at 11 months, all the cultures at 12 months being negative; and *(c)* 1 patient

TABLE 20

SHTW SERIES: RESULTS OF STREPTOMYCIN AND ISONIAZID SENSITIVITY TESTS. RELATED TO STREPTOMYCIN DOSAGE AND ISONIAZID INACTIVATION RATE

| Months after start of chemotherapy | Standardized percentage of patients [a] | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Contrast between streptomycin high-dosage and low-dosage patients | | | | | | | | Contrast between slow and rapid inactivators of isoniazid | | | | | | | |
| | Streptomycin sensitivity | | | | Isonlazid sensltlvltv | | | | Isoniazid sensitivity | | | | Streptomycin sensitivitv | | | |
| | Sensitive | | Resistant | | Sensitive | | Resistant | | Sensitive | | Resistant | | Sensitive | | Resistant | |
| | Low | High | Low | High | Low | High | Low | High | iapid | Slow | Rapid | Slow | Rapid | Slow | Rapid | Slow |
| 3 | 16 | 32 | 0 | 0 | 15 | 30 | 3 | 3 | 13 | 26 | 4 | 2 | 17 | 26 | 0 | 0 |
| 4 | 11 | IO | 1 | 3 | 8 | 9 | 4 | 4 | 7 | 9 | 4 | 4 | 9 | 11 | 2 | 2 |
| 5 | 6 | 9 | 0 | 3 | 1 | 6 | 4 | 5 | 9 | 2 | 4 | 4 | 13 | 4 | 0 | 2 |
| 6 | **7** | 3 | 4 | 5 | 5 | 3 | 7 | 5 | 5 | 3 | 9 | 4 | 7 | 4 | 7 | 3 |
| 7 | 4 | 0 | 4 | 5 | **1** | 0 | 1 | 5 | 0 | 1 | 7 | 5 | 0 | 3 | 7 | 3 |
| 8 | 4 | 2 | 4 | 5 | 2 | 2 | 7 | 5 | 4 | 0 | 7 | 5 | 4 | 2 | **7** | 3 |
| 9 | 0 | 3 | **8** | 5 | 1 | 0 | 1 | 6 | 0 | 1 | 7 | 7 | 0 | 2 | **7** | 6 |
| IO | 3 | 2 | **7** | 5 | 0 | 2 | IO | 5 | 2 | 0 | 11 | 5 | 7 | 0 | 7 | 5 |
| 11 | 3 | 2 | 9 | 5 | 3 | 2 | 9 | 5 | 2 | 2 | 7 | 6 | 2 | 2 | 7 | 6 |
| 12 | 2 | 0 | 7 | 5 | 0 | 0 | 9 | 5 | 0 | 0 | 9 | 5 | 2 | 0 | 7 | 5 |
| **Total** patients In analysis (range) [b] | 74-73 | **69–64** | **74–73** | **69–64** | 7M-73 | 69-64 | **74–73** | 69-64 | **I6–42** | 98-95 | 46-42 | 98-95 | **46–42** | **98–95** | **46–42** | 98-95 |

[a] The figures in bold type show contrasts that are statistically significant at the 5% level.

[b] The highestand thelowestnumber of patients in the analysis at any of the months. Patients who died, who discharged themselves against medical advice or who had their allocated chemotherapy terminated on account of toxicity are excluded thereafter. The policy for patients who had their allocated chemotherapy terminated on account of radiographic or clinical deterioration is described on pages 157 and 167.

TABLE 21

PATIENTS WITH DRUG-SENSITIVE CULTURES AT 10, 11 OR 12 MONTHS

| | | Isoniazld sensitivity | | | | Streptomycin sensitivity | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Patients with a test result at 10, 11 or 12 months [a] | Patients with a sensitive culture at one or more of these months | | Total no. of sensitive cultures at 10, 11 and 12 months | Patients with a test result at 10, 11 or 12 months [a] | Patients with a sensitive culture at one or more of these months | | Total no. of sensitive cultures at 10, 11 and 12 months |
| | | | No. | % [b] | | | No. | % [b] | |
| Regimen | SHOW | 34 | IO | 29 | 15 | 82 | 18 | 41 | 18 |
| | SHZOW | 26 | 12 | 46 | 23 | 22 | 10 | (45) | 20 |
| | SH/SHOW | 14 | 6 | (43) | 9 | 14 | 9 | (64) | 12 |
| | SHTW | 16 | 4 | (25) | 4 | 16 | 7 | (44) | 7 |
| Streptomycin dosage | High | 37 | 17 | 46 | 29 | 36 | 14 | 39 | 20 |
| | Low | 53 | 15 | 28 | 22 | 48 | 25 | 52 | 37 |
| Isoniazid inactivation rate | Slow | 34 | | **21** | **8** | **31** | 12 | 39 | 17 |
| | Rapid | 56 | 2: | **45** | **43** | **53** | 21 | 51 | 40 |

[a] Patients whose allocated chemotherapy was terminated for deterioration are included subsequently also (and regarded as having resistant cultures), provided the last 2 sensitivity test results *prior* to the termination were resistant.

[b] Parentheses indicate that the percentage is based on fewer than 25 observations.

(SHZOW), included in *(a)* and *(b)*, had cultures sensitive to both isoniazid and streptomycin throughout the year. Of these 9 patients (1 SH/SHOW, 6 SHZOW, 2 SHOW; 4 high, 5 low; 2 slow, 7 rapid), 7 received every single dose of chemotherapy throughout the year and the remaining 2 missed only 1 dose. It is of interest that 8 of the 9 patients had received the SHZOW or the SHOW regimen, that is, once-weekly chemotherapy from the beginning, and that 7 of the 9 patients were rapid inactivators of isoniazid.

In summary, the proportion of patients with an isoniazid-sensitive culture in the later months of treatment was higher among the rapid inactivators of isoniazid than among the slow inactivators. Similarly, there was a suggestion that the proportion with a streptomycin-sensitive culture was higher among the streptomycin low-dosage patients than among the high-dosage patients. Of 9 patients who persistently produced cultures sensitive to isoniazid or streptomycin (or to both the drugs) even in the later months of treatment, 8 had received once-weekly chemotherapy from the beginning.

*Sequence of emergence of resistance in patients with an unfavourable response*

In all, 81 patients had an unfavourable response to treatment. Of these, 9 had died or had had their allocated chemotherapy terminated in the first 3 months and 6, all of whom had received at least 90% of their allocated chemotherapy, had produced only drug-sensitive cultures (to both streptomycin and isoniazid) between 3 and 12 months, 1 (SHTW, low, slow) on 1 occasion, 1 (SHZOW, low, rapid) on 2 occasions, 3 (2 SH/SHOW, low, rapid; 1 SHZOW, high, rapid) on 4 occasions and 1 (SHZOW, low, rapid) on 9 occasions.

Resistance emerged to at least 1 drug in the remaining 66 patients with an unfavourable response; the sequence of the emergence is set out in Table 22 according to the regimen, streptomycin dosage and isoniazid inactivation rate.

Considering the two once-weekly regimens with similar and relatively low efficacies, streptomycin resistance emerged first in similar proportions in the two series–namely, in 10 (36%) of 28 SHOW patients and 6 (30%) of 20 SHZOW patients. Amalgamating these two series, streptomycin resistance emerged first (indicating a relative failure of isoniazid) in 16 (33%) of 48 patients, as compared with none of 8 who received the highly effective twice-weekly regimen (SHTW). This difference, although not statistically significant (P=0.1), suggests that in moving from twice-weekly to once-weekly chemotherapy, there has been a greater

TABLE 22

EMERGENCE OF RESISTANCE TO STREPTOMYCIN AND ISONIAZID IN PATIENTS WITH AN UNFAVOURABLE RESPONSE [a]

| | | Patients with an unfavourable response and resistance to one or both drugs | | | |
|---|---|---|---|---|---|
| | | Total | Sequence of emergence of resistance | | |
| | | | Streptomycin first | Simultaneous | Isoniazid first |
| Regimen | SHOW | 28 | 10(36%) | 1 | 17 |
| | SHZOW | 20 | 6 (30%) | 4 | 10 |
| | SH/SHOW | 10 | 3 (30%) | 1 | 6 |
| | SHTW | 8 | 0 | 2 | 6 |
| Streptomycin dosage | High | 30 | 14 (47%) | 6 | 10 |
| | Low | 36 | 5 (14%) | 2 | 29 |
| Isoniazid inactivation rate | Slow | 24 | 0 | 4 | 20 (83%) |
| | Rapid | 42 | 19 | 4 | 19 (45%) |

[a] An unfavourable response to treatment is defined as death from tuberculosis, or bacteriologically active disease (including termination of the allocated chemotherapy for radiographic or serious clinical deterioration) or bacteriologically relapsed disease at 1 year.

reduction in the efficacy of isoniazid than of streptomycin.

Streptomycin resistance emerged first in 14 (47 %) of 30 patients who received the high dosage of streptomycin, as compared with 5 (14%) of 36 who received the low dosage, a significant difference (P <0.01). Similarly, isoniazid resistance emerged first in 20 (83 %) of 24 slow inactivators of isoniazid as compared with 19 (45 %) of 42 rapid inactivators, a significant difference (P<0.01). Thus, in the patients with an unfavourable response and drug resistance, the resistance emerged relatively slowly to streptomycin when it was given in low dosage (indicating a relative deficiency of this drug), and relatively slowly to isoniazid when it was inactivated rapidly (indicating a relative deficiency of this drug).

*Influence of pretreatment drug susceptibility on response to treatment*

*Streptomycin.* Table 23 relates the response to treatment of patients in all four series combined to the streptomycin susceptibility of the first pretreatment culture; all these cultures were " streptomycin-sensitive " according to standard definitions in use at this Centre (page 149). Of 281 patients with an MIC of 4 µg/ml or less on the first positive culture, 14 % had an unfavourable response to treatment ; the corresponding proportions were 22% of 134 for patients with an MIC of 8 µg/ml and 27% of 33 for patients with an MIC of 16 µg/ml. The trend in these percentages is statistically significant (P=0.02). Similar trends were obtained with the RR (P=0.01), the proportion of the bacterial population resistant to 2 µg/ml (P <0.0001) and the proportion resistant to 4 µg/ml (P<0.01). These findings demonstrate that the degree of streptomycin susceptibility of the sensitive cultures influenced significantly the outcome of treatment.[1]

TABLE 23

RESPONSE TO TREATMENT RELATED TO STREPTOMYCIN SUSCEPTIBILITY ON ADMISSION [a]

| Streptomycin susceptibility on admission [b] | | Total no. of patients | Unfavourable response [c] | |
|---|---|---|---|---|
| | | | No. | % |
| Minimal inhibitory concentration (µg/ml) | ≤ 4 | 281 | 40 | 14 |
| | 8 | 134 | 29 | 22 |
| | 16 | 33 | 9 | 27 |
| Resistance ratio | ⩽0.5 | 229 | 31 | 14 |
| | 1 | 153 | 28 | 18 |
| | ⩾2 | 59 | 16 | 27 |
| Proportion resistant to 2 µg/ml | <1% | 301 | 43 | 14 |
| | 1%–9% | 81 | 15 | 19 |
| | ⩾10% | 60 | 23 | 38 |
| Proportion resistant to 4 µg/ml | <0.1% | 342 | 55 | 16 |
| | 0.1%–0.9% | 59 | 13 | 22 |
| | ⩾1.0% | 34 | 13 | 38 |

[a] All 4 treatment series combined.

[b] Result on first positive culture.

[c] That is, death from tuberculosis, or bacteriologically active disease (including termination of the allocated chemotherapy for radiographic or serious clinical deterioration) or bacteriologically relapsed disease at 1 year.

Table 24 examines, for each of the four series, the streptomycin susceptibility of the first pretreatment culture from patients with an unfavourable response and from those with a favourable response. There is some evidence in all the four series that the percentage of patients with less susceptible strains (determined by different measures, e.g., MIC of 8 µg/ml or more) was higher in the former than in the latter. The contrasts appear to be most marked in the SHTW series. For instance, in this series, the proportions with 10% or more growth on 2 µg/ml were 45% of 11 for the patients with an unfavourable response and 11% of 129 for the patients with a favourable response, asignificant difference (P <0.01); the corresponding proportions for 1% or more growth on 4 µg/ml were 36 % and 8 %, respectively (P=0.01).

*Isoniazid.* Analyses (not tabulated here) showed that there was no association between the response to treatment and the isoniazid susceptibility of the first pretreatment culture; all these cultures were " isoniazid-sensitive " according to standard definitions in use at this Centre (page 149).

[1] The degree of streptomycin susceptibility was broadly similar for the SHTW and SHOW series in phases I and II, and for the SHTW, SH/SHOW, SHZOW and SHOW series in phases II and III. Further, within each series in phases I plus II and in phases II plus III, it was broadly similar for streptomycin high-dosage and low-dosage patients, and for slow and rapid inactivators of isoniazid apart from 1 exception. This was in the SH/SHOW series in phases II plus III, in which there was clear-cut evidence that the proportion of patients with less susceptible strains was significantly lower in the slow inactivators than in the rapid inactivators. Statistical standardization was therefore undertaken but did not affect the conclusion (page 172), the proportions with a favourable response at 1 year being 95 % for the slow inactivators and 78 % for the rapid inactivators (P = 0.02).

TABLE 24

RESPONSE TO TREATMENT OF PATIENTS IN THE INDIVIDUAL SERIES, RELATED TO STREPTOMYCIN SUSCEPTIBILITY ON ADMISSION

| Series | Response to treatment [a] | Total patients | Percentage of patients [b] | | | |
|---|---|---|---|---|---|---|
| | | | MIC ≥8 µg/ml | RR ≥2 | Growth on 2 µg/ml ≥10% | Growth on 4 µg/ml ≥1% |
| SHTW | Unfavourable | 11 | (64) | (18) | (45) | (36) |
| | Favourable | 129 | 43 | 12 | 11 | 8 |
| SH/SHOW | Unfavourable | 12 | (50) | (33) | (33) | (17) |
| | Favourable | 89 | 31 | 9 | 10 | 6 |
| SHZOW | Unfavourable | 25 | 60 | 16 | 20 | 12 |
| | Favourable | 75 | 27 | 15 | 9 | 4 |
| SHOW | Unfavourable | 33 | 36 | 18 | 27 | 12 |
| | Favourable | 82 | 33 | 11 | 9 | 4 |

[a] An unfavourable response to treatment Is defined as death from tuberculosis, or bacteriologically active disease (including termination of the allocated chemotherapyfor radiographicor serious clinical deterioration) or bacteriologically relapsed disease at 1 year. A favourable response to treatment is defined as bacteriologically quiescent disease or disease of bacteriologically doubtful status at 1 year.

[b] Parentheses Indicate that the percentage Is based on fewer than 25 observations.

## PYRAZINAMIDE SENSITIVITY TEST RESULTS

Table 25 presents the results of pyrazinamide sensitivity tests in the SHZOW patients, as well as in the control (SHOW) patients. Considering first the SHZOW patients with sensitivity test results, the proportion resistant showed a gradual increase during treatment; thus, it was 7% on admission, 5% in months 3 and 4 combined, 11% in months 5 and 6 combined, 19 % in the period from month 7 to month 9 and 28% in the period from month 10 to month 12 (all the resistant cultures obtained during treatment were from patients with a sensitive culture on admission). In contrast, no such increase occurred in the control patients, the proportion resistant being 5 % on admission and 4 % at months 6 and 12 combined. These findings suggest that resistance to pyrazinamide emerged in some of the SHZOW patients.

There were 21 SHZOW patients who had bacteriologically active disease at 1 year, including 7 who had the allocated chemotherapy terminated (in the 6th month or subsequently) on account of radiographic or serious clinical deterioration. A detailed examination of the sensitivity test results for these patients showed clear-cut evidence of the emergence of

TABLE 25

RESULTS OF PYRAZINAMIDE SENSITIVITY TESTS

| Regimen | Months after start of chemotherapy | No. of patients with a sensitivity test result | Resistant [a] | |
|---|---|---|---|---|
| | | | No. | % |
| SHZOW | 0 [b] | 105 | 7 | 7 |
| | 3 | 29 | 1 | 5 |
| | 4 | 28 | 2 | |
| | 5 | 24 | 2 | 11 |
| | 6 | 14 | 2 | |
| | 7 | 18 | 2 | 19 |
| | 8 | 16 | 5 | |
| | 9 | 14 | 2 | |
| | 10 | 14 | 4 | 28 |
| | 11 | 14 | 3 | |
| | 12 | 12 | 4 | |
| Control (SHOW) | 0 [b] | 77 | 4 | 5 |
| | 6 | 15 | 0 | 4 |
| | 12 | 11 | 1 | |

[a] Resistance is defined as growth on 100 µg/ml pyrazinamide of at least 1% of the bacterial population.

[b] The sensitivity test result for the first positive culture has been considered.

pyrazinamide resistance (that is, at least 2 resistant cultures in the last 6 months of chemotherapy) in 5 patients. This represents an incidence of 24% in the 21 patients with bacteriologically active disease, at 1 year and an incidence of 5 % in the 105 patients treated with the SHZOW regimen.

## DRUG CONCENTRATIONS IN SERUM

The mean and range of serum drug concentrations attained at 1, 2, 3 and 6 hours after a dose of chemotherapy (streptomycin, 1 g or 0.75 g; isoniazid, approx. 15 mg/kg body-weight ; pyrazinamide, approx. 90 mg/kg body-weight) are set out in Table 26. It will be seen that:

(1) the mean streptomycin concentrations at 1, 2, 3 and 6 hours are proportional to the dose of streptomycin (1 g or 0.75 g) administered;

(2) the mean isoniazid concentrations are appreciably higher in the slow inactivators of isoniazid than in the rapid inactivators, the difference being the largest at 6 hours; and

(3) pyrazinamide continued to be absorbed over a long period, the serum concentrations of free pyrazinamide are high (a concentration of 25 µg/ml is known to inhibit a large proportion of the bacterial population in wild strains (Tripathy, 1966)), and the half-life is long.

## INFLUENCE OF SERUM DRUG CONCENTRATIONS ON RESPONSE TO TREATMENT AND TOXICITY

For each patient, the following measures were obtained from the estimates of streptomycin and isoniazid concentrations; (1) logarithm of the 6-hour concentration, (2) logarithm of the highest concentration, (3) logarithm of the geometric mean of the concentrations at 1, 2, 3 and 6 hours, (4) half-life of the drug, calculated from the concentrations at 3 and 6 hours. In addition, for the SHZOW patients, the values for measures (1), (2) and (3) were obtained for free pyrazinamide and total pyrazinamide (i.e., free pyrazinamide plus pyrazinoic acid); measure (4) was not considered for either since the 6-hour concentration was higher than or equal to the 3-hour concentration in appreciable proportions (28 % and 18 %, respectively) of the patients.

### *Response to treatment*

Analyses were undertaken relating the likelihood of a favourable response (that is, bacteriologically quiescent disease or disease of bacteriologically doubtful status at 1 year) to each of the above measures. In the case of streptomycin, high-dosage and low-dosage patients in all four series were considered together, since there was no clear-cut evidence that a favourable response had occurred more frequently in the former (page 169). For isoniazid, the analyses were performed separately for

TABLE 26

MEAN AND RANGE OF SERUM CONCENTRATIONS OF STREPTOMYCIN, ISONIAZID AND PYRAZINAMIDE

| Drug | Series | No. of patients | Serum concentration (µg/ml) at specified hours after the administration of chemotherapy | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 hour | | 2 hours | | 3 hours | | 6 hours | |
| | | | Mean | Range[a] | Mean | Range[a] | Mean | Range[a] | Mean | Range[a] |
| Streptomycin | High dosage (1 g) | 192 | 52 | 28-90 | 49 | 29-88 | 38 | 18-78 | 18 | 6-39 |
| | Low dosage (0.75 g) | 200 | 40 | 18-74 | 37 | 20-61 | 29 | 13-52 | 14 | 6-26 |
| Isoniazid | Slow inactivators | 242 | 7.9 | 0.9-24.0 | 12.2 | 3.4-24.8 | 11.2 | 6.2-20.1 | 6.5 | 3.8-10.8 |
| | Rapid Inactivators | 147 | 5.4 | 0.8–21.4 | 9.6 | 3.1–19.1 | 7.6 | 3.4–13.8 | 2.3 | 0.9–5.1 |
| Total pyrazinamide | – | 104 | 73 | 23-179 | 111 | 40-177 | 118 | 49-167 | 117 | 86-151 |
| Free pyrazinamide | | 104 | 89 | 24-170 | 102 | 39-158 | 107 | 45-146 | 97 | 72-131 |

[a] The figures given are the range for the middle 95% of values, that is, excluding 2.5% at each extreme.

the slow and the rapid inactivators, but amalgamating the three once-weekly series (SHOW, SHZOW and SH/SHOW) since the rate of inactivation of isoniazid was prognostically important in all of them (page 172); patients in the SHTW series were not considered, as for them the isoniazid inactivation rate had no prognostic importance. For total and free pyrazinamide, all the SHZOW patients were considered. The findings will be reported in detail later; in brief, none of the above measures was associated with the outcome of treatment.

*Toxicity*

*Streptomycin.* [1] As in the paragraph above, high-dosage and low-dosage patients in all four series were considered together, since the differences between them in the incidence of toxicity were small and non-significant (page 185). There was no difference in the serum streptomycin concentrations between patients who had minor symptoms of toxicity (giddiness, facial paraesthesia and tinnitus) that did not require a reduction in streptomycin dosage and those who had no symptoms. However, giddiness necessitating a reduction in dosage or cessation of streptomycin occurred significantly more frequently in patients with higher streptomycin concentrations. Thus, considering the geometric mean of the concentrations at 1, 2, 3 and 6 hours, the proportion with a reduction or cessation of streptomycin was 0% of 78 patients with a mean of less than 25 µg/ml, 1% of 94 in those with a mean of 25 µg/ml-31 µg/ml, 3% of 133 in those with a mean of 32 µg/ml-39 µg/ml, and 5% of 86 in those with a mean of 40 µg/ml or more, a significant trend (P=0.01). Significant trends were also obtained with the 6-hour concentration (P<0.01) and the highest concentration (P=0.02), but not with the half-life (P=0.2); the detailed findings will be reported later.

*Isoniazid.* Isoniazid toxicity occurred predominantly in the slow inactivators of isoniazid (page 187). However, among the slow inactivators, there was little evidence that it occurred more often in the patients with higher serum isoniazid concentrations; the detailed findings will be reported later.

*Pyrazinamide.* As there was little evidence of pyrazinamide toxicity (page 187), no attempt was made to relate it to the serum pyrazinamide concentration.

## VIII. PROGNOSTIC VALUE OF VARIOUS FACTORS ASSESSED ON ADMISSION TO TREATMENT

This section relates the likelihood of an unfavourable response to various factors assessed on admission to treatment, and is based on patients with an assessable response (that is, excluding those who died of non-tuberculous causes, discharged themselves against medical advice or had their allocated chemotherapy terminated on account of toxicity) from all three phases of the intake. An unfavourable response to treatment is defined as death from tuberculosis, or bacteriologically active disease (including termination of the allocated chemotherapy for radiographic or serious clinical deterioration) or bacteriologically relapsed disease at 1 year.

The findings are presented (1) for all patients (that is, irrespective of the regimen received) and (2) for individual regimens. As the likelihood of an unfavourable response cannot be smaller for patients with more severe disease at the beginning of treatment than for those with less severe disease, P values corresponding to l-tail tests of significance are reported in this section.

### ALL PATIENTS

Of 139 patients with extensive cavitation (Table 27) 23% had an unfavourable response as compared with 18% of 239 with moderate cavitation and 9% of 79 with slight or no cavitation; the trend in these percentages is statistically significant (P < 0.01). Considering next the total extent of disease, the proportions with an unfavourable response were 26%, 23%, 18%, 14% and 0% for patients with gross, extensive, moderate, limited and slight disease, respectively (P < 0.01). Considering the direct smear result of the first collection specimen, the proportions with an unfavourable response were 23 %, 20 %, 12 % and 14 % in patients with a 3-plus, 2-plus, 1-plus and negative result, respectively (P = 0.01).

[1] As the incidence of streptomycin toxicity cannot be lower in patients with higher serum concentrations, l-tail tests of significance have been employed.

TABLE 27

RESPONSE TO TREATMENT RELATED TO VARIOUS FACTORS ASSESSED ON ADMISSION [a]

| Condition on admission | No. of patients | Unfavourable response | |
|---|---|---|---|
| | | No. | %[b] |
| Extent of cavitation: | | | |
| Extensive | 139 | 32 | 23 |
| Moderate | 239 | 42 | 18 |
| Slight | 77 | 7 | 9 |
| Nil | 2 | 0 | (0) |
| *Total extent ofdisease:* | | | |
| *Gross* | 34 | 9 | 26 |
| Extensive | 102 | 23 | 23 |
| Moderate | 188 | 33 | 18 |
| Limited | 118 | 16 | 14 |
| Slight | 15 | 0 | (0) |
| *Direct smear result of first collection specimen:* | | | |
| 3-plus | 95 | 22 | 23 |
| 2-plus | 173 | 35 | 20 |
| 1-plus | 139 | 17 | 12 |
| Negative | 50 | 7 | 14 |
| Total | 457 | 81 | 18 |

[a] All 4 treatment series combined.
[b] Parentheses indicate that the percentage is based on fewer than 25 observations.

Analyses, not tabulated here, showed that 19 % of 294 males had an unfavourable response as compared with 15% of 163 females (P = 0.4); also, 13 % of 114 patients aged under 25 years, 19% of 264 aged 25-44 years and 20% of 79 aged 45 years or more had an unfavourable response, a non-significant trend (P = 0.2). The proportions with an unfavourable response were 20% in 148 patients weighing less than 80 lb, 16 % in 230 weighing 80 lb-99 lb, and 19% in 79 patients weighing 100 lb or more.

In summary, the extent of cavitation, the total extent of disease and the direct smear result of the first collection specimen of sputum influenced significantly the response to treatment, whereas the sex, the age and the weight did not do so.

TABLE 28

RESPONSE TO TREATMENT OF PATIENTS IN THE INDIVIDUAL SERIES, IN RELATION TO VARIOUS FACTORS ASSESSED ON ADMISSION

| Condition on admission | | SHTW | | SH/SHOW | | SHZOW | | SHOW | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. of patients | Unfavourable response (%) | No. of patients | Unfavourable response (%) [a] | No. of patients | Unfavourable response (%) [a] | No. of patients | Unfavourable response (%) |
| Extent of cavitation | Extensive or moderate | 111 | 9 | 89 | 12 | 88 | 27 | 90 | 32 |
| | Slight or nil | 29 | 3 | 12 | (8) | 13 | (8) | 25 | 16 |
| Total extent of disease | Gross, extensive or moderate | 98 | 9 | 75 | 11 | 69 | 33 | 82 | 30 |
| | Limited or slight | 42 | 5 | 26 | 15 | 32 | 6 | 33 | 24 |
| Direct smear result of first collection specimen | 3-plus or 2-plus | 72 | 10 | 69 | 12 | 63 | 33 | 64 | 33 |
| | 1-plus or negative | 68 | 6 | 32 | 12 | 38 | 11 | 51 | 24 |
| | Total | 140 | 8 | 101 | 12 | 101 | 25 | 115 | 29 |

[a] Parentheses indicate that the percentage is based on fewer than 25 observations.

### PATIENTS IN THE INDIVIDUAL SERIES

In the SHTW series and the SH/SHOW series, the numbers of patients with an unfavourable response were relatively small, and there was little or no evidence of an association between response to treatment and the various factors assessed on admission (Table 28), all the differences being clearly non-significant ($P \geq 0.3$). However, there was some evidence of associations in the SHZOW series and the SHOW series (both of which had an appreciable number of patients with an unfavourable response), especially the former. Statistical significance was attained in two of the contrasts, both in the SHZOW series–namely, an unfavourable response in 33 % of the patients with gross, extensive or moderate disease as compared with 6% of those with limited or slight disease ($P < 0.01$), and 33 % of those with a 3-plus or 2-plus smear result as compared with 11% in those with a 1-plus or negative result ($P = 0.02$). However, the latter contrast might have been influenced by the fact that the proportion of rapid inactivators was substantially higher in patients with a 3-plus or 2-plus result than in those with a 1-plus or negative result (46% and 13 %, respectively). Statistical standardization for isoniazid inactivation rate was therefore undertaken, and resulted in proportions with unfavourable response of 29% in the former group and 15% in the latter, still a significant difference ($P = 0.05$).

### PROGNOSTIC VALUE OF SERUM DRUG CONCENTRATIONS

It may be recalled that, except in the SHTW series, slow inactivators of isoniazid responded appreciably better than rapid inactivators (see pages 160 and 172). However, among the slow and among the rapid inactivators, considered separately, none of several measures obtained from the serum isoniazid concentrations at 1, 2, 3 and 6 hours after a dose of chemotherapy, influenced the outcome of treatment (page 183). Similarly, none of several measures obtained from the serum concentrations of streptomycin and pyrazinamide had an effect on the response to treatment (page 183).

## IX. DRUG TOXICITY

The findings in this section are based on 476 patients in the main analyses from all three phases combined. Patients were not questioned to elicit complaints of drug toxicity; however, every spontaneous complaint to the musing or medical staff was recorded, and was followed by careful questioning by a physician.

### STREPTOMYCIN

It will be recalled that neither the physicians nor the patients were aware of the dosage of streptomycin (1 g or 0.75 g) received by any individual patient.

In all, 11 patients had their streptomycin stopped or the dosage reduced. Of these, 1 (low, SHTW) had the allocated chemotherapy terminated in the 5th month on account of cutaneous hypersensitivity to streptomycin (and also to isoniazid), and 2 others (both high; 1 SHTW, 1 SH/SHOW) in the 11th and 9th month, respectively, for giddiness which had persisted despite a reduction in the dosage of streptomycin (by one-third) in the 4th and 3rd month, respectively. A further 6 patients, 3 on high dosage (2 SH/SHOW, 1 SHZOW) and 3 on low dosage (1 SHTW, 1 SH/SHOW, 1 SHOW), had a reduction in dosage (by one-third) on account of giddiness, in the 3rd, 6th, 2nd, 6th, 1st and 5th month, respectively. Two patients (both high; both SHTW) discharged themselves from treatment in the 6th and 11th month, respectively, on account of giddiness (in the former, a decision had already been taken to reduce the dosage of streptomycin).

Thus, streptomycin toxicity (giddiness) was the cause of a reduction in dosage or cessation of streptomycin, or a premature discharge, in 10 (2.1%) patients. The incidence was 0 % in 119 patients aged under 25 years, 1.3 % in 155 patients aged 25-34 years, and 4.0% in 202 patients aged 35 years or more, a significant trend ($P = 0.01$). Considering next the incidence in the four series (the age-distributions for the four series were similar), the proportions were 3 % of 148 in the SHTW, 4% of 106 in the SH/SHOW, 1% of 105 in the SHZOW and 1% of 117 in the SHOW series; thus, there was a slight suggestion of a higher incidence in the SHTW and the SH/SHOW series. It is of interest that of the 4 SH/SHOW patients who had a reduction in dosage of streptomycin, only 1 had the reduction while receiving daily streptomycin (that is, in the 1st month). Lastly, there was a suggestion that the

incidence was higher in the streptomycin high-dosage than in the low-dosage patients (the age-distributions for the two groups were similar), the proportions being 3.0 % of 232 and 1.2 % of 244, respectively (P = 0.3).

Minor complaints, not requiring a reduction in streptomycin dosage, were made by 74 (16%) patients. The incidence was *(a)* 17% in patients aged under 25 years, 16 % in those aged 25-34 years and 14% in those aged 35 years or more, *(b)* 14% in the SHTW, 15% in the SH/SHOW, 21% in the SHZOW and 13 % in the SHOW series, none of the differences being significant (P $\geq$ 0.2), and *(c)* 16% in the streptomycin high-dosage patients and 15 % in the low-dosage patients.

Some of the patients had more than one side-effect. Giddiness, usually commencing within 3 hours of the streptomycin injection and frequently lasting for the rest of the day or longer, was complained of by 34 high-dosage and 33 low-dosage patients-namely, 18 SHTW (9 high, 9 low), 15 SH/SHOW (8 high, 7 low), 20 SHZOW (11 high, 9 low) and 14 SHOW (6, high, 8 low) patients. The period the complaints referred to was less than 1 month in 9 high-dosage patients and 16 low-dosage patients, and 3 months or more in 11 and 6, respectively. Complaints of facial paraesthesia were made by 4 high-dosage (2 SHTW, 1 SH/SHOW, 1 SHOW) and 2 low-dosage (1 SHTW, 1 SH/SHOW) patients, and of tinnitus by 2 patients (both low, both SHTW). Three patients, 1 on high dosage (SHTW) and 2 on low dosage (both SHZOW), complained of itching after the injections (associated with urticaria in 1 of the latter 2), the complaint referring to a period of 2 weeks in the first patient, 7 months in the second and 8 months in the third; it is possible that pyrazinamide played a role in the 2 SHZOW patients.

In summary, streptomycin was stopped or the dosage reduced in only a small proportion of the patients; the incidence was significantly associated with age, and there was a suggestion that it was slightly higher in the SHTW and the SH/SHOW patients and in the patients who received the high dosage (1 g) of streptomycin. Minor complaints were made by about one-sixth of the patients, but the incidence was not influenced by the age of the patient, the dosage of streptomycin or the regimen.

*Rotating-chair test for vestibular function*

The test procedure was as follows. The patient was strapped to the seat of the rotating chair, fore-arms resting horizontally on the arms of the chair, feet spread apart against the vertical ends of the foot-rest, head bent down (to stimulate the horizontal canals) and eyes closed. The chair was manually rotated for 20 seconds, at a steady speed of 1 revolution in approximately 2 seconds, in the clockwise direction. At the end of this period, the chair was stopped and the patient asked to look straight (head erect) at a fixed point at a distance, while the assessor recorded, with the aid of an assistant and a watch, the duration of nystagmus. The end-point of the nystagmus was taken as the point at which the least quiver, horizontal or rotary, disappeared. The procedure was repeated with the chair being rotated in the anti-clockwise direction. The mean of the 2 readings (clockwise and anti-clockwise) has been employed for analyses.

About 90 % of the rotating chair tests in this study were undertaken by one of the Centre's physicians (the late Dr S. Velu) who was not involved in the day-to-day management of the patients. The detailed findings will be reported later; the main findings are summarized below.

There was little evidence that streptomycin in the high dosage (1 g) impaired vestibular function (as assessed by the duration of nystagmus) to a greater extent than in the low dosage (0.75 g). Thus, the mean duration of nystagmus on admission to treatment was 11.3 seconds for the high-dosage patients and 12.3 seconds for the low-dosage patients, and decreased at 12 months by 1.1 seconds in the former as compared with 0.8 second in the latter, a non-significant difference (P = 0.7). Also, analyses not presented here showed that the over-all changes in the duration of nystagmus between admission and 12 months in the SHTW, SH/SHOW, SHZOW and SHOW series were similar.

In all, 39 patients complained of giddiness on 2 or more occasions. At the time of the second complaint, the rotating-chair test was undertaken for each of these patients, as well as for a control patient of similar age (usually ± 5 years) who had received chemotherapy for a similar duration (± 2 months, in about 70% of cases) but who had made no complaints of giddiness. (The identity of the patient as test subject or control was unknown to the assessor.) The duration of nystagmus was less than 10 seconds in 69% of the patients who had the complaints of giddiness and in 45 % of the control patients, a significant difference (P = 0.05); the mean durations for the 2 groups were 7.2 and 10.1 seconds, respectively (P = 0.02).

In all, 8 patients had a reduction in streptomycin dosage on account of toxicity (giddiness). For these patients, the duration of nystagmus was 20, 16, 12, 12, 12, 9, 7 and 5 seconds on admission to treatment (mean 11.6 seconds) and 15, 5, 18, 0, 0, 6, 6 and 3 seconds, respectively, at the time of the reduction (mean 6.6 seconds); the decrease in the mean duration borders on significance (P = 0.06). Six of these patients completed the year of chemotherapy and 5 had test results at 12 months; their mean duration of nystagmus was 9.8 seconds at 12 months, the corresponding means being 8.8 seconds at the time of the reduction and 13.8 seconds on admission to treatment. The remaining 2 patients, who had values of 0 second and 6 seconds at the time of the reduction, failed to tolerate the reduced dosage also and had to have the streptomycin stopped, the duration of nystagmus at the time being 1 second and 5 seconds, respectively.

In summary, changes in the duration of nystagmus did not appear to be influenced either by the dosage of streptomycin or by the chemotherapeutic regimen. However, there was some evidence that patients who had complained twice of giddiness and those who had a reduction in streptomycin dosage on account of giddiness had impaired vestibular function at the time, as demonstrated by a significantly lowered duration of nystagmus.

## ISONIAZID

It will be recalled from page 146 that 6 mg of pyridoxine was administered with every dose of isoniazid.

One patient (rapid, SHTW) had the allocated chemotherapy terminated in the 5th month on account of cutaneous hypersensitivity to isoniazid (and streptomycin).

Isoniazid toxicity, which did not require a modification of the allocated chemotherapy, occurred in 16 patients, the incidence being 6 (4%) in the SHTW, 4 (4%) in the SH/SHOW, 2 (2%) in the SHZOW and 4 (3 %) in the SHOW series. It occurred more frequently in slow inactivators of isoniazid (5.0% of 299) than in rapid inactivators (0.6% of 177), the difference being significant (P = 0.01). The details are presented below.

Three patients (all slow inactivators) had convulsions. Of these, 2 had a single attack, 1 (SH/SHOW) on the day of starting treatment (5 hours after the administration of high-dosage isoniazid–see page 148) and the other (SHTW) in the 8th month; the third patient (SHOW) had 2 convulsions, both on the same day, in the 3rd month of treatment. A further 3 patients lost consciousness (it was uncertain whether they had fainted or had had a convulsion) once each, 1 (slow, SHTW) for half an hour in the 5th month, 1 (slow, SHZOW) for 10 minutes in the 8th month and 1 (rapid, SH/SHOW) for about 10 hours in the 12th month. (It is of interest that the episode occurred after several weeks of treatment in 5 of these 6 patients, despite the administration of 6 mg of pyridoxine with every dose of isoniazid.) Complaints of paraesthesia in the feet or limbs were made by 11 patients–namely, 10 slow inactivators (4 SHTW, 2 SH/SHOW, 1 SHZOW, 3 SHOW) and the rapid inactivator (SH/SHOW) who lost consciousness in the 12th month; one of the 10 slow inactivators (SHTW) developed signs of peripheral neuropathy.

In summary, complaints or episodes of isoniazid toxicity, none of which required a modification of the allocated chemotherapy, occurred in about 3 % of the patients despite the administration of 6 mg of pyridoxine with every dose of isoniazid. The incidence did not appear to be influenced by the regimen, but was significantly higher in the slow inactivators of isoniazid than in the rapid inactivators.

## PYRAZINAMIDE

### *Joint pains*

Of the 105 patients who received pyrazinamide (SHZOW regimen), 5 complained of joint pains. Of these, 2 had joint swellings as well, involving both knees in one and the right knee and ankle in the other. In all 5 patients, the allocated chemotherapy was continued, phenylbutazone or aspirin being prescribed, whenever necessary, to relieve the pain.

### *Toxicity to the liver*

Jaundice occurred in 2 SHZOW patients and in 1 SHOW patient in the lst, 6th and 5th month, respectively. One of the 2 SHZOW patients had an SGOT activity of 90 Karmen units and an SGPT activity of 50 Karmen units on admission to treatment; jaundice was detected on the 16th day and had cleared by the 28th day despite the patient having received, in error, a dose of pyrazinamide during this period; this patient may well have been incubating infective hepatitis on admission. In the second SHZOW patient, the pyrazinamide was withdrawn for 8 weeks and then reintroduced uneventfully.

Routine determinations of SGOT and SGPT activity (see pages 147 and 148) did not reveal any

evidence of toxicity to the liver in the SHZOW series. Thus, the mean SGOT value in this series was 36.4. Karmen units on admission, 34.7 Karmen units at 1 month and 35.2 Karmen units at 12 months, the corresponding values in the control series (SHOW) being 36.6, 37.6 and 32.9 Karmen units, respectively. Further, the proportion of patients who had a high SGOT, that is, 50 Karmen units or more (Sigma Chemical Company, 1961), was 15 % on admission, 8 % at 1 month and 13 % at 12 months in the SHZOW series, and 16 %, 13 % and 12%, respectively, in the control series. The findings with the SGPT activity were very similar.

Routine (once-weekly) tests for urobilinogen in urine did not reveal any evidence of toxicity to the liver in the SHZOW series. Thus, including the patients with jaundice, 17 (0.4%) of 4749 tests in SHZOW patients yielded a positive result as compared with 21 (0.6 %) of 3506 in the control (SHOW) patients; the proportions of patients who produced one or more positive results were 8 % and 10%, respectively. The patients with jaundice apart, a positive result at 2 or more successive attendances was obtained from 1 SHZOW and 2 SHOW patients; in none of these was the finding associated with an elevated SGOT or SGPT activity.

In summary, there was little evidence of pyrazinamide toxicity.

### COMPLICATIONS REQUIRING ADMISSION TO HOSPITAL OR SANATORIUM

Admission to hospital or sanatorium became necessary for 15 patients (3 SHTW, 4 SH/SHOW, 2 SHZOW, 6 SHOW) on account of pulmonary tuberculosis, the period in hospital or sanatorium being less than 1 week for 4 (1 SH/SHOW, 3 SHOW), 1-4 weeks for 4 (2 SHTW, 2 SH/SHOW), 5-8 weeks for 3 (1 SH/SHOW, 1 SHZOW, 1 SHOW), and 11 weeks (SHTW), 15 weeks (SHOW), 34 weeks (SHOW) and 49 weeks (SHZOW) for the remaining 4 patients. Further, 1 patient (SHTW) was hospitalized for 3 weeks on account of hypersensitivity to streptomycin and isoniazid, and another (SHOW) for 1 day on account of convulsions. In all, therefore, 17 (3.6%) of the 476 patients in the main analyses required admission to hospital or sanatorium on account of tuberculosis or drug toxicity.

## X. REGULARITY OF ADMINISTRATION OF CHEMOTHERAPY

This section presents information on (1) the proportion of the allocated chemotherapy received by the patients, (2) the relationship between this proportion and the response to treatment, and (3) the acceptability of the four regimens. The analyses are based on patients with an assessable response (defined on page 183) from all three phases of the intake, apart from 7 (2 SHTW, 2 SHZOW, 3 SHOW) who failed to complete 1 month of treatment due to death from tuberculosis or termination of the allocated chemotherapy on account of serious clinical deterioration; none of the 7 had missed any of the prescribed doses of drugs. The number of patients in the analyses is 450 (138 SHTW, 101 SH/SHOW, 99 SHZOW, 112 SHOW), including 16 who did not complete the year of treatment, 1 (SHOW) having died of tuberculosis in the 2nd month and 15 (1 SHTW, 7 SHZOW, 7 SHOW) having had their allocated chemotherapy terminated on account of radiographic or serious clinical deterioration in the 2nd month or later; for these 16 patients, the period up to the time of death or termination has been considered.

For patients who completed the year of treatment, the scheduled number of doses was 104 for the SHTW regimen, 72 for the SH/SHOW regimen and 52 for the SHZOW and SHOW regimens.

### PROPORTION OF ALLOCATED CHEMOTHERAPY RECEIVED

Most of the patients received a very high proportion of their allocated chemotherapy during the year. Table 29 summarizes the findings by setting out, for the various contrasts, the percentages of patients who had received at least 90% of their allocated chemotherapy. All but one of the percentages are 90 or above. Similar analyses were undertaken for the first 3 months of chemotherapy (as the early months of treatment are known to be especially important prognostically), and yielded the same conclusion. Thus, there was no evidence that patients allocated to the SHZOW or SHOW regimens, both of which proved to be unsatisfactory, had received *proportionately* fewer doses of the allocated chemotherapy than those allocated to the more

TABLE 29

PERCENTAGES OF PATIENTS WHO RECEIVED AT LEAST 90% OF THEIR ALLOCATED CHEMOTHERAPY DURING THE YEAR

| | | Phases I and II | | Phases II and III | | | |
|---|---|---|---|---|---|---|---|
| | | SHTW | SHOW | SHTW | SH/SHOW | SHZOW | SHOW |
| Streptomycin dosage | High | 96 | 100 | 93 | 96 | 98 | 100 |
| | Low | 95 | 96 | 88 | 96 | 98 | 95 |
| Isoniazid inactivation rate | Slow | 95 | 98 | 90 | 97 | 95 | 97 |
| | Rapid | 97 | 98 | 91 | 95 | 100 | 97 |
| Total | | 96 | 98 | 91 | 96 | 97 | 97 |

effective SHTW or SH/SHOW regimens, nor did rapid inactivators of isoniazid or streptomycin low-dosage patients in any of the four series receive fewer doses than the corresponding slow inactivators or high-dosage patients.

### RESPONSE TO TREATMENT RELATED TO THE PERCENTAGE OF ALLOCATED CHEMOTHERAPY RECEIVED

Table 30 relates the response to treatment in the four series to the percentage of allocated chemotherapy received during the year. In the SHTW, SH/SHOW and SHZOW series, there was no evidence that an unfavourable response occurred more frequently in patients who had received less than 95% of their chemotherapy than in those who had received 95 % or more. In the SHOW series, however, 5 of 10 patients in the former category had an unfavourable response as compared with 25 of 102 in the latter, a suggestive but non-significant difference (P = 0.1). Amalgamating the four series, an unfavourable response was observed in 17 %, 15 %, 15 % and 17 % of the patients who had received less than 90 %, 90 %-94 %, 95 %-99 % and 100 %, respectively, of their allocated chemotherapy.

In summary, there was little evidence of an association between response to treatment and the percentage of allocated chemotherapy received; however, it should be noted that only 18 patients (4%) in this study missed more than 10% of their chemotherapy.

TABLE 30

RESPONSE To TREATMENT IN RELATION TO THE PERCENTAGE OF ALLOCATED CHEMOTHERAPY RECEIVED DURING THE YEAR

| Percentage of allocated chemotherapy received | SHTW series | | SH/SHOW series | | SHZOW series | | SHOW series | | All series | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of patients | Unfavourable response [a] No. | No. of patients | Unfavourable response [a] No. | No. of patients | Unfavourable response [a] No. | No. of patients | Unfavourable response [a] No. | Total no. of patients | Unfavourable response [a] No. |
| < 90 | 9 | 0 | 4 | 1 | 3 | 0 | 2 | 2 | 18 | 3 (17) |
| 90-94 | 10 | 1 (5) | 8 | 0 (8) | 7 | 1 (10) | 8 | 3 (50) | 33 | 5 15 |
| 95-99 | 78 | 6 | 42 | 9 | 19 | 4 | 24 | 6 | 163 | 25 15 |
| 100 | 41 | 2 7 | 47 | 2 12 | 70 | 18 25 | 78 | 19 25 | 236 | 41 17 |

[a] That is, death from tuberculosis or bacteriologically active disease (including termination of the allocated chemotherapy for radiographic or serious clinical deterioration) or bacteriologically relapsed disease at 1 year.

[b] Parentheses indicate that the percentage is based on fewer than 25 observations.

ACCEPTABILITY OF THE REGIMENS

In general, patients were expected to make their own arrangements to attend the Centre for treatment. However, an ambulance was employed to bring them to the clinic on 55 occasions (that is, 0.2 % of a total of approximately 31 600 occasions on which chemotherapy was administered in the study), and chemotherapy was administered at home on 138 (0.4%) occasions for patients who were very ill. In a further 133 (0.4%) occasions, chemotherapy was administered to patients while they were in hospital or sanatorium. When assessing the acceptability of the regimens, the above 326 (1.0%) occasions have been excluded.

*Regularity of attendance on the appointed day*

Table 31 sets out the distribution of patients in the four series according to the percentage of occasions on which they attended the Centre punctually for treatment; attendances which were early by 1 or more days did not cause any extra work for the Centre's staff, and have also been regarded as punctual. (For the SH/SHOW patients, only the once-weekly phase of chemotherapy (that is, from week 4 to week 52) has been considered. During the daily phase, the patients were very regular, 95% of them attending on at least 90 % of the occasions.)

All four regimens were highly acceptable, the mean regularity being 93 % in the SHTW series, 91% in the SH/SHOW, 91% in the SHZOW and 93 % in the SHOW series.

*Punctual attendance related to duration of treatment*

The regularity with which patients attended the Centre punctually during the four quarters of the year of treatment is summarized in Table 32. In the SHTW series, the proportion of patients who attended the Centre punctually on at least 90% of the occasions was 89 % in the first quarter, 75 % in the second, 70% in the third and 63 % in the fourth quarter; the trend in these percentages is highly significant ($P < 0.00001$). The trend was less marked in the SH/SHOW ($P = 0.1$), the SHZOW ($P < 0.01$) and the SHOW series ($P < 0.01$). Considering all the three once-weekly series together, punctual attendance on at least 90 % of the occasions was noted in 82 %, 75%, 73 % and 68 % of the patients in the four quarters, respectively, the trend being highly significant ($P < 0.0001$). In summary, there was a tendency, particularly prominent in patients receiving the twice-weekly regimen, for fewer punctual attendances in the later months of treatment. However, this did not greatly affect the amount of chemotherapy received in the later months, since the patients usually came for their treatment a day or two later, either on their own or because of the efforts made by the clinic staff (see page 147).

*Patients who took their discharge against medical advice*

In all, 13 (2.7 %) of the 476 patients in the main analyses took their discharge against medical advice

TABLE 31

REGULARITY OF ATTENDANCE FOR ADMINISTRATION OF DRUGS

| Percentage of occasions on which patients attended on the appointed day (or earlier) | SHTW | | SW SHOW [a] | | SHZOW | | SHOW | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % |
| 100 | 14 | 55 | 21 | 49 | 18 | 46 | 28 | 59 |
| 96-99 | 62 | | 28 | | 30 | | 38 | |
| 90-94 | 32 | 23 | 22 | 22 | 24 | 24 | 20 | 18 |
| 80-89 | 21 | 15 | 17 | 17 | 16 | 16 | 15 | 13 |
| 70-79 | 6 | 4 | 9 | 9 | 8 | 8 | 8 | 7 |
| <70 | 3 | 2 | 4 | 4 | 5 | 5 | 3 | 3 |
| Total patients | 138 | 99 | 101 | 101 | 99 | 99 | 112 | 100 |
| Mean regularity | 93% | | 91% | | 91% | | 93% | |

[a] Excluding the first 4 weeks, during which the patients received daily chemotherapy.

TABLE 32

PERCENTAGES OF PATIENTS WHO ATTENDED ON THE APPOINTED DAY (OR EARLIER) ON AT LEAST 90% OF THE OCCASIONS

| Period (months) | Twice-weekly series | Once-weekly series | | | |
|---|---|---|---|---|---|
| | SHTW | SH/SHOW | SHZOW | SHOW | Total |
| 0–3 | 89 | 74 [a] | 83 | 88 | 82 |
| 3–6 | 75 | 73 | 75 | 78 | 75 |
| 6–9 | 70 | 70 | 70 | 79 | 73 |
| 9–12 | 63 | 65 | 66 | 72 | 68 |

[a] Excluding the first 4 weeks, during which the patients received daily chemotherapy.

during the year of treatment-namely, 5 (2 high, 3 low) of 148 SHTW, 3 (1 high, 2 low) of 106 SH/SHOW, 4 (1 high, 3 low) of 105 SHZOW and 1 (low) of 117 SHOW patients. The incidence did not appear to be influenced either by the dosage of streptomycin or the rhythm of administration of chemotherapy. Thus, it was 1.7% of 232 in high-dosage patients as compared with 3.7% of 244 in low-dosage patients (P = 0.3), and 3.4% of 148 in the twice-weekly series as compared with 2.4% of 328 in the three once-weekly series combined (P = 0.8).

Of the 13 patients who took their discharge against medical advice, 46% attended punctually on less than 75% of the occasions (before they took their discharge) as compared with only 5% of the 450 patients (see page 188) who did not, a highly significant difference (P<0.001). The mean proportion for punctual attendance was 74 % (range 30 %-94 %) for the former, as compared with 92 % (range 46 %-100%) for the latter.

### URINE TESTS FOR INGESTION OF ISONIAZID

In all, 1225 urine specimens were collected at surprise visits to patients' homes, 2-24 hours after the supervised administration of chemotherapy. Of these, 94% yielded a positive result for acetyl-isoniazid or isonicotinic acid. Thus, there was little evidence of patients not having swallowed isoniazid, when it was administered under the supervision of a nurse.

Of a total of approximately 20 500 urine specimens, collected once weekly from all the patients (at their routine visits to the clinic during the year of treatment) *prior* to the administration of drugs (that is, 3-7 days after the previous dose of drugs), 141 (0.7%) yielded a positive result for acetyl-isoniazid or isonicotinic acid. This suggests that patients did not supplement their allocated chemotherapy with isoniazid from other sources; in other words, the administration of chemotherapy in this study was, in fact, truly intermittent.

## XI. PATIENTS WITH DRUG-RESISTANT ORGANISMS ON ADMISSION TO STUDY

In all, 56 patients were excluded from the main analyses because they had drug-resistant organisms on admission. Careful questioning by the physicians prior to admission and at 3 months failed to elicit a history of more than 2 weeks of previous chemotherapy in any instance. It may therefore be presumed that all 56 patients had been *infected* with resistant organisms. Of these, 32 had isoniazid-resistant cultures and 37 streptomycin-resistant cultures, including 13 with cultures resistant to both the drugs. Thus, the incidence of primary drug resistance was 5.9% to isoniazid and 6.8% to streptomycin, including 2.4 % to both the drugs (these percentages are based on a total of 542 patients).

The response to treatment of the 56 patients with primary drug resistance is summarized below. The findings are not presented separately for the four regimens, in view of the small numbers of patients involved.

### RESISTANCE TO ISONIAZID ONLY

Of 19 patients who had organisms resistant to isoniazid only, 14 (74%) had a clear-cut bacteriological response initially, including 8 (42%) with a favourable response at 1 year (Table 33). There is some evidence that a favourable response at 1 year occurred more frequently in slow inactivators of isoniazid than in rapid inactivators (P = 0.05), and a suggestion that it occurred more frequently in patients who received the high dosage of streptomycin than in those who received the low dosage.

### RESISTANCE TO STREPTOMYCIN ONLY

Of 24 patients who had organisms resistant to streptomycin only, 22 (92 %) had a clear-cut bacteriological response initially, including 13 (54%) with a favourable response at 1 year (Table 33). Again, there is a suggestion that slow inactivators of isoniazid and patients receiving the high dosage of streptomycin had a more satisfactory response.

### RESISTANCE TO EITHER ISONIAZID OR STREPTOMYCIN

In all, there were 43 patients with primary resistance to either isoniazid or streptomycin (but not both). Of these, 36 (84%) had a clear-cut bacteriological response initially, including 21 (49%) with a favourable response at 1 year (Table 33). The proportions with a favourable response were 72% of 18 for slow inactivators of isoniazid and 33 % of 24 for rapid inactivators, a significant difference (P = 0.03), and 59 % of 27 for streptomycin high-dosage patients and 31% of 16 for low-dosage patients (P = 0.1).

RESISTANCE TO BOTH ISONIAZID AND STREPTOMYCIN

Of 13 patients with primary resistance to both isoniazid and streptomycin, 4 had a clear-cut bacteriological response initially. Of these, one had a favourable response at 1 year and another had the allocated chemotherapy terminated in the 10th month on account of persisting sputum positivity; the other two took their discharge against medical advice in the 6th and 7th month, respectively, both having had only negative cultures in the preceding 4 months (no specimens could be obtained subsequently from either patient).

In summary, a favourable response to treatment was observed in about half the patients with primary resistance to either isoniazid or streptomycin; there was some evidence that it occurred more often in slow inactivators of isoniazid than in rapid inactivators, and in streptomycin high-dosage patients than in low-dosage patients. In patients with primary resistance to both isoniazid and streptomycin, the response was almost always unfavourable. It must be emphasized, however, that these conclusions are based on small numbers of patients, and do not take into account the radiographic and bacteriological condition of the patients on admission to treatment..

## XII. DISCUSSION

The investigations reported here constitute virtually two studies, the patients in both of which were prescribed intermittent chemotherapy for a year. The first study was a concurrent controlled comparison of a twice-weekly regimen of streptomycin (1 g or 0.75 g) plus high-dosage isoniazid (15 mg/kg body-weight), the SHTW regimen, and a once-weekly regimen consisting of the same two drugs in the same dosages, the SHOW regimen. In the second controlled study, the same two regimens were investigated together with two modifications of the once-weekly regimen. One of these was the SHZOW regimen, in which high-dosage pyrazinamide (90 mg/kg body-weight) was administered at the same time as the streptomycin plus high-dosage isoniazid, making a once-weekly triple-drug regimen. The other was the SH/SHOW regimen, in which an initial *daily* phase of four weeks of streptomycin (1 g or 0.75 g) plus moderate-dosage isoniazid (400 mg) preceded the once-weekly phase of 48 weeks of streptomycin plus high-dosage isoniazid. In both studies, the regimen and the streptomycin dosage for each patient were determined by a random allocation process; further, the studies were conducted double-blind in respect of streptomycin dosage, in order to avoid the possibility of bias in the assessment of streptomycin toxicity. There was a period of overlap between the two studies, which resulted in over half the SHTW and the SHOW patients being common to them. The results of these two controlled clinical trials are considered separately when comparing therapeutic efficacies; however, for certain other aspects (for example, toxicity, acceptability), it is advantageous to consider the findings in all patients who were prescribed the same regimen, regardless of the study to which they were admitted.

In both studies, despite random allocation to treatment, there were unusually large differences between the series in the proportion of rapid inactivators of isoniazid. As the response of rapid inactivators was considerably less satisfactory than that of slow inactivators (pages 160 and 172), statistical standardization of the results was undertaken to allow for these differences, and only statistically standardized percentages have been employed when making comparisons of therapeutic effectiveness. In the event, however, the differences between the standardized and the unstandardized percentages were almost always small (for example, see Tables 9 and 15).

EFFICACY

### *Comparisons between the SHTW and SHOW regimens*

The comparisons are based on 123 SHTW and 117 SHOW patients, all of whom had a positive sputum and the majority of whom had moderate or extensive cavitation on admission. In all, 90% of the SHTW and 72% of the SHOW patients had a favourable response at 12 months ($P<0.001$), defined purely in bacteriological terms. Thus, twice-weekly chemotherapy with isoniazid plus streptomycin, even when given from the very outset of treatment, was highly effective, confirming the findings in an earlier study from this Centre (Tuberculosis Chemotherapy Centre, Madras, 1964). In contrast, the once-weekly regimen (SHOW) was substantially inferior. Even so, it is noteworthy

TABLE 33. RESPONSE TO TREATMENT OF PATIENTS WITH PRIMARY RESISTANCE TO A SINGLE DRUG

| | | Resistance to isoniazid only | | | Resistance to streptomycin only | | | Resistance to either isoniazid or streptomycin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of patients | Clear-cut bacteriological response initially | Favourable response at 1 year [a] No. | Favourable response at 1 year [a] % [b] | No. of patients | Clear-cut bacteriological response initially | Favourable response at 1 year [a] No. | Favourable response at 1 year [a] % [b] | No. of patients | Clear-cut bacteriological response initially No. | Clear-cut bacteriological response initially % [b] | Favourable response at 1 year [a] No. | Favourable response at 1 year [a] % [b] |
| Isoniazid inactivation rate | Slow | 10 | 10 | 7 | (70) | 8 | 8 | 6 | (75) | 18 | 18 | (100) | 13 | (72) |
| | Rapid | 8 | 4 | | (12) | 16 | 14 | 7 | (44) | 24 | 18 | (75) | 8 | (33) |
| Streptomycin dosage | High | 11 | 8 | 6 | (55) | 16 | 14 | 10 | (62) | 27 | 22 | 81 | 16 | 59 |
| | Low | 8 | 6 | 2 | (25) | 8 | 8 | 3 | (38) | 16 | 14 | (88) | 5 | (31) |
| Total | | 19 [c] | 14 | 8 | (42) | 24 | 22 | 13 | (54) | 43 [c] | 36 | 84 | 21 | 49 |

[a] That is, bacteriologically quiescent disease or disease of bacteriolog: .ally doubtful status.
[b] Parentheses indicate that the percentage is based on fewer than 25 observations.
[c] Including 1 patient with no isoniazid inactivation test result, who died of tuberculosis on the sixth day.

that the efficacy 'of this regimen is practically the same as that attained with daily isoniazid (as a single dose), in a dosage of 9 mg/kg body-weight (Tuberculosis Chemotherapy Centre, Madras, 1960) or in a dosage of 14 mg/kg body-weight (Tuberculosis Chemotherapy Centre, Madras, 1963b).

The inferiority of the SHOW regimen was also demonstrated by (1) the numbers of patients who died from pulmonary tuberculosis or had their allocated chemotherapy terminated on account of radiographic or serious clinical deterioration (3 SHTW, 11 SHOW), (2) the proportions of patients with considerable or exceptional radiographic improvement over the year (SHTW 76%, SHOW 60%), and (3) the proportions of patients with resistance to isoniazid (SHTW 8 %, SHOW 19%) and resistance to streptomycin (SHTW 7%, SHOW 18 %) at 1 year.

*Influence of the rate of inactivation of isoniazid and streptomycin dosage*

In the SHTW series, there was no evidence that either the rate of inactivation of isoniazid or the dosage of streptomycin influenced the response to treatment, the proportions with a favourable response being almost identical for slow and rapid inactivators and identical for streptomycin high-dosage and low-dosage patients (Table 9). In contrast, in the SHOW series, there was a substantial difference in response between the slow and the rapid inactivators of isoniazid, 82 % and 60 %, respectively, having a favourable response at 12 months ($P < 0.01$). There was also a suggestion that the dosage of streptomycin played a role, for 78 % of the patients on the high dosage and 67 % on the low dosage had a favourable response ($P = 0.2$). Further evidence of the influence of streptomycin dosage in the SHOW series is available from the pattern of the sensitivity test results during treatment (Table 17).

It may be concluded that the SHTW regimen, which consisted of a weight-adjusted dosage of isoniazid and one of two dosages of streptomycin (1 g or 0.75 g), was highly effective, and uninfluenced either by the rate of inactivation of isoniazid or by the dosage of streptomycin; these findings suggest that it can be applied with considerable confidence in populations where the patients are, on the average, heavier (the average weight of the patients in this study was 85 lb (38.6 kg)), or which contain a higher proportion of rapid inactivators of isoniazid (the proportion was approximately one-third in this study). The SHOW regimen was substantially

inferior in therapeutic efficacy, considerably influenced by the rate of inactivation of isoniazid and probably influenced by the streptomycin dosage.

*Comparisons between the SHTW, SH/SHOW, SHZOW and SHOW regimens*

The comparisons are based on 104 SHTW, 106 SH/SHOW, 105 SHZOW and 79 SHOW patients. The addition of once-weekly pyrazinamide to the SHOW regimen resulted in little improvement in the therapeutic efficacy, 74 % of the SHZOW and 68 % of the SHOW patients having a favourable response at 12 months ($P = 0.4$). On the other hand, the introduction of an *initial* daily phase of streptomycin plus moderate-dosage isoniazid for 4 weeks led to a significant increase in efficacy ($P < 0.01$), 88 % of the SH/SHOW patients having a favourable response; this proportion approaches the level of success attained with the SHTW regimen, namely 94 %.

It is noteworthy that all of 13 patients who had their allocated chemotherapy terminated on account of radiographic or serious clinical deterioration and 5 of 6 patients who died of tuberculosis had received either the SHZOW or the SHOW regimen, that is, once-weekly chemotherapy from the outset of treatment.

Other criteria of efficacy-radiographic progress and emergence of drug resistance-ranked the four regimens in the same order. Thus, over the year, considerable or exceptional radiographic improvement was shown by 79 % of the SHTW, 73 % of the SH/SHOW, 65 % of the SHZOW and 57% of the SHOW patients. Further, the proportions of patients with an isoniazid-resistant culture at 12 months were 5 %, 9%, 16% and 22%, respectively, while those with a streptomycin-resistant culture were 4%, 8 %, 16 % and 19 %, respectively.

*Influence of the rate of inactivation of isoniazid and streptomycin dosage*

In the SHTW series, the isoniazid inactivation rate was of little prognostic importance. However, in all the three once-weekly series, the slow inactivators responded significantly better than the rapid inactivators, the proportions with a favourable response being 95 % and 76 % with the SH/SHOW regimen, 87 % and 53 % with the SHZOW regimen (85% and 60% after standardization for pretreatment differences in the bacterial content of the sputum), and 76% and 56% with the SHOW regimen. Considering next the influence of streptomycin dosage, there was no evidence in the SHTW and the SHZOW series that the response of the high-dosage (1 g) patients was better than that of the low-dosage (0.75 g) patients. In the other two series, there was a suggestion of a dosage effect, the proportions with a favourable response being 74 % in the high-dosage and 63 % in the low-dosage patients in the SHOW series, and 92 % and 84 %, respectively, in the SH/SHOW series; neither difference was significant ($P \geq 0.2$). However, in the SHOW series, there was other evidence of a streptomycin dosage effect, from the pattern of the sensitivity test results during treatment (Table 17).

In conclusion, the SHTW regimen was highly effective and uninfluenced either by the rate of inactivation of isoniazid or by the dosage of streptomycin. Of the three once-weekly regimens, the SH/SHOW regimen approached it in terms of overall therapeutic efficacy; however, it was considerably influenced by the rate of inactivation of isoniazid, and possibly influenced by the streptomycin dosage. Therefore, if this regimen is applied in populations with a high proportion of rapid inactivators-for example, Eskimos (Armstrong & Peart, 1960) or Japanese (Sunahara, 1962)–the results are likely to be appreciably less satisfactory than those reported here. They might also be less satisfactory in heavier patients than those under treatment in the present study, on account of a streptomycin inadequacy. The SHZOW regimen was substantially inferior to the SHTW regimen, especially in rapid inactivators of isoniazid, and the SHOW regimen was the least effective, and was considerably influenced by the rate of inactivation of isoniazid and probably influenced by the streptomycin dosage.

A point of immediate practical importance arises from the finding of high efficacy (95%) of the SH/SHOW regimen in slow inactivators of isoniazid. This is that the regimen would be of great value, if patients could be identified both easily and speedily as slow or rapid inactivators of isoniazid and the regimen prescribed only for the slow inactivators. However, the determination of the rate of inactivation of isoniazid, whether by chemical or microbiological assay, requires a considerable degree of technical skill and cannot be readily undertaken as a routine procedure in many laboratories. A new test, the sulfadimidine test, is technically less difficult to perform, requires an examination of urine rather than blood (which is usually necessary with the other methods), and can easily and speedily be undertaken on large numbers of patients. This test, based on the work of Evans & White (1964), has been devel-

oped at this Centre by Rao et al. (1970), who have demonstrated very satisfactory agreement between the classification of patients (as slow or rapid inactivators) based on this method and that based on microbiological assay of isoniazid by a vertical diffusion method.

## FACTORS OF PROGNOSTIC IMPORTANCE

Amalgamating all the series and considering the factors usually investigated for prognostic importance, the extent of cavitation, the total extent of disease and the bacterial content in sputum on admission were all associated significantly with response, but sex, age and weight were not. The associations were more prominent with the less effective SHOW and SHZOW regimens.

Serum concentrations of streptomycin and isoniazid, and pyrazinamide also for the SHZOW patients, were determined at 1, 2, 3 and 6 hours after an appropriate dose of chemotherapy (streptomycin, 1 g or 0.75 g; isoniazid, 15 mg/kg body-weight; pyrazinamide, 90 mg/kg body-weight). Several measures (for example, highest concentration, 6-hour concentration, geometric mean) were obtained from these estimations for each patient, and related to the response to treatment. In the case of isoniazid, since it was known that the slow inactivators had responded substantially better than the rapid inactivators (page 172), the analyses were undertaken separately for the two groups. None of the measures was associated with the outcome of treatment, a finding of considerable importance in view of the recommendation made by Russell & Middlebrook (1961) that serum concentrations should be estimated and the dosages of the drugs then adjusted appropriately for each *individual* patient until a satisfactory concentration is obtained. It follows that there is a need to view more critically this approach to the chemotherapy of tuberculosis. The value of serum drug concentrations in adjusting dosage with a view to prevent drug toxicity is, however, a separate issue (page 200).

## BACTERIOLOGICAL FINDINGS DURING TREATMENT

The bacteriological findings in this study will now be summarized and the mechanisms that may explain them discussed.

### *Speed of sputum conversion*

A remarkable feature of this study was the finding that the *rates* of sputum conversion (to culture negativity) in the first 2 months of treatment were broadly similar for the four regimens (Fig. 3 and 4), despite considerable differences between them in the frequency of drug administration. It will be recalled that the latter ranged from daily administration in the first month (SH/SHOW regimen) to once-weekly administration from the outset of treatment (SHOW and SHZOW regimens). It follows, therefore, that intermittent chemotherapy was highly effective in reducing the population of viable bacilli from the outset of treatment. Next, amalgamating all four series, the speed of sputum conversion in the first 2 months was the same for slow and rapid inactivators of isoniazid, and for streptomycin high-dosage and low-dosage patients. Lastly, in patients with bacteriologically quiescent disease at 1 year, there was no evidence that persisting culture negativity had commenced earlier with the more effective regimens or in streptomycin high-dosage patients or in slow inactivators of isoniazid.

Very different findings have been obtained in experimental tuberculosis with the mouse. For instance, lung viable counts at 3 months after the start of treatment were much lower in mice receiving a daily regimen of streptomycin plus isoniazid than in those receiving a twice-weekly regimen of streptomycin plus isoniazid (Grumbach et al., 1964) or, indeed, a regimen consisting of isoniazid daily and streptomycin on alternate days (Grumbach, 1962). This discrepancy raises the possibility that in man, unlike in the mouse, the bactericidal activity of drugs is largely determined by the physiological state of the tubercle bacilli, that is, by the proportion of organisms that are actively metabolizing at the time.

### *Emergence of differences between the four series in culture results and occurrence of drug resistance*

At 3 months, clear differences emerged between the four series in the proportion of patients with a positive culture (Fig. 4). These differences persisted for the rest of the year, the proportions with a positive culture at monthly examinations during this period (4-12 months) ranging from 25 % to 31% in the SHOW, 18 % to 26% in the SHZOW, 7% to 13 % in the SH/SHOW, and 4 % to 10% in the SHTW series (Table 12). The proportion of patients with an isoniazid-resistant culture at 4-12 months ranged from 19% to 24%, 12% to 16%, 3% to 9% and 3 % to 6 % in the four series, respectively, and the proportion with a streptomycin-resistant culture from 9% to 19%, 10% to 16%, 1% to 8% and 2% to

6%, respectively (Table 13). Thus, drug resistance emerged more frequently with the less effective SHOW and SHZOW regimens. It also occurred more rapidly with these regimens; for instance, the proportions of positive cultures with resistance to isoniazid at 3 months were 47 % in the SHOW, 35 % in the SHZOW, 16% in the SH/SHOW and 10% in the SHTW series. These findings suggest that failure of chemotherapy was often associated with the emergence of drug resistance.

*Elimination of drug-sensitive organisms*

A further feature of the sensitivity test results (available from 3 months onwards) was the slower elimination of drug-sensitive organisms by the less effective SHOW and SHZOW regimens (Table 16). This is also illustrated by the finding that of 222 patients treated with the SHOW or the SHZOW regimen, 8 persistently produced isoniazid-sensitive or streptomycin-sensitive cultures even in the later months of treatment, as compared with only 1 of 254 patients treated with the SHTW or the SH/SHOW regimen. All 9 patients were very regular in receiving their supervised chemotherapy, none having missed more than one dose during the whole year. This phenomenon, namely, persistent production of sensitive cultures despite a high degree of regularity in drug-intake, has not been observed in any of 6 previous studies at this Centre, in which a total of 916 patients was treated with a daily regimen of isoniazid alone, of isoniazid plus PAS or of isoniazid plus thioacetazone (Tuberculosis Chemotherapy Centre, Madras, 1959, 1960, 1963a, 1963b, 1964, 1966).

At first sight, it seems paradoxical that, on the one hand, drug-sensitive organisms were eliminated more slowly by the less effective SHOW and SHZOW regimens, and, on the other, drug resistance emerged more frequently and more rapidly with these regimens. However, an examination of the pattern of the sensitivity test results *within* each of the four series provides some explanation.

*Pattern of sensitivity test results within each series*

With the SHOW regimen (Table 17), isoniazid-sensitive organisms were eliminated more slowly by rapid inactivators of isoniazid than by slow inactivators, indicating a relatively low efficacy of isoniazid in the former. These isoniazid-sensitive organisms must have included streptomycin-resistant mutants, which increased in number on account of multiplication of the organisms between successive once-weekly doses (see below), thereby causing the frequent and rapid emergence of streptomycin resistance. After an interval of several months, secondary resistance emerged to the first drug, namely, isoniazid. Similarly, an inadequacy of streptomycin in the low-dosage patients was indicated by a slower elimination of streptomycin-sensitive organisms, frequent and rapid emergence of isoniazid resistance and, finally, secondary resistance to streptomycin.

Employing the same method of interpretation, an isoniazid inadequacy was detected in rapid inactivators in the SHZOW series (Table 18) and in the SH/SHOW series (Table 19); however, in neither series was there any evidence of a streptomycin inadequacy in the streptomycin low-dosage patients. With the SHTW regimen (Table 20), there was no evidence of an inadequacy of either isoniazid or streptomycin, using the above method of interpretation.

*Multiplication of drug-sensitive organisms*

As indicated above, a feature of the sensitivity pattern in the three once-weekly series was the slower elimination of organisms sensitive to a drug acting with relatively low efficacy, and the frequent emergence of resistance to the companion drug. In explaining this phenomenon, it was tacitly assumed that multiplication of drug-sensitive organisms occurred between successive doses of once-weekly chemotherapy. The evidence for this assumption will now be considered.

During daily chemotherapy, intervals when drug concentrations are low exist, but even so, there is evidence, reviewed by Mitchison (1965), that multiplication of sensitive organisms ceases soon after the start of treatment. Among the lines of evidence quoted are, first, that growth of sensitive organisms has been found to be inhibited for several days following an exposure to isoniazid or streptomycin *in vitro*. Secondly, if it is really necessary for a bacteriostatic concentration of isoniazid to be present throughout the day in order to prevent growth, the efficacy of daily regimens containing isoniazid may be expected to depend on the length of time for which a bacteriostatic concentration of isoniazid is maintained, and in particular, the efficacy may be expected to be lower in rapid inactivators of the drug than in slow inactivators. However, no such relationship has been found with daily regimens of isoniazid alone; instead, the efficacy was found to be related to the peak serum concentration attained (Gangadharam et al., 1961). Further, no appreciable differences in response have been found between

slow and rapid inactivators of isoniazid treated with daily regimens, either at this Centre (Table 34) or elsewhere (Harris, 1959, 1961; Scottish Thoracic Society, 1962; see also the review by Schmidt, 1962). Thirdly, if sensitive organisms did multiply during treatment, it might be expected that some patients, even though regular in their intake of drugs, would produce sensitive cultures persistently; however, such a phenomenon has not been observed with any daily regimen at this Centre (page 196).

It is likely that the SHTW regimen, although an intermittent one, also inhibited the multiplication of drug-sensitive organisms soon after the start of treatment. In the *in vitro* experiments of Dickinson & Mitchison (1966), the maximal lag period before growth restarted was 10 days after exposure to streptomycin and 7 days after exposure to isoniazid, periods which were considerably longer than the interval of 3-4 days between successive doses of the SHTW regimen. Next, although it has been estimated that, following a dose of chemotherapy which included isoniazid 15 mg/kg body-weight, a bacteriostatic concentration of isoniazid (0.2 µg/ml) is maintained for a considerably longer period in slow inactivators of the drug than in rapid inactivators–namely, for 30 hours and for 14 hours, respectively (Tuberculosis Chemotherapy Centre, Madras, unpublished data)-there was little difference between them in their response to the SHTW regimen, either in this study (Table 9), or in an earlier one (Tuberculosis Chemotherapy Centre, Madras, 1964) in which the proportions with a favourable response were 92% of 36 for slow inactivators and 97% of 36 for rapid inactivators. Finally, of 227 patients treated with the SHTW regimen in this and the earlier study, none produced isoniazid-sensitive or streptomycin-sensitive cultures persistently, although there were 9 patients who were persistently culturepositive during the year of treatment.

In contrast, there are reasons for presuming that multiplication of sensitive organisms occurred between doses in patients who received once-weekly regimens of chemotherapy. First, the interval between the doses approached fairly closely the duration of the maximal lag induced by exposure to streptomycin (10 days) or isoniazid (7 days) in the *in vitro* experiments of Dickinson & Mitchison (1966); it is likely, therefore, that on some occasions, growth would have just restarted before the next dose of chemotherapy was administered. Secondly, unlike the experience with daily regimens and the SHTW regimen, the response of rapid inactivators of isoniazid was substantially inferior to that of slow inactivators with each of the three once-weekly regimens. (In the experiments of Dickinson & Mitchison (1966), a lag before the recommencement of growth occurred if the period of exposure to isoniazid was 24 hours or more, but did not occur if the period of exposure was 12 hours or less. This finding suggests that the multiplication of sensitive organisms between once-weekly doses of chemotherapy was greater in the rapid inactivators of isoniazid than in the slow inactivators.) Finally, unlike the experience with daily regimens and the SHTW regimen, there were 9 patients in the once-weekly series who, although extremely regular in receiving their supervised chemotherapy, persistently produced drug-sensitive cultures even in the later months of treatment.

Thus, the most likely explanation for the differences in therapeutic efficacy between the once-weekly regimens on the one hand and the twice-weekly regimen on the other is that multiplication of drug-sensitive organisms had occurred, particularly in patients with an unfavourable response, between the widely spaced doses of the once-weekly regimens, whereas no such multiplication had occurred between doses of the twice-weekly regimen. If this were so,

TABLE 34

INFLUENCE OF ISONIAZID INACTIVATION RATE ON RESPONSE TO TREATMENT WITH DAILY REGIMENS OF CHEMOTHERAPY

| Regimen | Isoniazid inactivation rate | No. of patients | Favourable response [a] | |
|---|---|---|---|---|
| | | | No. | % |
| Low-dosage isoniazid (4.5 mg/kg) | **Slow** | **46** | **22** | **48** |
| | **Rapid** | **36** | **16** | **44** |
| Moderate-dosage isoniazid (8.7 mg/kg) | Slow | 69 | 48 | 70 |
| | Rapid | 59 | 36 | 61 |
| High-dosage isoniazid (14 mg/kg) | Slow | 81 | 56 | 69 |
| | Rapid | 62 | 41 | 66 |
| Isoniazid (4.5 mg/kg) plus PAS (0.2 g/kg) | Slow | 140 | 125 | 89 |
| | Rapid | 75 | 61 | 81 |
| Isoniazid (6.9 mg/kg) plus thioacetazone (3.4 mg/kg) | Slow | 33 | 30 | 79 |
| | Rapid | 27 | 23 | 35 |

[a] That is, bacteriologically quiescent disease or disease of bacteriologically doubtful status at 1 year.

the SHOW regimen would be inferior to the SHTW regimen because the multiplication of sensitive organisms would frequently produce large numbers of resistant mutants, or occasionally result in the persistence of sensitive cultures. The substantial superiority of the SH/SHOW regimen over the SHOW regimen suggests that once the growth of sensitive organisms had been halted by the initial phase of *daily* chemotherapy, their further growth during the once-weekly phase was relatively small and much delayed. It is of interest that of 12 SH/SHOW patients who had an unfavourable response, 6 had a sputum conversion to culture negativity followed by a bacteriological relapse during the year of treatment (Table 15), as compared with 4 of 26 in the SHOW series (none of the 10 patients who had a relapse was irregular in drug-intake, all having received more than 95% of the allocated chemotherapy).

In view of the evidence from 3 months onwards that the elimination of drug-sensitive organisms occurred more slowly with the less effective regimens, the finding that the rates of sputum conversion in the first 2 months of treatment were broadly similar for the 4 regimens may seem surprising. In this context, it may be noted that with the once-weekly regimens, the majority of patients who were culture-positive at 1 and 2 months eventually had a *favourable* response. In these patients, as well as in others who had a favourable response, it is likely that little multiplication of drug-sensitive organisms had occurred between successive doses of chemotherapy, and consequently the bactericidal activity of streptomycin and isoniazid was not adversely affected by the fact that the rhythm of administration was once weekly. On the other hand, the patients who remained positive from the third month onwards were mainly those with an eventual *unfavourable* response. In these patients, multiplication of drug-sensitive organisms had probably occurred to a greater extent between successive doses, the result being a slower elimination of sensitive organisms and the emergence of drug resistance.

It is likely that early tuberculous death and early serious clinical deterioration, which occurred predominantly in the SHOW and the SHZOW series, were caused by multiplication of sensitive organisms to a considerable extent, particularly in the first few weeks of treatment. It follows, therefore, that a short initial course of daily chemotherapy would be valuable because it would halt the multiplication of sensitive organisms in the early stages of treatment.

*Role of pyrazinamide in the SHZOW regimen*

The addition of once-weekly pyrazinamide to the SHOW regimen appeared to have compensated for a streptomycin deficiency in patients receiving the lower dosage (0.75 g) of streptomycin but not for an isoniazid deficiency in the rapid inactivators of isoniazid (Tables 17 and 18). In consequence, the efficacy of the SHZOW regimen was unaffected by the dosage of streptomycin (1 g or 0.75 g), but was considerably higher in the slow inactivators of isoniazid than in the rapid inactivators. A possible explanation for these findings is offered below.

Streptomycin is more active at an alkaline pH than at an acid pH (Waksman et al., 1944; Mitchison & Spicer, 1949), pyrazinamide is active only at a very acid pH (McDermott & Tompsett, 1954; Wasz-Höckert et al., 1956) and the activity of isoniazid is little affected by pH (Mitchison, 1952). Therefore, it is possible that, with the SHOW regimen, the lowering of the streptomycin dosage to 0.75 g reduced the activity of the drug on organisms growing in an acid environment (mainly intracellularly) to a greater extent than on those growing under more alkaline conditions (mainly extracellularly and in caseous material). In these circumstances, isoniazid-resistant mutants present in the intracellular acid environment would grow better in patients receiving the lower dosage of streptomycin, resulting eventually in a lowered efficacy of the regimen. In such a situation, the addition of pyrazinamide would inhibit the growth of the isoniazid-resistant mutants, thereby compensating for the streptomycin deficiency in the low-dosage patients.

In contrast, the growth of streptomycin-resistant mutants (this would be greater in rapid inactivators of isoniazid) would be only marginally affected by the addition of pyrazinamide, since this drug is active only at a very acid pH, and there is evidence suggesting that the proportion of organisms in an acid environment is relatively small (see below). Consequently, the difference in response between slow and rapid inactivators of isoniazid would not alter appreciably due to the addition of pyrazinamide to the SHOW regimen.

Finally, although the SHZOW patients received a high dosage (90 mg/kg body-weight) of pyrazinamide, only 5 (24%) of 21 patients with bacteriologically active disease at one year showed clear-cut evidence of the emergence of pyrazinamide resistance. Also, it has been demonstrated that, *at acid pH levels*, even a short exposure to pyrazinamide can produce a lag in the growth of tubercle bacilli that

can last for at least 1 week (Mitchison, paper in preparation), so that multiplication of sensitive organisms between successive doses would be very limited, Taken together, these findings suggest that the proportion of organisms present in an acid environment in the lesions was small, in which case it is not surprising that the efficacy of the SHZOW regimen was not appreciably higher than that of the SHOW regimen.

*Relative efficacies of streptomycin and isoniazid*

In order to develop intermittent regimens further on a logical basis, it would be useful to examine the causes for unfavourable response with the regimens in the present study.

The response to the SHTW regimen was highly satisfactory, and similar in slow and rapid inactivators of isoniazid and in patients receiving high and low dosages of streptomycin. Even so, an examination of the causes of failure in the few patients who had an unfavourable response showed that the streptomycin susceptibility of the pretreatment strains tended to be lower for these patients than for those who had a favourable response (Table 24). No such association was, however, present with isoniazid susceptibility. (Consistent variations in susceptibility to streptomycin and isoniazid have been demonstrated in pretreatment 'sensitive' strains from British patients (Lefford et al., 1966) and Madras patients (Tuberculosis Chemotherapy Centre, Madras, unpublished data).) These findings suggest that the few instances of failure of the SHTW regimen were due more to a failure of streptomycin than of isoniazid.

The response to each of the three once-weekly regimens was substantially inferior in the rapid inactivators of isoniazid than in the slow inactivators. Even so, no association was found between isoniazid susceptibility of the pretreatment strains and response to treatment. It may therefore be concluded that the relatively poor response in the rapid inactivators was due more to multiplication of isoniazid-sensitive organisms between doses than to variations in isoniazid susceptibility of the pretreatment strains. Considering next the influence of streptomycin dosage, there was some evidence of a dosage effect in the SHOW series (Tables 9 & 17), and a suggestion of such an effect in the SH/SHOW series (Table 15). In both the series, however, the influence of streptomycin dosage was considerably less than that of the rate of inactivation of isoniazid. Finally, in the SHZOW series, there was no evidence of a streptomycin-dosage effect (Tables 15 & 18).

A consideration of the sequence of emergence of drug resistance in patients with an unfavourable response at 1 year suggested that a deficiency of isoniazid was a more important cause of failure with the three once-weekly regimens than with the twice-weekly regimen. Thus, streptomycin resistance emerged first, indicating a relative failure of isoniazid, in 36% of 28 SHOW patients, 30 % of 20 SHZOW and 30% of 10 SH/SHOW patients as compared with 0% of 8 SHTW patients. However, the failure of isoniazid in the once-weekly regimens was largely in rapid inactivators of isoniazid (Tables 17, 18 and 19). In this context, it is of interest that Dickinson et al. (1968) found, in experimental tuberculosis of the guinea-pig, that an increase in the interval between successive doses from 4 days to 8 days resulted in a larger decline in the efficacy of isoniazid than in that of streptomycin. The dosages employed in these experiments included some which yielded serum concentrations similar to those obtained in the treatment of tuberculous patients; furthermore, the half-life of isoniazid in the guinea-pig was fairly similar to that of human rapid inactivators of the drug.

In conclusion, the few instances of failure of the SHTW regimen were due more to a failure of streptomycin than of isoniazid. The addition of a third drug-for instance, pyrazinamide, since it appeared to compensate for a streptomycin deficiency in streptomycin low-dosage patients (Tables 17 and 18)–might eliminate most, or even all, of these failures. Alternatively, since the pattern of sensitivity test results suggested that there was an inadequacy of streptomycin in SHOW patients who received the low dosage of the drug (Table 17) but not in the corresponding SH/SHOW patients (Table 19), an initial phase of daily chemotherapy with streptomycin (1 g) plus moderate-dosage isoniazid (400 mg) might be prescribed for 4 weeks prior to starting treatment with the SHTW regimen. In the three once-weekly regimens, isoniazid appeared to be the more deficient drug. However, should it prove possible to increase the efficacy of isoniazid in rapid inactivators of the drug, then streptomycin is likely to be the more deficient drug. There appear to be, therefore, two stages in the process for strengthening once-weekly regimens. The first is to increase the efficacy of isoniazid in rapid inactivators by providing more sustained serum concentrations; this might be achieved by an

increase in the dosage of isoniazid or by the addition of PAS [1] (which also might enhance serum isoniazid concentrations-see Gangadharam et al., 1961) or by the use of a slow-release preparation of isoniazid in which absorption from the gut would be prolonged. The second is to replace streptomycin with a drug that might be even more potent in intermittent chemotherapy, for example, ethambutol (Dickinson et al., 1968) or rifampicin (Dickinson, 1969), or to add an appropriate third drug (for example, pyrazinamide, as indicated above) to the regimen.

## TOXICITY

### *Streptomycin*

The study was conducted double-blind in respect of streptomycin dosage-that is, neither the physicians nor the patients knew whether an individual patient received the high dosage (1 g) or the low dosage (0.75 g) of streptomycin. In all, 7 (3.0% of 232 high-dosage patients and 3 (1.2%) of 244 low-dosage patients had a reduction in streptomycin dosage or took their discharge on account of giddiness (P = 0.3); in 2 of the high-dosage patients, the giddiness persisted despite the reduction and the streptomycin had to be stopped. There was a suggestion that the incidence was slightly higher in the SHTW (3%) and the SH/SHOW (4%) series than in the SHZOW (1%) and the SHOW (1%) series. Finally, there was a significant association between age and the incidence, the latter being 0% of 119 for patients aged under 25 years, 1.3 % of 155 for those aged 25-34 years and 4.0 % of 202 for those aged 35 years or more (P = 0.01). A similar association has been reported with daily streptomycin by Johnston et al. (1964).

Minor complaints (mainly giddiness), not requiring a reduction in streptomycin dosage, were made by 74 (16%) patients; the incidence was *not* influenced by the age of the patient, the dosage of streptomycin or the regimen.

Considering the influence of serum streptomycin concentrations on toxicity, reduction in dosage or cessation of streptomycin became necessary significantly more frequently in patients with higher concentrations; for instance, the proportions were 0 % of 78, 1% of 94, 3 % of 133 and 5 % of 86 in patients with (geometric) mean concentrations of less than 25 µg/ml, 25 µg/ml- 31 µg/ml, 32 µg/ml-39 µg/ml and 40 µg/ml or more, respectively (P = 0.01). However, patients who had minor complaints of streptomycin toxicity had concentrations similar to those who had no complaints.

As regards impairment of vestibular function, the *over-all* change between the commencement and the end of the year of treatment in the duration of nystagmus after the rotatingchair test was not influenced either by the streptomycin dosage or by the chemotherapeutic regimen. However, patients who complained twice of giddiness and those who had a reduction in streptomycin dosage on account of giddiness had impaired vestibular function at the time, as demonstrated by a significantly lowered duration of nystagmus.

### *Isoniazid*

No patient had the allocated chemotherapy terminated on account of isoniazid toxicity. However, toxicity which did not require a modification of the allocated chemotherapy occurred in 16 (3.4%) patients, despite the administration of 6 mg of pyridoxine with every dose of isoniazid. This tiding suggests that the dosage of pyridoxine was probably inadequate; however, it should be noted that even a high dosage may not be able to prevent toxicity in all patients (Past African/British Medical Research Council Isoniazid Investigation, 1960).

The incidence of toxicity was similar in the four series,–namely, 4% in the SHTW, 4% in the SH/SHOW, 2% in the SHZOW and 3% in the SHOW series. It was significantly higher (P = 0.01) in slow inactivators of isoniazid (5.0% of 299) than in rapid inactivators (0.6 % of 177), suggesting that the toxicity was due, in fact, to the isoniazid (among the slow inactivators, however, there was little evidence that it was higher in the patients with higher serum isoniazid concentrations). Similar associations have been reported with daily moderate-dosage (9 mg/kg body-weight) isoniazid (Devadatta et al., 1960) and daily high-dosage (14 mg/kg body-. weight) isoniazid (Tuberculosis Chemotherapy Centre, Madras, 1963b).

Considering the details of isoniazid toxicity, 3 patients (all slow inactivators) had convulsions, 2 on a single occasion and the third on 2 occasions. Loss of consciousness on a single occasion occurred in 3 other patients (2 slow, 1 rapid); it was uncertain whether the patients had had a convulsion or had fainted. One of these (rapid) complained of paraesthesia in the limbs, as did 10 others (all slow).

[1] A subsequent controlled study at this Centre has shown that neither an increase in the dosage of isoniazid nor the addition of PAS improves the efficacy of the SH/SHOW regimen in rapid inactivators of isoniazid.

*Pyrazinamide*

Of 105 patients treated with the SHZOW regimen (it may be recalled that the individual dose of pyrazinamide was very high–namely 90 mg/kg body-weight), 5 complained of joint pains and 2 had jaundice; there is suggestive evidence (page 187) that 1 of the latter was incubating infective hepatitis on admission. Routine liver function tests (SGOT, SGPT activity) and urine tests for urobilinogen were undertaken on all the patients and did not reveal any evidence of hepatic damage.

## ACCEPTABILITY

In an earlier study (Tuberculosis Chemotherapy Centre, Madras, 1964), 9% of 79 SHTW patients (all of whom received 1 g of streptomycin) took their discharge against medical advice as compared with 1% of 71 patients who received a standard daily regimen of isoniazid plus PAS; this tiding raised the possibility that undetected side-effects due to streptomycin might have resulted in the greater degree of non-cooperation with the SHTW regimen. However, in the present study, the corresponding proportions for the SHTW regimen were 2 (3%) of 71 among the patients who received 1 g of streptomycin and 3 (4%) of 77 among the patients who received 0.75 g, findings which suggest that toxicity to streptomycin is unlikely to have been an important cause for non-cooperation.

In all, 3.4% of 148 patients in the twice-weekly series took their discharge against medical advice as compared with 2.4% of 328 patients in the three once-weekly series combined (P = 0.8). Further, among the remaining patients, all four regimens were acceptable to a high and similar extent, the mean proportion of punctual attendances (that is, attendances on the appointed day or earlier) being 93 % in the SHTW, 91% in the SH/SHOW, 91% in the SHZOW and 93% in the SHOW series (it may be recalled that the scheduled numbers of attendances in a year were 104, 72, 52 and 52 in the four series, respectively). However, in all four series, there was a tendency for fewer punctual attendances in the later months of treatment.

It must be noted that the patients in this study had to attend the clinic from distances of up to 5 miles (8 km), not infrequently on foot, in a hot humid tropical climate. However, they were selected initially as being co-operative and were well indoctrinated on the importance of regular drug-intake; furthermore, facilities at this Centre for retrieving defaulters are very good. Under field conditions, indoctrination is likely to be leas intense and facilities would not be so good. Therefore, the aim should be to decentralize the actual administration of the supervised chemotherapy to sub-clinics, dispensaries and injection centres, so that the patient can receive his chemotherapy at or near his home or place of work or *en route* between them.

If regular contact with the staff of a clinic can motivate patients (as is often supposed), it is possible that the frequent attendance for supervised administration of chemotherapy would be self-perpetuating, thereby reducing the occurrence of default.

## PRIMARY DRUG RESISTANCE

The incidence of primary drug resistance, based on a total of 542 patients, was 5.9 % to isoniazid and 6.8% to streptomycin, including resistance to both drugs in 2.4 %.

An interesting finding in this study, in view of the fact that all the patients received intermittent chemotherapy, is that 36 (84%) of 43 patients with primary resistance to either isoniazid or streptomycin (but not both) had a clear-cut bacteriological response initially, including 21 (49%) with a favourable response at 1 year. The proportions with a favourable response at 1 year were 72 % of 18 for slow inactivators of isoniazid and 33% of 24 for rapid inactivators, a significant difference (P=0.03), and 59% of 27 for streptomycin high-dosage patients and 31% of 16 for low-dosage patients (P=0.1).

Patients with primary resistance to both isoniazid and streptomycin had a relatively bad prognosis, for only 4 (31%) of 13 had a clear-cut bacteriological response initially, including 1 with a favourable response at 1 year and 2 who took their discharge against medical advice.

It may be concluded that, even when chemotherapy is administered intermittently, primary drug resistance to either isoniazid or streptomycin does not automatically imply that the response to treatment will be unfavourable. A similar conclusion was reached with respect to primary isoniazid resistance in patients treated with daily regimens of isoniazid alone or isoniazid plus PAS (Devadatta et al., 1961; Tripathy et al., 1969).

## XIII. CONCLUSIONS

An intermittent regimen of isoniazid (14 mg/kg-15 mg/kg body-weight) plus streptomycin (1 g), both drugs being administered twice weekly (at the same time) from the very outset of treatment to newly diagnosed tuberculous patients with cavitated disease and drug-sensitive cultures, has been demonstrated to be highly effective in this study as well as in an earlier one (Tuberculosis Chemotherapy Centre, Madras, 1964). The efficacy of this regimen was unaffected by lowering the streptomycin dosage from 1.0 g to 0.75 g. Also, the efficacy was very similar in slow and rapid inactivators of isoniazid. These findings suggest that the regimen is likely to be highly effective even in populations with heavier patients and higher proportions of rapid inactivators of isoniazid. Finally, bacteriological quiescence attained with this regimen has been demonstrated to be at least as stable over a 4-year period of follow-up as that attained with a standard daily regimen of isoniazid plus PAS (Ramakrishnan et al., 1969).

Several other groups of workers have reported favourably on the twice-weekly regimen, nearly all having used it after an initial period of daily chemotherapy (Dawson, 1966; Chaulet et al., 1968; Sbarbaro & Johnson, 1967; International Union Against Tuberculosis [1]; Polansky [2]). It may therefore be concluded that the twice-weekly regimen of streptomycin plus high-dosage isoniazid is no longer an experimental regimen but is of established value in the primary treatment of tuberculosis.

A regimen consisting of daily chemotherapy for 4 weeks with isoniazid 400 mg plus streptomycin 1 g followed by once-weekly chemotherapy for the rest of the year with isoniazid 15 mg/kg body-weight plus streptomycin 1g approached closely the twice-weekly regimen in terms of over-all therapeutic efficacy but, unlike the twice-weekly regimen, it was considerably less effective in rapid inactivators of isoniazid than in slow inactivators. If a method of compensating for this deficiency can be found, the prospects for evolving a highly effective once-weekly regimen, as a valuable alternative to the twice-weekly regimen, are excellent.

[1] International Union Against Tuberculosis (1969) *A controlled trial of three regimens of self-administered and supervised chemotherapy for pulmonary tuberculosis.* Paper presented to the Twentieth International Tuberculosis Conference, New York, September, 1969.

[2] Polansky, F. (1969) *Study of sanatorium treatment including a comparison of standard and intermittent continuation chemotherapy.* Paper presented to the Twentieth International Tuberculosis Conference, New York, September, 1969.

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## RÉSUMÉ

### ÉTUDE COMPARATIVE CONTRÔLÉE D'UN SCHEMA COMPORTANT UNE PRLSE BIHEBDOMADAIRE DE MÉDICAMENTS ET DE TROIS SCHÉMAS COMPORTANT UNE PRISE HEBDOMADAIRE DANS LE TRAITEMENT INITIAL DE LA TUBERCULOSE PULMONAIRE

On a traité 554 patients atteints de tuberculose pulmonaire par chimiothérapie intermittente pendant un an, en utilisant 4 schémas de cure ambulatoire: *a)* schema SHTW: streptomycine (1 g ou 0,75 g) et isoniazide (15 mg/kg de poids corporel) donnés simultanément deux fois par semaine; *b)* schema SHOW: streptomycine (1 g ou 0,75 g) et isoniazide (15 mg/kg) donnés simultanément une fois par semaine; *c)* schéma SHZOW: streptomycine (1 g ou 0,75 g), isoniazide (15 mg/kg) et pyrazinamide 90 mg/kg) donnés simultanément une

fois par semaine; *d)* schéma SH/SHOW: streptomycine (1 g ou 0,75 g) et isoniazide (400 mg) donnés quotidiennement pendant 4 semaines, puis streptomycine (1 g ou 0,75 g) et isoniazide (15 mg/kg) administrés simultanément une fois par semaine. Tous les malades ont reçu 6 mg de pyridoxine avec chaque dose d'isoniazide pour prévenir les effets toxiques secondaires de ce dernier produit.

Chaque patient s'est vu assigner un schéma de traitement et un dosage de streptomycine (1 g ou 0,75 g) par repartition aléatoire; le double anonymat a été respecté en ce qui conceme les doses de streptomycine.

L'étude a comporté trois phases. Au cours de la premiere, on a administré l'un des schémas SHTW ou SHOW à 106 malades; au cours de la deuxième, les quatre schémas ont été utilisés (364 malades); enfin, dans un troisième temps, 84 malades ont reçu l'un des schémas SHTW, SHZOW ou SH/SHOW.

L'analyse a porté essentiellement sur 476 malades qui, au debut du traitement, présentaient des cultures sensibles à l'isoniazide et à la streptomycine. La grande majorité d'entre eux (93%) n'avait jamais bénéficié de la chimiothérapie, les autres n'y ayant été soumis que pendant 2 semaines au maximum. Lors de la mise en traitement, 83 % des malades étaient porteurs de lesions cavitaires moyennes ou étendues, 72% étaient modérément, fortement ou très fortement atteints et 89% avaient été recormus positifs à l'examen direct du premier échantillon de crachats. On comptait parmi les malades près de deux tiers d'inactivateurs lents de l'isoniazide et un tiers d'inactivateurs rapides.

L'efficacité respective des schémas SHTW et SHOW a été comparée chez les patients traités dans les 1re et 2e phases; celle des quatre schémas l'a été chez les malades inclus dans les 2e et 3e phases. Au debut du traite ment, les données cliniques, radiographiques et bactériologiques étaient en général semblables pour les patients appartenant aux différentes series, et dans chaque série pour les sujets traités par la streptomycine à forte ou faible dose ainsi que pour les inactivateurs lents ou rapides de l'isoniazide. On relevait cependant deux exceptions: *a)* la proportion des inactivateurs rapides était notablement plus élevée dans la série SHOW et *b)* dans la série SHZOW, les inactivateurs rapides excrétaient un nombre nettement plus élevé de bacilles que les inactivateurs lents. On s'est efforcé par une normalisation statistique de tenir compte de ces différences.

L'étude comparative de 123 malades SHTW et de 117 malades SHOW traités aux 1re et 2e phases permet un certain nombre de constatations. Durant l'année, 4 malades (1 SHTW et 3 SHOW) sont morts de tuberculose pulmonaire, et 10 (2 SHTW et 8 SHOW) ont dû cesser le traitement par suite d'une aggravation des signes radiologiques ou d'une deterioration sérieuse de l'état de santé. Après un an, 90% des malades SHTW et 72% des malades SHOW ont été considérés comme ayant réagi favorablement au traitement sur la base des résultats des cultures des 10e, 11e et 12e mois. Durant l'année, on a noté une amelioration considérable ou exceptionnelle des signes radiographiques chez 76% des malades SHTW et 60% des malades SHOW, avec dans respectivement 48% et 43% des cas disparition des cavernes. Une resistance à l'isoniazide est apparue chez 4% des malades SHTW et 17% des malades SHOW après 3 mois, chez 6% et 16% d'entre eux après 6 mois et chez 8% et 19% après 12 mois. En ce qui regarde la resistance à la streptomycine, les chiffres correspondants ont été de 0% et 3 % au 3e mois, de 6% et 10% au 6e mois et de 7% et 18% au 12e mois.

La comparaison des résultats obtenus après emploi de doses fortes ou faibles de streptomycine chez les malades SHTW et SHOW traités aux 1re et 2e phases fait ressortir des taux de reactions favorables après un an de 90 % (doses élevées) et de 90 % (doses faibles) dans la série SHTW et de 78% et 67% dans la série SHOW. Pendant l'année, des proportions similaires de malades traités à fortes ou à faibles doses, dans chaque série, ont présenté une amelioration considérable ou exceptionnelle des signes radiographiques.

Une comparaison portant sur les inactivateurs lents et rapides de l'isoniazide des séries SHTW et SHOW traités aux 1re et 2e phases a montré que la proportion des patients réagissant favorablement au traitement après un an était de 92 % chez les inactivateurs lents et de 91% chez les inactivateurs rapides dans la série SHTW contrastant avec une proportion de 82% et 60% respectivement dans la série SHOW. Au cours de l'année, la proportion des améliorations radiographiques notables ou exceptionnelles a été du même ordre parmi les inactivateurs lents ou rapides dans chaque série.

L'étude comparative de 104 malades SHTW, de 106 malades SH/SHOW, de 105 malades SHZOW et de 79 malades SHOW traités aux 2e et 3e phases révèle un certain nombre de faits. Durant l'année, 6 malades (1 SHTW, 2 SHZOW et 3 SHOW) sont morts de tuberculose pulmonaire et 13 (7 SHZOW et 6 SHOW) ont dû interrompre le traitement en raison d'une aggravation des signes radiologiques ou d'une deterioration notable de l'état général. Après un an, 94% des malades SHTW, 88 % des malades SH/SHOW, 74 % des malades SHZOW et 68% des malades SHOW ont été considérés comme ayant réagi favorablement au traitement d'après les résultats des cultures des 10e, 11e et 12e mois. Pendant l'année, on a constaté une amelioration nette ou exceptionnelle des signes radiographiques chez 79% des malades SHTW, 73 % des malades SH/SHOW, 65 % des malades SHZOW et 57% des malades SHOW, avec disparition des cavernes dans respectivement 48 %, 43 %, 29 % et 45% des cas. Une resistance à l'isoniazide est apparue au 3e mois chez 2 % des malades SHTW, 3 % des malades SH/SHOW, 11% des malades SHZOW et 19 % des malades SHOW; au 6e mois, les proportions correspondantes étaient de 5 %, 5 %, 12 % et 20 % et au 12e mois, de 5 %, 9%, 16% et 22%. Pour ce qui est de la resistance à la streptomycine, les chiffres ont été au 3e mois de 0 % (SHTW), 2 % (SH/SHOW), 6 % (SHZOW)

et 5% (SHOW), au 6e mois de 4%, 2%, 10% et 11%, et au 12e mois de 4%, 8%, 16% et 19%.

La comparaison des résultats obtenus après emploi de doses faibles ou fortes de streptomycine chez les malades SHOW, SH/SHOW, SHZOW et SHOW traités aux 2e et 3e phases révèle une proportion de reactions favorables après un an de 93% pour les doses élevées et de 95% pour les doses faibles dans la série SHTW, de 92% et 84% dam la série SH/SHOW, de 70 % et 78 % dans la série SHZOW et de 74 % et 63 % dans la série SHOW. Pendant l'année, des proportions similaires de malades traités par des doses fortes ou faibles, dans chaque série, ont présenté une amelioration importante ou exceptionnelle des signes radiologiques.

Lorsque la comparaison a porté sur les inactivateurs lents ou rapides de l'isoniazide, pour l'ensemble des malades des series SHTW, SH/SHOW, SHZOW et SHOW traités aux 2e et 3e phases, la proportion des patients réagissant favorablement au traitement après un an a été de 97 % (inactivateurs lents) et de 91% (inactivateurs rapides) dans la série SHTW, de 95 % et 76 % dans la série SH/SHOW, de 85 % et 60 % dans la série SHZOW et de 76% et 56 % dans la série SHOW. Au cows de l'année, on a noté une proportion similaire d'améliorations notables ou exceptionnelles des signes radiographiques parmi les inactivateurs lents ou rapides dans chaque série.

Au cours des deux premiers mois de traitement, les taux de négativation de l'expectoration ont été dans l'ensemble similaires dans les séries SHTW, SH/SHOW, SHZOW et SHOW, en dépit de fortes differences dans la fréquence d'administration des médicaments. En outre, chez les patients présentant après un an une affection bactériologiquement non évolutive rien n'indique que la négativation soit survenue plus tôt chez ceux qui recevaient les traitements les plus actifs, ou chez ceux qui recevaient de fortes doses de streptomycine, ou encore chez les inactivateurs lents de l'isoniazide.

Dans la série SHOW, un manque de streptomycine chez les patients traités par de faibles doses (0,75 g) s'est manifesté par une élimination plus lente des germes sensibles à partir du 3e mois et par une incapacité relative d'empêcher l'apparition de la resistance à l'isoniazide et, par la suite, de la resistance secondaire à la streptomycine. De même, chez les inactivateurs rapides de l'isoniazide, la carence en ce produit s'est traduite par une élimination plus lente des bacilles sensibles à l'isoniazide et par une impuissance relative à empêcher le développement de la resistance à la streptomycine, puis de la résistance à l'isoniazide.

Si l'on analyse de la même manière les résultats des épreuves de sensibilité, on ne relève dans les séries SHZOW, SH/SHOW et SHTW aucun signe d'une carence en streptomycine chez les patients traités par de faibles doses (0,75 g). Quant au manque d'isoniazide, il est trés apparent chez les inactivateurs rapides dans les series SHZOW et SH/SHOW, mais non dans la série SHTW.

Chez 9 malades, dont aucun n'avait négligé de prendre sa dose de médicament à plus d'une reprise, les cultures se sont révélées constamment sensibles à l'isoniazide et à la streptomycine, même pendant les derniers mois du traitement. Huit d'entre eux (6 SHZOW, 2 SHOW) avaient été traités par chimothérapie hebdomadaire dès le debut et le 9e (SH/SHOW) dès la 4e semaine du traitement.

Sur 21 malades SHZOW atteints d'une affection bactériologiquement évolutive après un an, 5 (24%) montraient des signes évidents d'apparition d'une resistance à la pyrazinamide, ce qui correspond à une incidence de 5 % pour l'ensemble des 105 malades de la série.

Les différences notées entre malades sous le rapport des concentrations sériques de streptomycine et de pyrazinamide n'ont eu que peu d'influence sur la réponse au traitement. Néanmoins, on a été beaucoup plus fréquemment amené à réduire les doses de streptomycine ou à interrompre le traitement (en raison de vertiges) chez les malades présentant des concentrations sériques de streptomycine élevées. Les differences entre les taux sériques d'isoniazide chez lea inactivateurs lents et chez les inactivateurs rapides n'ont pas eu d'action appreciable sur les résultats du traitement et l'apparition de reactions toxiques.

L'étendue des lésions cavitaires, la gravité globale de la maladie et la richesse en bacilles de l'expectoration lors de la prise en charge du malade ont eu une influence nette sur la réponse au traitement. Cette influence a été très perceptible chez les malades recevant les schémas les moins actifs, SHZOW et SHOW.

Il semble que, dans la série SHTW notamment, les souches initialement sensibles à la streptomycine l'étaient dans une mesure moindre chez les malades qui n'ont guère bénéficié du traitement que chez ceux qui y ont réagi favorablement. Une telle difference de sensibilité n'a pas été retrouvée pour les souches sensibles à l'isoniazide avant le traitement.

Les effets toxiques de la streptomycine ont amené à réduire les doses du médicament ou à le supprimer chez 10 malades (2,1%). La fréquence de, ces reactions a atteint 3 % (sur 148 malades) dans la série SHOW, 4 % (sur 106) darts la série SH/SHOW, 1% (sur 105) dans la série SHZOW et 1% (sur 117) dans la série SHOW; elle a été de 3,0% chez 232 malades traités par de fortes doses (1 g) et de 1,2% chez 244 malades recevant de faibles doses (0,75 g). L'étude du nystagmus provoqué (épreuve rotatoire) a permis de déceler une atteinte de la fonction vestibulaire chez les malades qui, par suite de vertiges, avaient vu leur traitement par la streptomycine réduit ou supprimé, ainsi que chez ceux qui s'étaient plaint de ces symptômes à deux reprises.

Des effets toxiques dus à l'isoniazide, qui n'ont pas contraint à modifier les doses prescrites, ont été observes chez 16 malades (3,4%) malgré l'administration concomitante de 6 mg de pyridoxine. Leur fréquence a été de 4% dans les séries SHTW et SH/SHOW, de 2% dans la série SHZOW et de 3 % dans la série SHOW; ils se sont manifestés chez 5% des 299 inactivateurs lents et chez

0,6% des 177 inactivateurs rapides. Sur les 16 malades, 3 (1 SHTW, 1 SH/SHOW et 1 SHOW) ont présenté des convulsions et 3 autres (1 SHTW, 1 SH/SHOW et 1 SHOW) ont perdu connaissance à une occasion.

La pyrazinamide n'a posé aucun problème de toxicité. Les mesures systématiques des taux des transaminases sériques et de l'urobilinogène urinaire n'ont mis en évidence aucun trouble de la fonction hépatique chez les malades de la série SHZOW.

Au total, 13 malades (2,7%) ont abandonné le traitement au cours de l'année, malgré l'avis contraire de l'autorité medicale. On comptait parmi eux 5 malades SHTW (sur 148), 3 SH/SHOW (sur 106), 4 SHZOW (sur 105) et 1 SHOW (sur 117). Le taux moyen d'assiduité de ceux qui se sont présenté au jour fixé (ou plus tôt) au centre de traitement a été de 93% (series SHTW et SHOW) et de 91% (series SH/SHOW et SHZOW).

Du point de vue bactériologique, de bons résultats ont été obtenus imtialement chez 14 malades, sur 19, présentant une resistance primaire à l'isoniazide uniquement, et chez 22 malades, sur 24, porteurs de bacilles uniquement résistants à la streptomycine. Dans 43 cas de résistance primaire à l'un ou l'autre médicament, 21 reactions favorables (49%) ont été notées après un an. Les taux de réponses favorables ont atteint 72 % chez 18 inactivateurs lents de l'isoniazide et 33 % chez 24 inactivateurs rapides (les resultats de l'épreuves d'inactivation faisant défaut dans un cas), 59% chez 27 malades recevant des doses élevées de streptomycine et 31% chez 16 malades traités par de faibles doses. Sur 13 malades présentant une resistance primaire double à l'isoniazide et à la streptomycine, 4 ont réagi au debut du traitement d'une façon nettement favorable du point du vue bactériologique, ces résultats se maintenant dans 1 cas après un an.

Cette étude confirme qu'administré sous contrôle strict un schéma bihebdomadaire associant l'isoniazide à forte dose (14-15 mg/kg) a la streptomycine (1 g) pendant un an permet de traiter très efficacement les patients atteints de tuberculose pulmonaire récemment diagnostiquée et porteurs de bacilles sensibles aux médicaments. Cette efficacité n'est pas influencée par le taux d'inactivation de l'isoniazide ou par une reduction du dosage de la streptomycine à 0,75 g. Un schéma comportant l'administration quotidienne d'isoniazide à doses modérées (400 mg) et de streptomycine (1 g) pendant les quatre premières semaines, puis la chimiothérapie hebdomadaire par l'isoniazide à forte dose (15 mg/kg) et la streptomycine (1 g) pendant le reste de l'année donne des résultats tout aussi favorables que le traitement bihebdomadaire chez les inactivateurs lents, mais se révele beaucoup moins actif chez les inactivateurs rapides.

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