Controlled Comparison of Oral Twice-weekly and Oral Daily Isoniazid plus PAS in Newly Diagnosed Pulmonary Tuberculosis

Tuberculosis Chemotherapy Centre, Madras

Summary

A controlled clinical trial was undertaken in 247 patients with newly diagnosed pulmonary tuberculosis to assess the relative efficacies of a fully supervised twice-weekly oral regimen of isoniazid plus PAS (para-aminosalicylic acid) and a standard self-administered daily regimen of the same drugs following an initial intensive phase of two weeks of daily streptomycin, PAS, and isoniazid. Among patients who had isoniazid-sensitive cultures initially and who attended the clinic regularly the numbers with a favourable bacteriological response at the end of the year of chemotherapy were 79 (88%) out of 90 for the twice-weekly regimen and 72 (87%) out of 83 for the daily regimen; the numbers of patients with considerable radiographic improvement were 54 (60%) and 53 (64%) respectively. Complaints of vomiting or diarrhoea that did not require a reduction of the PAS dosage were made on one or two occasions by 23 (21 %) out of 109 twice-weekly and 25 (23%) out of 108 daily patients, and on at least three occasions by 4 (4%) and 12 (11%) respectively. Finally, all five patients who had chemotherapy changed on account of hypersensitivity to PAS had been receiving the daily regimen, as also had one patient who died of agranulocytosis.

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Introduction

The efficacy in both the short and the long term of a twice-weekly regimen of streptomycin plus high-dosage isoniazid in the treatment of newly diagnosed pulmonary tuberculosis has been well established by studies at this centre (Tuberculosis Chemotherapy Centre, Madras, 1964, 1970; Ramakrishnan *et al.*, 1969). However, the regimen is not readily applicable in rural areas of developing countries, where facilities for giving injections are limited. In such situations fully supervised oral intermittent regimens could be of great value. A controlled study was therefore undertaken to compare the efficacy of a twice-weekly oral regimen of PAS (para-aminosalicylic acid) plus high-dosage isoniazid with that of a daily regimen of PAS plus conventional low-dosage isoniazid. PAS was chosen as the substitute for streptomycin because it has been widely used for many years and is readily available in developing countries.

Plan and Conduct of Study

The patients came from the poorest sections of the population of the City of Madras and had reported at tuberculosis clinics with symptoms. The criteria for admission to the study were similar to those used in previous studies (see Tuberculosis Chemotherapy Centre, Madras, 1960). In brief, the patients were aged 12 years or more and had newly diagnosed tuberculosis with at least two sputum cultures positive for *Mycobacterium tuberculosis* (patients were provisionally admitted if they had two or more positive sputum smears).

Chemotherapeutic Regimens.– For the first two weeks all the patients attended the outpatient clinic daily and received, under supervision, streptomycin 1 g, sodium PAS 6 g, and isoniazid 400 mg (incorporating pyridoxine 6 mg). For the next 50 weeks the patients received on an outpatient basis either a twice-weekly regimen (group 1) or a daily regimen (group 2). The twice-weekly regimen comprised sodium PAS 0.2 g/kg body weight plus isoniazid 15 mg/kg body weight, both drugs being given at the same time in a single oral dose twice a week under the close supervision of a nurse in the clinic (table I). In order to prevent isoniazid neuropathy 6 mg of pyridoxine was incorporated in

TABLE I—*Dosage Schedule of Drugs*

Weight (kg)	Twice Weekly* (Group 1)		Daily† (Group 2)	
	Sodium PAS (g)	Isoniazid (mg)	Sodium PAS (g)	Isoniazid (mg)
<30·0	7·5	400	7·50	150
30·0–44·9	9·0	600	8·75	175
≥45·0	10·5	750	10·00	200

*Administered as cachets, each containing 1.5 g of sodium PAS, and tablets of isoniazid.
† Prcscribed as cachets, each containing 1.25 g of sodium PAS and 25 mg of isoniazid.

every dose of isoniazid (Tuberculosis Chemotherapy Centre, Madras, 1963). The daily regimen comprised sodium PAS 0.2 g/kg body weight plus isoniazid 4.7 mg/kg body weight, both drugs to be self-administered daily in two divided doses by mouth (table I). The patients were allocated at random to the two treatment groups at the time of admission to the study, after stratification by the isoniazid inactivation rate and the smear result of an overnight collection specimen of sputum.

General Management.– Progress was assessed mainly by bacteriological examination of one clinic spot specimen and two overnight collection specimens of sputum at monthly intervals, and also by routine posteroanterior chest radiographs at one, six, and 12 months; a radiograph was taken at other times if a sputum smear was positive or if a physician deemed it necessary. Patients on the daily regimen attended once a week to receive a supply of drugs. The regularity of self-administration of drugs was assessed by examining, by the sodium nitroprusside test (Rao *et al.,* 1967), a urine specimen produced at the clinic each week. In addition two visits were made to the patient's home each month and the stock of cachets was counted; if the patient was available a urine specimen was collected. If a patient on either the daily or the twice-weekly regimen failed to attend on the appointed day a health visitor visited the home the next day. No patient in this study had collapse therapy or resection.

Bacteriological Procedures.-Sputum specimens were examined by fluorescence microscopy and cultured on Lowenstein-Jensen medium. Positive cultures were tested for sensitivity to isoniazid and streptomycin by standard methods (Tuberculosis Chemotherapy Centre, Madras, 1960). Sensitivity to PAS was determined by the proportion method (Canetti et al., 1969) and resistance was defined as growth, on a medium containing 1 µg of PAS per ml, of at least 1% of the bacterial population; this criterion was chosen as it best distinguished sensitive strains from those with acquired resistance in this study. Positive cultures were tested for niacin production and for susceptibility to sodium p-nitrobenzoate (Tsukamura and Tsukamura, 1964).

Rate of Inactivation of Isoniazid.– The concentration of isoniazid in the serum four and a half hours after an intramuscular test dose of 3 mg/kg body weight was estimated (Tuberculosis Chemotherapy Centre, Madras, 1970). Patients with a concentration of 0.90 µg/ml or more were classified as slow inactivators of isoniazid and those with a concentration of 0.89 µg/ml or less as rapid inactivators.

Radiographic Assessment by Independent Assessor.– The extent of cavitation and the total extent of the disease on admission and the radiographic changes over the 12-month period were assessed from posteroanterior chest radiographs, as described previously (Tuberculosis Chemotherapy Centre, Madras, 1960), by an independent assessor, Dr. K. V. Krishnaswami, who was unaware of the treatment and clinical and bacteriological findings for any individual patient.

Patients

Altogether 247 patients (122 in group 1, 125 in group 2) were provisionally admitted to the study. It was subsequently found that six failed to conform to the criteria for admission and that 21 initially had strains resistant to isoniazid. Of the remaining 220 patients (111 in group 1, 109 in group 2) 203 (92%) had received no previous chemotherapy and 17 (8%) had received up to two weeks of previous chemotherapy.

No patient was excluded on account of initial resistance to PAS (for reasons see Selkon *et al.,* 1960; Tuberculosis Chemotherapy Centre, Madras, 1960, 1966). Seven patients initially had strains resistant to streptomycin but were not excluded because the numbers in the two treatment groups were similar (four in group 1, three in group 2) and the duration of streptomycin therapy was only two weeks.

Results

Of the 220 patients 47 are excluded from the main analysis. Three of these patients did not start the second phase of their chemotherapy-two in group 1 died of tuberculosis on the 3rd and 14th day respectively while they were receiving daily triple-drug chemotherapy, and the third patient (in group 2) was continued on the triple-drug chemotherapy beyond two weeks on account of serious clinical deterioration. Of the remaining 44 patients 3 (1 in group 1, 2 in group 2) died from non-tuberculous causes (myocardial infarction, agranulocytosis, suicide) with negative sputum cultures, 5 (group 2) had their chemotherapy changed on account of toxicity to PAS, 8 (5 in group 1, 3 in group 2) took their discharge against medical advice, and 28 (13 in group 1, 15 in group 2) missed a large proportion of the allocated chemotherapy. Thus the main analysis is based on 173 patients–90 in group 1 and 83 in group 2.

CONDITION ON ADMISSION TO TREATMENT

The mean age of the 173 patients was 32 years (95% range 17-59 years) and the mean weight 38 kg (95% range 26-50 kg); 107 (62%) were males. Altogether 153 patients (88%) had cavitated disease and a positive sputum smear and 70 (40%) were rapid inactivators of isoniazid.

The two groups of patients were similar with respect to age, sex, and weight (data not tabulated here), radiographic and bacteriological condition on admission to treatment (table II), and the proportion of rapid inactivators of isoniazid.

TABLE II – CONDITION ON ADMISSION TO TREATMENT

	Group 1 Patients		Group 2 Patients	
	No.	%	No.	%
Moderate or extensive cavitation	64	71	54	65
Moderate, extensive, or gross disease	70	78	59	71
2-plus or 3-plus smear result on first collection specimen of sputum	54	60	50	60
Rapid inactivators of isoniazid	38	42	32	39
Total	90	100	83	100

RESPONSE TO TREATMENT

Radiographically the response to treatment was similar in the two series of patients. Thus 85 (94%) in group 1 and 80 (96%) in group 2 showed improvement over the 12-month period, including 54 (60%) and 53 (64%) with considerable improvement. Cavitation, present initially in 80 group 1 and 77 group 2 patients on posteroanrerior radiography, had disappeared by 12 months in 41 (51%) and 35 (45%) respectively and become less in 34 (42%) and 39 (51%) respectively. Cavitation was observed at 12 months in three out of 10 group 1 and two of six group 2 patients in whom it had not been apparent on admission.

The numbers of patients with a negative culture from a single overnight collection specimen of sputum at monthly intervals were similar in the two groups (table III). An isoniazid-resistant

culture was obtained from 7 (8%) out of 88 group 1 and 3 (4%) out of 82 group 2 patients at three months, 10 (11%) and 5 (6%) respectively at six months, 10 (12%) and 5 (6%) at nine months, and 9 (10%) and 8 (10%) at 12 months; none of the differences was statistically significant. Out of 70 positive cultures that we isolated between seven and 12 months from the group 1 patients 61 (87%) were isoniazid-resistant, compared with 36 (68%) out of 53 cultures isolated from the patients in group 2.

TABLE III- *Patients with a Negative Culture from a Single Collection Specimen of Sputum**

Months after Start of Chemotherapy	Group 1 Patients			Group 2 Patients		
	Total	Culture-negative		Total	Culture-negative	
		No.	%		No.	%
0	90	2	2	83	1	1
1	90	21	23	81	16	20
2	87	46	53	83	40	48
3	89	65	73	82	66	80
6	90	78	87	80	70	88
9	87	78	90	80	69	86
10	86	77	90	82	74	90
11	86	77	90	77	67	87
12	88	77	88	79	71	90

*Patients who, after the initial intensive phase of two weeks, died of tuberculosis (1 in group 1, 1 in group 2) or had their chemotherapy changed on account of radiographic or clinical deterioration (4 in group 1, 2 in group 2) are included throughout and considered as having a positive culture at each month after the event.

The proportions of patients with a favourable response to treatment at one year were also very similar in the two series –namely, 88% and 87% (table IV) respectively. The unfavourable responses included one patient in each group who died of tuberculosis on the 29th and 27th days respectively and four group 1 and two group 2 patients who had their chemotherapy changed, all between eight and 10 months, on account of radiographic or clinical deterioration in the presence of positive sputum; the radiographic deterioration was confirmed in all instances by an independent assessor, Dr. K. S. Sanjivi.

TABLE IV – *Response to Treatment, Assessed at One Year*

	Group 1 Patients		Group 2 Patients	
	No.	%	No.	%
All cultures (usually 7–9) negative at 10, 11, and 12 months	75	83	67	81
All cultures negative at 3 or more consecutive monthly examinations but a single positive culture at 10, 11, or 12 months*	4	4	5	6
Total with favourable response	79	88	72	87
All cultures negative at 3 or more consecutive monthly examinations but a total of 2 or more positive cultures at 10, 11, and 12 months	3	3	3	4
Cultures never all negative at 3 consecutive monthly examinations	3	3	5	6
Termination of allocated chemotherapy on account of:				
(*a*) Radiographic deterioration	2	2	2	2
(*b*) Serious clinical deterioration	2	2	0	0
Tuberculous death	1	1	1	1
Total with unfavourable response	11	12	11	13
Grand total	90	100	83	100

*These patients were regarded as having a favourable response in view of experience with similar groups of patients (Dawson *et al.*, 1966; Ramakrishnan *et al.*, 1969).

Among the 20 failures (10 on each treatment regimen) who had received at least one month of chemotherapy 15 (9 in group 1, 6 in group 2) produced three or more isoniazid-resistant cultures during treatment. In the remaining five patients (one in group 1, four in group 2) there was no evidence that isoniazid resistance had emerged. Thus the group 1 patient, who received 97% of his chemotherapy, produced isoniazid-sensitive cultures at 1, 2, 3, 10, and 11 months and negative cultures at all the other months. The four group 2 patients repeatedly produced isoniazid-sensitive cultures during treatment. Although they had collected 80%, 91%, 98%, and 98% of their medicaments they were very irregular in self-administering them, the proportions of negative urine test results being 44%, 71%, 73 %, and 90% respectively.

INFLUENCE OF ISONIAZID INACTIVATION RATE ON RESPONSE TO TREATMENT

The condition on admission to treatment was broadly similar for the rapid and slow inactivators of isoniazid in both treatment series. There was a suggestion that the response to the twice-weekly regimen was better in slow inactivators than in rapid inactivators, the numbers with a favourable response at one year being 48 (92%) and 31 (82%) respectively ($P = 0.2$). The corresponding numbers for those on the daily regimen were 45(88 %) and 27 (84%) ($P > 0.2$).

PROGNOSTIC IMPORTANCE OF VARIOUS FACTORS

In patients on the twice-weekly regimen the response to treatment was greatly influenced by the initial bacterial content in the sputum and probably by the extent of disease and the extent of cavitation on admission. Thus of the 54 patients with a three-plus or two-plus smear result in an overnight collection specimen of sputum 11 (20%) had an unfavourable response at one year, compared with none of the 36 patients with a one-plus or negative smear result ($P < 0.01$). The corresponding response rates for the 64 patients with extensive or moderate cavitation and for the 26 with slight or no cavitation were 10 (16%) and 1 (4%) ($P = 0.1$), and for the 70 patients with gross, extensive, or moderate disease and for the 20 with limited or slight disease 10 (14%) and 1 (5%) ($P = 0.2$). In patients on the daily regimen there was no evidence that any of these factors influenced the response.

Sex and age were of no prognostic importance in either series.

PAS-SENSITIVITY TEST RESULTS

At least one PAS-resistant culture was obtained before treatment from 21 of the 173 patients (9 in group 1, 12 in group 2); 5 (24%) (2 in group 1, 3 in group 2) had an unfavourable response to treatment, as compared with 17 (11%) (9 in group 1, 8 in group 2) out of 152 patients (81 in group 1, 71 in group 2) who had PAS-sensitive cultures on admission to treatment ($P = 0.1$).

Eight patients on the twice-weekly regimen and six on the daily regimen had PAS-sensitive cultures before treatment and either produced positive cultures at 10, 11, and 12 months or had chemotherapy changed during the year on account of deterioration. In four patients in each group at least two of the last three cultures tested were PAS-resistant.

ACCEPTABILITY OF REGIMENS

Eight patients (five in group 1, three in group 2) took their discharge against medical advice for reasons not connected with the drugs, four (three in group 1, one in group 2) refused further treatment, and four moved out of Madras. A further 28 patients (13 in group 1, 15 in group 2) were known definitely to have missed more than 25% of their chemotherapy in the first six months or over the whole year, or had received no chemotherapy for a continuous period of more than four weeks; in 10 (4 in group 1, 6 in group 2) this was largely due

to complications such as hypersensitivity reactions or jaundice. All the above 36 patients are excluded from the main analysis.

Of 89 patients on the twice-weekly regimen who are included in the main analysis (excluding 1 who died in the fifth week) 77 (87%) received at least 90% of their allocated chemotherapy. Of these, 9 (12%) had an unfavourable response compared with 1 (8%) of 12 who received less than 90% of their chemotherapy. There was no evidence that any of the patients supplemented their twice-weekly chemotherapy with isoniazid from other sources, for out of 4,569 urine specimens collected immediately before the administration of a dose of medicaments 4,526 (99%) yielded negative results by the acetylisoniazid test of Eidus and Hamilton (1964).

At least 90% of the allocated chemotherapy was collected by 76 (93%) of 82 patients on the daily regimen included in the main analysis (excluding 1 who died in the fourth week). Some of the patients, however, were very irregular in self-administering their medicaments, and this had therapeutic implications. Thus an unfavourable response was observed in seven out of 14 (50%), two out of 25 (8%), and one out of 43 patients (2%) who had negative urine test results on 50% or more, 25-49%, and less than 25% of the occasions respectively-a significant trend ($P = 10^{-5}$).

DISEASE STATUS AT ONE YEAR IN DISCHARGED AND IRREGULAR PATIENTS

Of the eight patients who took their discharge against medical advice one (group 2) died in her village (presumably of tuberculosis) and three (all in group 1) produced at least one positive culture between 10 and 12 months; all four were culture-positive at the time of their discharge in the second, third, third, and fourth months respectively. Three patients (one in group 1, two in group 2) produced only negative cultures between 10 and 12 months; all of them were culture-negative at the time of discharge and none received chemotherapy subsequently from any source. No specimens could be collected between 10 and 12 months for the eighth patient (in group 1).

With regard to the 28 patients who missed large proportions of their allocated chemotherapy, nine out of 13 on the twice-weekly regimen (69%) and four out of 15 on the daily regimen (27%) had a favourable response at one year ($P = 0.06$). There proportions are much smaller than those in the patients included in the main analysis–namely, 79 (88%) out of 90 on the twice-weekly regimen ($P = 0.09$) and 72 (87%) out of 83 on the daily regimen ($P < 10^{-5}$).

When the above 36 patients are included the proportions with a favourable disease status at one year are 89 out of 107 (83%) on the twice-weekly regimen and 78 out of 101 (77%) on the daily regimen ($P > 0.2$).

DRUG TOXICITY

The findings below are based on the 217 patients (109 in group 1, 108 in group 2) who were eligible for the study and who started the second phase of their chemotherapy, and pertain to the second phase. Patients were not questioned to elicit symptoms of drug toxicity; however, every spontaneous complaint was followed by careful questioning by a physician and then recorded. Findings indicating toxicity to PAS are presented in table V.

TABLE V-Toxicity to PAS in the 217 Patients who started Second Phase of Chemotherapy

	Group 1 Patients (n = 109)	Group 2 Patients (n = 108)
Death due to agranulocytosis	0	1
Hypersensitivity to PAS	1	10*
At least 3 complaints of vomiting or diarrhoea	4	12
Jaundice	2	4
Total	7 (6%)	23† (21%)

* Of these, 5 had to have their chemotherapy changed.
† Some patients appear in more than one category.

Agranulocytosis.– One patient (in group 2) developed agranulocytosis (total leucocytes 1,600/mm^3, polymorphonuclear leucocytes 8%) with anaemia (haemoglobin 7.2 g/ 100 ml, packed cell volume 35%), high fever, and delerium in the third month; the antituberculosis drugs were stopped immediately and the patient was admitted to hospital, but he died seven days later.

*Hypersensitivity to PAS.**– One patient in group 19 developed cutaneous hypersensitivity to PAS compared with 10 patients in group 2 ($P < 0.01$). Of these 11 patients three (all in group 2) developed jaundice at the time, including one who had a hypersensitivity reaction to isoniazid also.

The group 1 patient developed the cutaneous hypersensitivity reaction in the fourth month, was desensitized, and resumed the allocated treatment. Of the 10 group 2 patients 8 developed the reaction in the second month and 2 in the third month. Six of these 10 patients were desensitized and resumed the daily regimen (one had his chemotherapy changed subsequently on account of severe vomiting and recurrence of the cutaneous hypersensitivity); the remaining four had their chemotherapy changed, desensitization not having been attempted on account of the severity of the hypersensitivity reaction or other clinical complications.

Gastrointestinal Complaints.– Chemotherapy had to be changed in the fourth month in one patient (group 2) on account of severe vomiting and cutaneous hypersensitivity to PAS (see above). Complaints of vomiting or diarrhoea that did not require a reduction of the PAS dosage were made on one occasion by 15 (14%) of the group 1 patients and 21 (20%) of the group 2 patients, on two occasions by 8 (7%) and 4 (4%) respectively, and on three or more occasions by 4 (4%) and 12 (11%) respectively; the contrast between the two series was significant ($P = 0.04$).

Jaundice.– In addition to the three patients (all in group 2) mentioned above three (two in group 1, one in group 2) developed jaundice in the fourth, fifth, and third months respectively. PAS was withheld until the jaundice cleared, which was five, five, and two weeks later; when PAS was reintroduced jaundice did not reappear.

Neurological Complaints Attributed to Isoniazid.– One patient (in group 1, slow inactivator of isoniazid) had a single attack of convulsions in the ninth month, two and a half hours after the administration of a dose of chemotherapy. Symptoms suggestive of peripheral neuropathy were reported on two or more occasions by three group 1 patients (two slow, one rapid) and six group 2 patients (five slow, one rapid), including one patient (group 2, slow) who had physical signs. All 10 patients continued on their allocated chemotherapy.

Discussion

The main advantage of intermittent chemotherapy over daily chemotherapy is that it is practicable to administer it under full supervision and thereby eliminate concealed irregularity–a major problem with self-administered daily regimens. Furthermore, for any given combination of drugs intermittent regimens are usually less toxic and invariably less expensive. Previous studies from this centre showed that a twice-weekly regimen consisting of streptomycin injections and high-dosage oral isoniazid, without an initial intensive phase, was at least as effective, in both the short and the long term, as a daily regimen of isoniazid plus PAS in conventional dosage (Tuberculosis

*One patient developed hypersensitivity to PAS manifested by urticaria and jaundice in the first phase of chemotherapy-that is, when he was receiving 6 g of the drug daily. He was desensitized and subsequently received the allocated twice-weekly regimen.

Chemotherapy Centre, Madras, 1964; Ramakrishnan *et al.,* 1969).

The findings in this study with the fully oral twice-weekly regimen of isoniazid plus PAS are encouraging. Thus, at the end of one year of chemotherapy 79 (88%) of the 90 patients who received this regimen had a favourable bacteriological response, compared with 72 (87%) of the 83 patients who received a standard daily regimen of isoniazid plus PAS; 54 (60%) and 53 (64%) respectively showed considerable radiographic improvement. Chemotherapy was changed on account of hypersensitivity to PAS in five of the daily patients, compared with none of the twice-weekly patients, and the incidence of gastrointestinal complaints was lower in the latter. Thus the less expensive twice-weekly regimen, in which the total weekly dosage of PAS was less than a third of that in the daily regimen, was better tolerated. This finding is similar to the experience of Tempel *et al.* (1950) with streptomycin-namely, toxicity in 38 out of 66 patients (58%) who received daily streptomycin 1 g or 2 g for four months, compared with only five out of 97 patients (5%) who received the same dose twice a week.

The incidence of hypersensitivity to PAS with the daily regimen was 9% in the present study and 3%, 3%, 4%, and 6% in the earlier studies at this centre (Tuberculosis Chemotherapy Centre, Madras, 1959, 1960, 1964, 1966), the mean for all studies, based on 532 patients, being 4.7%. The incidence was 1 (0.9%) out of 109 with the twice-weekly regimen in this study, and 1 (0.6%) out of 178 with a once-weekly regimen of sodium PAS (6 g), isoniazid, and streptomycin in an earlier study (Tuberculosis Chemotherapy Centre, Madras, 1973). The tendency for a lower incidence with an increase in the interval between successive doses was significant (P = 0.001). This finding is different from the experience with rifampicin, toxicity to which occurs, possibly due to an immunological mechanism, more frequently during intermittent administration than during daily administration of the drug (Mary Aquinas et al., 1972).

Although the twice-weekly and daily regimens were of similar efficacy in the present study there is reason to believe that the former regimen would have been marginally less effective if the regularity in drug intake had been equal for the two regimens. In the event there was greater irregularity with the daily regimen, and the association between regularity and response was strong in the case of this regimen only. Next, the proportion of failures with isoniazid-resistant cultures was higher with the twice-weekly regimen. Finally, the efficacy of the twice-weekly regimen, unlike that of the daily regimen, was much influenced by the size of the initial bacterial population, probably by the extent of disease and the extent of cavitation on admission, and probably also by the rate of inactivation of isoniazid. These findings indicate that if taken regularly a given dose of PAS is slightly less effective twice-weekly than daily, in keeping with earlier experimental work (Karlson and Carr, 1958; P. Venkataraman, S. Subbammal, and S. P. Tripathy, unpublished datat). It would therefore be valuable to strengthen the twice-weekly regimen. This could be done by extending the initial period of triple-drug chemotherapy from two weeks to four weeks or more in view of the evidence that an initial intensive phase greatly enhances the therapeutic efficacy (Medical Research Council, 1962; East African/British Medical Research Council, 1970; Tuberculosis Chemotherapy Centre, Madras, 1970; International Union Against Tuberculosis, 1970).

† At this centre 32 guinea-pigs were infected intramuscularly with 0.1 mg (moist weight) of the H37Rv strain of M. tuberculosis. From the 10th day PAS 0.2 g/kg was administered by gastric intubation daily to eight animals, on alternate days to eight animals, and once in four days to eight animals; the remaining eight animals were left untreated as controls. At the end of six weeks of treatment the root index of disease was determined by employing the procedures described by Mitchison *et al.* (1961). The mean root indices were 0.88, 0.98, and 1.03 for guinea-pigs that had received treatment daily; alternate days, and once in four days, respectively, and 1.32 for the

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