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SHORT COURSE CHEMOTHERAPY

When specific anti-microbial drugs with potent *in vivo* action on *M. Tuberculosis* started becoming available, hopes ran high. It was thought that this epoch-making discovery would lead to tuberculosis being quickly and finally licked. The hope, however, still remains elusive in large parts of the world because problems seldom have perfect solutions. When a problem is solved, the solution itself generates new problems. Every time some problem is solved, it undoubtedly helps to extend the frontiers of knowledge but because of the newly arisen problems, the horizon too seems to recede a little farther and endeavour continues.

Very soon after deployment of these drugs, the big gap between what was being actually achieved in the field and the 100% favourable results under ideal research conditions became obvious. Failure on the part of the patients to take drugs regularly in adequate doses for a prolonged period even after disappearance of all symptoms was the main reason for the shortfall. The patients' non-compliance being primarily a socio-psychological problem directly proportionate to the duration of chemotherapy, the best remedial measure appeared to be to reduce the duration of treatment. Till a few years ago, this was not feasible because of the deficient action of even the most potent of the available drugs, viz., INH, on slowly and periodically multiplying bacilli. Rifampicin, and to some extent, Pyrazinamide also, with their sterilising action on such bacilli, have given a new dimension to the chemotherapy of tuberculosis and it has become possible to reduce its duration substantially.

Many studies with different combinations, rhythms and durations have been reported during the last few years from all parts of the world, including the third world. But how short can and should 'short course' chemotherapy be is still not finally settled. Even 3 months' treatment with three-drug regimens containing Rifampicin and INH can give 100% sputum conversion but relapse rates remain high. Six months' regimens cut down significantly the relapse rates too, though some workers advocate 9 months' treatment for advanced cavitary cases. However, a nine month regimen does not remain short enough and may, to a certain extent, defeat its objective.

Though there is still no universally accepted short course regimen, guidelines for clinical practice are fairly clear. There is no justification for denying short-course therapy to a patient who can afford the cost. Rifampicin, INH and Pyrazinamide are essential in the initial intensive phase and the total duration should not be less than six months for a smear positive case

although Pyrazinamide can be withdrawn after the initial 2-3 months. Monitoring with enzyme tests is not obligatory except where liver damage is suspected because of alcoholism, etc.

The position in respect of its incorporation in the national programme is however far from clear. Aneja & his associates have highlighted some of the issues involved therein in an article published in this issue. An optimum regimen, i.e., a regimen of the shortest possible duration consistent with maximum immediate and long-term effectiveness and manageable cost for a poor country with high prevalence, is not the only unsolved problem. Logistics of drug delivery pattern at the periphery, rhythm of the regimen and supervision of the administration of drugs, quantum of surveillance, etc. have yet to be worked out.

It has also to be kept in mind that short course chemotherapy is not an unqualified panacea. Rules of good chemotherapy of the erstwhile prolonged treatment are no less essential for short course chemotherapy too. Patients' compliance and their surveillance do not become redundant. Neither the experience of conventional chemotherapy nor the results of clinical trials of short course chemotherapy under ideal research conditions would apply necessarily and fully to a service programme. It is imperative that organisational problems along with efficiency, acceptability and cost of promising regimens be studied forthwith with scientific thoroughness and under actual field conditions, especially in the rural areas.

Financial implications of adopting short course chemotherapy under the national programme are also relevant. Since Rifampicin and Pyrazinamide are very costly, short course regimens are definitely much more expensive than conventional regimens of 1 or 1½ years' duration. But this high cost is compensated to a large extent by the tangible and intangible^ benefits of the former, viz., quick conversion of sputum in almost all cases with resultant reduction in fresh infections, negligible relapse rate, higher compliance by the patient, reduced work-load of the clinics including surveillance of the patients during treatment, etc. In short, increased governmental expense on 'short course' regimens appears to be justified even for a developing country. If much larger amounts can be made available for other schemes and projects, there is no reason why additional funds should also not be made available for control of tuberculosis which is at present our Public Health Enemy No.1.

REVIEW ARTICLE

SHORT COURSE CHEMOTHERAPY OF PULMONARY TUBERCULOSIS

S.P. TRIPATHY*

The last four decades have seen spectacular developments in the management of pulmonary tuberculosis. The discovery of streptomycin in 1943 by Waksman was soon followed by other drugs with anti-tuberculosis activity, such as PAS, isoniazid, pyrazinamide, thioacetazone, ethambutol, rifampicin and others. The discovery of the anti-tuberculosis activity of isoniazid in 1952 was a great land-mark which revolutionised the treatment of tuberculosis. Because of its high efficacy, low toxicity and low cost, isoniazid soon became the drug of choice in tuberculosis. Administered alone daily for 12 months, it has a potential of producing bacteriological quiescence in approximately 70% of pulmonary tuberculosis cases excreting isoniazid-sensitive cultures in their sputum. The concomitant administration of thioacetazone or PAS daily for 1 year increases the efficacy of the regimen to about 85%. However, approximately 20% of the patients with quiescent disease at 1 year have a bacteriological relapse after stopping chemotherapy, so that the overall efficacy of the 2-drug regimens is reduced to less than 70% even among those patients who consume the drugs regularly. Such relapses can be prevented by continuing chemotherapy beyond 12 months for another 6-12 months. It is, therefore, customary to prescribe regimens of 18-24 months to tuberculosis patients.

The routine application of the conventional regimens in tuberculosis control programmes has been found to be difficult. Many patients become irregular in taking treatment as the months advance; indeed, over half the patients discontinue treatment by 12 months, and very few complete the prescribed 18 to 24 months of treatment. Regularity of treatment, however, is generally high in the early months of treatment. This factor has provided the basis for developing effective regimens which produce rapid sputum conversion, so that they need be administered for durations considerably shorter than the conventional 12-24 months. The discovery of rifampicin, a bactericidal drug with activity matching that of isoniazid, provided the necessary stimulus for evolving short-course regimens.

The first report of effective short-course regimens came from East Africa.^{1,2} In this study,

nary tuberculosis was investigated in comparison with a standard daily regimen of thioacetazone plus isoniazid for 18 months. It was found that the 3-drug combination of streptomycin plus isoniazid plus rifampicin—SHR—caused sputum conversion in 100% by the end of 6 months; further, these patients continued “to have quiescent disease even after stopping chemotherapy, with only 2% having a relapse by the end of 5 years. This study was the forerunner of several other studies in East Africa and other countries, including India.

The success of short-course regimens depends upon a proper choice of drugs which have bactericidal as well as sterilising activity. Evidence regarding bactericidal activity can be obtained from laboratory studies on the effect of the drugs on cultures of tubercle bacilli *in vitro*, efficacy of the drugs in experimental tuberculosis in laboratory animals, the speed of sputum conversion in patients undergoing treatment and the magnitude of the fall in the bacterial content of sputum within a short period of initiation of chemotherapy. The sterilising activity of drugs is assessed from the proportion of patients who have bacteriological relapses after stopping chemotherapy.

Isoniazid, rifampicin, streptomycin and pyrazinamide are drugs which exert bactericidal activity and Table I summarises their relative bactericidal properties as assessed by their activities in laboratory studies *in vitro* and against experimental tuberculosis in animals. Isoniazid and rifampicin have the highest bactericidal activity, while streptomycin and pyrazinamide are relatively less active. The evidence in man, however, is indirect. Ethical considerations prevent the study of single-drug regimens in clinical practice with the object of determining the relative efficacies of individual drugs. We have, however, a wealth of information on the relative efficacy of combinations of these drugs from carefully conducted controlled trials in man, and it has been possible to apportion the contribution of individual drugs to the overall efficacy of regimens. The clinical results are generally in conformity with the laboratory findings and, together, they provide the scientific basis for formulating short-course regimens for tuberculosis control programmes.

*Director, Tuberculosis Research Centre (Indian Council of Medical Research), Madras-600 031,

TABLE 1
Bactericidal activity of main antituberculosis drugs

Drug	Bactericidal activity		
	In vitro	In mouse	In guinea-Pig
Isoniazid	2+	2+	2+
Rifampicin	2+	2+	2+
Streptomycin	3+	1+**	2+
Pyrazinamide	2+*	2+**	0**

*pH 5.2 – 5.6

** Drug given in a dosage considerable higher than that used in man

Two important indices are used to assess the relativity efficacy of short-course regimens, namely the speed with which the bacilli are

Killed, measured as the proportion of sputum-positive cases who convert to negativity by the end of two months of chemotherapy and the ability to kill bacilli which have a tendency to persist during chemotherapy, measured as the proportion of patients with quiescent disease who have a bacteriological relapse later.

Table 2 summarises findings from bacteriologically positive patients on Madras,³ East Africa^{2,4} and Hong Kong⁵ and presents the bactericidal activity of various regimens measured in terms of proportions of sputum-positive cases who convert to negativity by the end of two months of chemotherapy. Although the data on the H, TH, PH and EH regimens pertain to regimens of conventional 12-months duration in Madras, they are relevant for the present analyses. The regimens of isoniazid alone in Madras produced sputum conversion in 44% of patients, an achievement reflecting the high bactericidal potential of the drug. The addition of the bacteriostatic drug thioacetazone, PAS or ethambutol to isoniazid did not result in any significant increase of the bactericidal activity. The proportion of 49% achieved in East Africa with the two-drug combination, streptomycin plus isoniazid, is not much higher than what was achieved with isoniazid alone in Madras, suggesting that the contribution of streptomycin to the

TABLE 2
Bactericidal activity of daily regimens in Sputum-positive patients

Regimen	Percent culture-negative at 2 months
H	44
TH	44
PH	42
EH	49
SH	49
STH	42
SHZ	66
HR	64
SHR	70
SHRZ	95
SHER	81

H – Isoniazid
T – Thioacetazone
P – PAS

E – Ethambutol
Z – Pyrazinamide
R – Rifampicin

bactericidal activity of the regimen is small. In contrast, the addition of pyrazinamide or rifampicin contributes significantly to the bactericidal activity. Thus, the clinical evidence suggests that isoniazid, rifampicin and pyrazinamide are drugs which kill the bacilli and are

PAS or ethambutol are unlikely to make significant contribution to the activity of short-course regimens. The contribution of streptomycin also would appear to be small. Further evidence on the activity of the drugs is derived from the findings on bacteriological relapse.

Examples of sterilising activities of different drug combinations in man are presented in Table 3.

It is clear that the addition of thioacetazone to SH did not contribute to the sterilising activity of the regimen and the relapse rate continued to be high, namely, 22%; pyrazinamide, on

TABLE 3
Sterilising activity of persisting bacilli^{2,5,6,8}

Regimen	Duration of chemotherapy (months)	Relapses 1-2 yrs after stopping drugs (%)
6SH*	6	29
6SHT	6	22
6SHZ	6	8
6HR	6	7
6 SHR	6	2
2 SHRE/SHE ₂ **	6	23
2 SHRZ /SHZ ₂	6	7
2 SHRE/SHE ₂	8	10
2 SHRZ/SHZ ₂	8	3

*The prefix indicates the number of months of chemotherapy.

**The suffix indicates the number of doses of the drugs during the week

the other hand, made a significant contribution, and reduced the relapse rate from 29% to 8%. The contrast between pyrazinamide and ethambutol clearly shows that the sterilising activity of ethambutol is inferior to that of pyrazinamide. The low relapses associated with the 6 HR and the 6 SHR regimens speak eloquently of the substantial and significant contribution of rifampicin in achieving sterilisation.

The proportion, of patients with negative cultures at 2 months is only an indirect and partial evidence of the efficacy of the regimen. While a low proportion negative at 2 months indicates a low efficacy, a high proportion is no guarantee of a sterilising activity; the outcome would depend upon the potency of the drugs administered during the succeeding months. The proportion of patients who have relapses after the end of the scheduled course of chemotherapy provides a more direct and definite evidence of the sterilising activity of regimens. A critical review of the findings of several controlled clinical trials would show that isoniazid, rifampicin, pyrazinamide and streptomycin are drugs with bactericidal and sterilising activity and can be employed in appropriate combinations in short-course chemotherapy.^{9, 10} Etha-

mbutol, PAS and thioacetazone are largely bacteriostatic in action, and therefore have a limited role in short-course chemotherapy.

Role of individual drugs in drug combinations

Relapse rates associated with short-course regimens of varying durations and containing different combinations of drugs provide clues to the contribution of each drug to the overall efficacy of the regimens.

It is generally accepted that isoniazid is the antituberculosis drug *par excellence*. Given alone in high dosage, isoniazid produces sputum conversion in about 70% of sputum-positive cases and most of those who convert remain free from relapse. Due to ethical considerations, the efficacy of isoniazid *vis-a-vis* any other antituberculosis drug cannot be investigated by conducting controlled clinical trials with regimens with and without isoniazid; there is no such limitation in the case of other drugs. Many controlled clinical trials with short-course regimens have been designed with the aim of measuring the contribution of individual drugs. The findings from those trials lead to the following conclusions.

Pyrazinamide when added to combinations of SH or SHR makes a significant contribution to the sterilising activity of the regimens; the evidence clearly suggests that while the administration of pyrazinamide during the first two months enhances the bactericidal activity of the regimen, its continued administration beyond 2 months does not confer any additional benefit. Rifampicin, similarly, makes a substantial and significant addition to the sterilising activity of the combinations SH and SHZ but, unlike pyrazinamide, it continues to make an important contribution even during the continuation phase beyond two months.

Streptomycin is a poor companion drug to isoniazid. While the addition of streptomycin to HRZ or HR reduces the relapse rates, the extent of reduction is small.

In addition to the findings from the clinical trials, evidence from mouse experiments conducted at the Pasteur Institute, Paris¹¹, from *In vivo* and *in vitro* laboratory experimental work of Prof. Mitchison's Unit in London^{12, 13}, and from studies in East Africa¹⁴ on the reduction in viable bacterial counts in sputum achieved with 2 days of chemotherapy have also provided valuable data on the activity of antituberculosis drugs. On the basis of these findings, Prof. Mitchison¹⁵ has suggested the existence of four types of bacterial populations according

to their anatomical location. The first is a population of actively growing bacilli present in the liquefied caseous material. This is by far the largest fraction of the total bacterial population and contributes to the entire bulk of the bacilli excreted in the sputum, in untreated patients and in the early months of treatment. These bacilli are killed by isoniazid, and, to a smaller extent, by rifampicin and streptomycin. Even when administered alone, isoniazid can effectively eliminate nearly all of this population; the only bacilli which would survive are the small number of drug-resistant mutants.

The second population consists of slow-growing bacilli situated within the macrophages in an acidic milieu; they escape the action of all antituberculosis drugs except pyrazinamide and, to some extent, rifampicin. The third population consists of small number of bacilli which are present extra-cellularly in solid caseous lesions and exhibit brief spurts of metabolic activity; rifampicin is the only drug which acts rapidly and kills bacilli during the brief periods of activity. There is possibly a fourth population of dormant bacilli which are not killed by any drug. All these populations exist in the lesions and hence it is necessary to give at least 3 drugs—isoniazid, rifampicin and pyrazinamide, and possibly streptomycin as well, to ensure sterilisation of the lesion.

Rhythm of administration of drugs

In conventional chemotherapy, intermittent regimens have been shown to be highly effective. Intermittent regimens permit drugs to be administered under full supervision so that concealed drug irregularity is eliminated; adverse reactions are generally less frequent with intermittent regimens than when the drugs are given daily, and finally, intermittent regimens are often less expensive. Intermittent regimens can also be employed in short-course chemotherapy. Thus, in one study in Hong Kong,¹⁶ a combination of SHZ administered for 9 months was equally effective when administered daily, three times a week or twice a week, the relapse rates being of the order of 5-6%. Many of the short-course regimens investigated in the past have applied the principle of intermittency in the continuation phase following an initial daily phase. Since regimens which are intermittent from the start of treatment would have practical advantages, studies should be undertaken to evolve effective fully intermittent regimens.

Duration of chemotherapy

A regimen of rifampicin plus isoniazid daily for 9 months, with an initial daily supplement

of streptomycin or ethambutol during the first 2 months, is associated with a 0% relapse rate during 2 years of follow-up and is now standard chemotherapy in technically advanced countries. Reviewing data from two BTA and two French controlled trials with 9 months of HR (with 2 or 3 months of daily streptomycin initially), Fox¹⁰ observed that the 9-month regimens were highly effective, with only 3 (1%) of 298 patients having had a relapse during a follow-up of 9-45 months. Six month regimens of HR, however, have generally been associated with relapses of up to 10%. The relapse rates, however, are substantially lower if pyrazinamide is administered in addition to 6 HR. Indeed, as already stated, pyrazinamide need be administered only for the first 2 months. A combination of SHRZ daily for 2 months is highly potent and renders approximately 95% of patients sputum-negative by 2 months, so that continuation of chemotherapy with HR daily or SHZ twice a week for 4 months produces results as good as those attained with 9 months of HR. Examples of highly effective 6-7 month regimens are indicated in table 4.

The first four regimens require daily administration of drugs and hence it may be difficult to organise supervised chemotherapy on an ambulatory basis throughout the period of chemotherapy; the drugs may have to be self-administered by the patient during the continuation phase. The next 4 require daily attendance for only 2 or 3 months, with twice-weekly chemotherapy thereafter. The last 2 regimens require only thrice a week chemotherapy, so that fully supervised chemotherapy can be easily organised. Regimens 2 EHRZ/HR and EHRZ₃ are fully oral regimens so that they can be employed in rural areas where injection facilities may not be adequate.

In summary, there is a wide variety of highly effective 5-7 month regimens which offer the physician opportunities to adapt the regimen to the need of a particular patient or to suit the infra-structure in the local health services.

Table 5 gives examples of regimens of shorter durations, namely 3 or 4 months. These regimens all have relatively higher relapses rates, namely, 8-16% for the 4-month regimens, and 6-14% for the 3-month regimens.

Although the relapse rates appear to be unacceptable, it should be appreciated that the overall results achieved with these regimens are still over 80%, and because of the short duration of chemotherapy, the likelihood of most patients completing their scheduled chemotherapy is very high. Conventional regimens of 12 months'

SHORT COURSE CHEMOTHERAPY OF PULMONARY TUBERCULOSIS

TABLE 4

Bacteriological relapses associated with highly effective 6-month regimens^{10,17-21}

Regimen	Duration (months)	Study	Bact. relapses (%)
2 SHRZ/HR ₂	6	Singapore/East Africa/U.K.	0-2
2 SHRZ/HRZ	6	Singapore/ East Africa	0
2 EHRZ/HR	6	U.K	1
3 SHRZ/RH	5	Agra	2
2 SHRZ/SHZ ₂	7	Madras	0
SHRZ/HR ₃	6	Poland	0
SHRZ/SHZ ₃	5	Madras	3
3 SHRZ/SHZ ₂	5	Agra	2
SHRZ ₃	6	Hong Kong	1
EHRZ ₃	6	Hong Kong	2

TABLE 5

Bacteriological relapse rates : regimens of 3 or 4 month' duration

Regimen	Duration (months)	Study	Bact. relapses (%)
2 SHRZ/RH(Z)	4	Singapore/East Africa	8-16
SHRZ	3	Madras/ Agra	6-14
SHR	3	France	17

duration such as PH or TH are associated with about 15% failures during chemotherapy in patients who have drug-sensitive cultures initially and have taken the drugs regularly, and an additional 15-20% have bacteriological relapses after stopping chemotherapy. Thus, the overall efficacy of such conventional regimens rarely exceeds 70% even under the best conditions, and often the results are much poorer under programme conditions. An overall success rate of over 80% achieved with the 3-month regimen

is an acceptable alternative to the conventional regimen for developing countries. Indeed, the efficacy can be further improved by evolving a system by which patients are administered 3 months of SHRZ under full supervision, and are then given a further 3-month supply of isoniazid to be self-administered by the patient daily at home. Assuming that only some of the patients take the continuation chemotherapy, the overall result would be a reduction in the relapse rate.

Regimens without rifampicin

Pyrazinamide and rifampicin contribute to the bulk of the cost of short course regimens. Many developing countries with limited resources would find it difficult to provide the large financial outlay necessary for employing rifampicin in mass treatment programmes.

In a study conducted at Madras, a 7-month non-rifampicin regimen of 2 SHZ/SHZ₂ was highly effective in patients having drug-sensitive cultures initially, with a relapse rate of only 3%, and this regimen is therefore likely to be useful in developing countries if the level of initial drug-resistance is not high. The results of a study²³ conducted by the Tuberculosis Association of India are of particular interest. A 20-week regimen of SHER was found to be associated with a relapse rate (including bacteriological and clinical relapses) of 16%, compared with 32 % in patients treated with SHEZ, thus, the efficacy of the pyrazinamide regimen was substantially lower than that of the rifampicin regimen, suggesting that regimens which do not contain rifampicin may have to be given for longer periods. It must, however, be emphasised that while non-rifampicin pyrazinamide regimens of 6 or 7 months duration can be formulated for application in situations where the level of initial drug resistance is not high, they are likely to be associated with failures in some patients with isoniazid resistance, and especially in those with resistance to both streptomycin and isoniazid. The use of regimens containing both pyrazinamide and rifampicin should be considered in all situations where the level of initial drug-resistance is high.

Smear-negative pulmonary tuberculosis

In the Eighth Report of the WHO Tuberculosis Expert Group,²⁴ a case of pulmonary tuberculosis was defined as one who was bacteriologically positive, and those who were bacteriologically negative were termed as "suspects". To many this gave the impression that the World Health Organisation did not want the sputum-negative cases to be treated. This is far from the truth, as has been clarified in the Ninth Report.²⁵ Smear-negative symptomatic patients with X-ray abnormality do need treatment and should be treated. Support for such a policy is provided by the conclusive evidence from a recent study on smear-negative pulmonary tuberculosis in Hong Kong.^{26, 27} In this study, patients were randomly allocated to four series—the first, a selective chemotherapy series wherein patients were closely followed up by periodic bacteriological and X-ray examination and were given specific antituberculosis treatment only if

they become culture-positive or, if there was radiographic or clinical deterioration. Two other groups were given short-course chemotherapy with 4 drugs—SHRZ—daily for 2 or 3 months (2 SHRZ, 3SHKZ). The fourth group of patients received a standard chemotherapy with daily streptomycin, PAS and isoniazid for 3 months, followed by streptomycin and isoniazid twice a week (or, exceptionally, by isoniazid and PAS daily) for a further 9 months. This study clearly showed that as many as 71 % of 283 patients in the Selective Chemotherapy series who were initially left untreated had chemotherapy started within 30 months because of confirmation of active disease, a finding which underscores the necessity for treating such cases.

Information on the efficacy of short-course regimens in smear-negative pulmonary tuberculosis is limited. Results of two such studies^{10, 27} are summarised in Table 6. The top half of the table pertains to data on patients who had smear-negative culture-passive tuberculosis, and those in the lower section refer to patients with smear-negative and culture *negative* disease. Considering the culture-positive cases, the results clearly show that the 2-month regimen with a relapse rate of 28% was inadequate, and even the 3-month regimen was not a sterilising regimen. These results suggest that the behaviour of *smear-negative* culture-positive disease is not significantly different from that of *smear-positive* culture-positive disease in respect of response to treatment.

Considering patients with culture-negative disease, the relapse rates of 1-10% with the four drug regimens are substantially lower than the 56% break-down rate observed in the Selective Chemotherapy series, clearly indicating the beneficial effect of chemotherapy. It is, however, clear that the 2-month regimen was inadequate, and only the 4-month regimen was able to completely prevent the occurrence of relapses.

Duration of treatment in relation to sputum results

In the light of the findings discussed above, marginal adjustments can be made in the duration of chemotherapy according to the sputum smear and culture results. The optimum durations of chemotherapy for the various categories of patients are summarized in Table 7.

The three categories of patients differ widely in their bacterial content. The smear-positive cases generally excrete millions of bacilli in their sputum each day, and constitute the greatest risk from the epidemiological stand-point.

TABLE 6

Patients with smear-negative disease : Relapse rates in two Hong Kong studies

Sputum culture result	Regimen and duration (months)	Follow-up (months)	Patients assessed	Bact. relapses (%)	All relapses (%)
Positive	2 SHRZ	46	69	19	28
	3 SHRZ	45	68	6	12
	4 SHRZ	8+	78	3	4
	4 SHRZ ₃	8+	63	0	0
	6 SHRZ ₃	6+	81	0	2
Negative	2 SHRZ	46	154	6	10
	3 SHRZ	45	154	2	5
	3 SHRZ ₃	9+	181	1	3
	4 SHRZ ₃	8+	146	0	1
	Selective Chemotherapy	48	171	42	56

TABLE 7

Optimum duration of chemotherapy

Sputum results	Optimum duration
Smear-positive	6 months
Smear-negative, culture-positive	5 or 6 months
Smear-negative, culture-negative	4, 5 or 6 months

Contacts of patients positive by sputum smear microscopy run a much higher risk of infection compared with contacts of patients with culture-negative tuberculosis, and yet from the therapeutic point of view the culture-negative cases with no demonstrable bacilli in their sputum seem to be requiring almost as much chemotherapy as the smear-positive cases. The explanation for this paradox possibly lies in the distribution and nature of the bacilli in the three

categories. The three categories of patients probably differ very little in their content of slowly multiplying bacteria (which alone determine the occurrence of relapse) and this common factor probably dictates the need for almost similar durations of treatment.

Other low-cost regimens

Both rifampicin and pyrazinamide are expensive, and many developing countries may not be able to afford the regimens if both the drugs are prescribed for the total duration. One way of making the regimen relatively inexpensive is by limiting the two drugs to the first two months only. Thus, a course of RSHZ daily for 2 months may be followed by maintenance chemotherapy with an inexpensive combination—thioacetazone plus isoniazid (TH), which can be self-administered by the patient. Table 8²⁸ summarises the results of a study in East Africa, employing such inexpensive regimens.

It will be seen that the 6-month regimens are unsatisfactory and the duration of treatment should be increased to 8 months if TH is employed in the continuation phase. The three 8-month regimens are all highly effective, the best

TABLE 8
Low cost short-course regimens

Regime n	Relapses (%)	
	6 month	8 month
2 SHRZ/TH	12	0
1 SHRZ/TH	19	7
2 SHR/TH	18	6

results being obtained with the regimen containing a 2-month intensive phase with the 4 drugs, RSHZ. Reducing the duration of the intensive phase to 1 month or the number of drugs during this phase to three (i.e. excluding pyrazinamide) results in a slightly lower efficacy, with relapse rates of only 6 or 7%. Thus, all the three inexpensive regimens have high and acceptable levels of over-all efficacy. In another study, results of continuation chemotherapy with isoniazid alone for 6 months (after 2 SHRZ) were highly encouraging, with about 1 % relapses during a 6-month follow-up.

Regimens for high prevalence of initial resistance

All the results presented in the earlier sections

are based on patients infected with drug sensitive cultures. Table 9 summarises findings on patients with initial drug-resistance admitted to two short-course studies in Madras^{18, 19}. The data are presented separately for the rifampicin regimens (2 SHRZ/3 SHRZ₂, 2 SHRZ/5 SHZ₂, 3 SHRZ, and 3 SHRZ/2 SH₂) and non-rifampicin regimens (2 SHZ/5 SHZ₂ and 3 SHZ/2 SHZ₃).

It will be seen that streptomycin resistance was of no consequence. With the rifampicin regimens, resistance to isoniazid alone was of little consequence, and while 23 % failed in the presence of resistance to both the drugs, the over-all results were very encouraging, with a failure rate of only 12 %. The proportions of failure are substantially higher in the group of patients treated with the non-rifampicin regimens- Indeed, this is one justification for employing the rifampicin regimens in preference to those without, especially in countries where the level of initial drug-resistance is high. In such situations it might be prudent to add a fifth drug (ethambutol) during the initial intensive phase while treating serious forms of tuberculosis such as tuberculous meningitis.

Short-course chemotherapy for other forms of tuberculosis

The efficacy of short-course regimens in pulmonary tuberculosis has been very clearly established in several controlled trials and in

TABLE 9

Patients with bacteriologically positive disease and initial drug-resistance response to short-course regimens

Resistance to :	Rifampicin regimens			Non-rifampicin regimens		
	Patients assessed	Failure during chemotherapy (%)	Relapses (%)	Patients assessed	Failure during chemotherapy (%)	Relapses (%)
S	36	0	11	24	4	4
H	68	7	6	33	36	14
Both	69	23	6	42	74	0
Any drug	173	12	8	99	44	7

diferent countries. There is, in contrast, very little information on the efficacy of such regimens in extra-pulmonary tuberculosis such as meningitis, lymphadenitis and tuberculosis of the spine. Many trials in extra-pulmonary tuberculosis are in progress, and it is hoped that this lacuna will be filled. One can safely assume that regimens which have been found to be effective in pulmonary tuberculosis with very large bacterial populations will be at least as effective in extra-pulmonary tuberculosis with much smaller numbers of bacilli. However, the problem of the blood-brain barrier in tuberculous meningitis and the possible impairment of the immune mechanism in tuberculous lymphadenitis may require special consideration in the choice of drug-regimens.

The choice of short-course regimens for Tuberculosis Programmes

By now we have many short-course regimens, with a wide range of cost and high levels of efficacy. Not all of them, however, are suitable for application under programme conditions in developing countries where tuberculosis is a major public health programme. The following are some of the important factors:

- (1) While an individual patient can be bestowed special attention, can be given more effective drugs, and can be monitored more frequently, such attention and care cannot be possible under mass chemotherapy under programme conditions. Treatment schedules for the programme should be simple and easy to operate and should not require too much of monitoring.
- (2) *Cost:* For most developing countries, cost of drugs is a major factor. There is a need to reduce the number of doses of pyrazinamide and rifampicin so that the regimen can be employed on a mass scale. The efficacy of the regimen may be compromised to some extent in the process, but this can be acceptable, provided the reduction in efficacy is not large.
- (3) *Level of success needed.* This is a basic decision which must be taken, keeping the cost of the regimens and the financial resources in view. Developing countries can ill-afford the 100% regimens used by technically advanced countries, employing rifampicin daily for 6 months or 9 months. The conventional 12-month regimens achieve less than 60% cure rate under programme conditions

in these countries, and short-course regimens with cure rate of 80% or over would be attractive and acceptable under such conditions. To begin with, one should aim for realistic short-course regimens, and when resources improve, one could aim to achieve the 100% or near 100% level.

- (4) *Facilities for injection:* In developing countries, most patients reside in rural areas where injection facilities may be limited, or indeed non-existent. The use of fully oral short-course regimens would be necessary in such a situation.
- (5) *Fully-supervised or self-administered regimens:* Again, in rural areas, it would be necessary to employ oral regimens capable of self-administration. In urban areas, however, fully supervised regimens may be preferred. Thus, the policy for the programme should be flexible and must take into consideration local operational factors.
- (6) *Toxicity:* The possibility of occurrence of adverse reactions to the drugs and the possible potentiating effect of one drug on the incidence and severity of adverse reactions due to a companion drug need to be borne in mind. The concomitant use of three potentially hepatotoxic drugs, rifampicin, isoniazid and pyrazinamide may pose a problem in special groups such as alcoholics and in patients with possible hepatic involvement in miliary tuberculosis. In general, intermittent regimens are likely to be less often associated with adverse reactions and hence may be preferred to daily regimens.
- (7) *Availability of the drugs:* One factor that is well appreciated is the non-availability of adequate and timely supply of drugs. Many developing countries depend almost entirely on imports for their requirements of anti-tuberculosis drugs, and especially so for rifampicin and pyrazinamide. This obviously poses limitations on the scale on which these drugs can be prescribed. Further, one must also take into consideration logistics of transportation of drugs from central locations to remote rural areas where the bulk of the tuberculosis patients reside.

It would be desirable that all the above

factors are taken into consideration while formulating short-course regimens for the programme. It is true that the short-course regimens have not been tried under programme conditions, and hence there is a justification for studying their efficacy and applicability under programme conditions. It should, however, be appreciated that the results of such studies would not be available in the near future. It would be unfair to deny the tuberculosis patients the benefits of the bactericidal drugs pyrazinamide and rifampicin merely because they have not been investigated under programme conditions. It is time that developing countries adopt short-course regimens for the programme, but build in systems of monitoring the acceptability and efficacy into the programme. Provided it is agreed that the regimens can be modified at a later date in the light of experience gained in the early stages, there should be no objection to the introduction of appropriate short-course regimens in the National Tuberculosis Programme.

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**SHORT-TERM CHEMOTHERAPY OF PULMONARY TUBERCULOSIS
INTERIM REPORT ON SECOND TUBERCULOSIS
ASSOCIATION OF INDIA TRIAL***

RESEARCH COMMITTEE OF THE TUBERCULOSIS ASSOCIATION OF INDIA

The first Short-term Chemotherapy Trial of the Tuberculosis Association of India was carried out under the supervision of its Research Committee from 3 institutions of Delhi in 1974-78. In that trial two regimens *viz.* Rifampicin (RMP) plus INH plus Streptomycin (SM) plus Ethambutol (EMB) and Pyrazinamide (PZA) plus INH plus SM plus EMB were tried. Although the sputum conversion after 20 weeks' treatment was almost 100% in both regimens, cumulative relapse rates during the subsequent 112 weeks were 32 % in the latter as compared to 16% in the former regimen. It showed that PZA could not replace RMP but the relapses even in RMP regimen were unacceptably high, probably because the duration of treatment, *viz.* 20 weeks, was not enough for the type of cases included in the trial. Another important finding of that trial was that the relapses were much more frequent in those where the sputum took longer than 8 weeks to convert.

Further, some other studies had shown that EMB had practically no place in short-term chemotherapy and if PZA was withdrawn after two months from a regimen containing at least RMP and INH, it did not detract from the over-all efficacy of the regimen.

Based on these findings, and also the desirability of reducing the cost of drugs as far as possible, the second trial was planned.

Methods and Material

Two regimens are being tried:

Regimen A

RMP plus IHN plus PZA for 8 weeks. Those who are sputum negative by direct smear at 8 weeks are randomly allocated to one of two sub-groups :

Group A₁: RMP+INH for 4 weeks followed by placebo for 14 weeks.

Group A₂ : RMP+INH for 18 weeks.

Those who are still positive by direct smear at 8 weeks continue RMP+INH to complete 26 weeks' total treatment.

Regimen B

The same as regimen A except that Streptomycin is given for first 8 weeks in addition to RMP+INH+PZA, other particulars of the regimen being exactly the same as for Regimen A.

The dosage schedules are as follows :

RMP	600 mg once daily.
INH	300 mg once daily.
PZA	750 mg twice a day.
SM	0.75 gm once daily.

Patients included in the trial had to fulfil the following conditions:

1. They should be between 15 and 45 years of age.
2. They should be residents of the city and there should be a reasonable chance of their continuing to stay in the city for at least 1½ years.
3. They should have had no or less than 10 days' anti-TB treatment previously.
4. Their sputum must have been positive at least twice by direct smear.
5. Extent of disease should not be more than 3 lung zones.
6. They should be willing for injection or any other treatment which is prescribed for them.

Patients falling in the categories mentioned below are ineligible for inclusion in the study:

1. Moribund patients.
2. Patients having pleural effusion obscuring more than 1/3rd of the lung field.
3. Patients suffering from any tuberculous or non-tuberculous complications, for example, diabetes, extra-pulmonary tuberculosis, etc., likely to interfere with management of the disease.
4. Patients known to be pregnant at the start of the study.
5. Patients whose weight is less than 35 kg.

All patients are to be hospitalised while on drugs. Four institutions in Delhi *viz.* New Delhi Tuberculosis Centre, L.R.S. TB Hospital,

*Paper presented at the 36th National Conference on TB & Chest Diseases held at Baroda in November 1981.

Mehrauli, R.B, IB Hospital, and Patel Chest Institute are participating in the trial.

During the course of treatment, x-ray chest is repeated at 8, 12 and 26 weeks. Two specimens of sputum are collected at the start of treatment and at 4, 8, 12, 16, 20 and 26 weeks thereafter. All specimens of sputum are put up for culture and sensitivity tests for the four drugs used in the trial are carried out on all positive cultures. Culture and sensitivity testing for sputum specimens from all the participating institutions are being carried out centrally in the laboratory of the New Delhi Tuberculosis Centre,

SGOT and SGPT tests are carried out for every patient before and on completion of treatment. In case of jaundice, liver function tests including bilirubin and thymol turbidity tests are to be carried out immediately. Haemoglobin, total RBC, total and differential WBC count, urine examination, etc. are carried out at the start of treatment and thereafter when necessary.

During the follow-up period, x-ray chest is to be carried out at 3, 6 and 12 months & sputum examination at 3, 6, 9 and 12 months. These examinations are to be repeated if the patient attends with symptoms at any time in the interval between the various tests.

Patients are to be withdrawn from the study only in case of major toxic reaction or intolerance to any drug. However, replacement of Streptomycin by PAS is permissible.

The intake was started in January, 1980 and this interim report is based on results upto 31st August, 1981.

Results

Table I shows that 146 patients have been included in the trial up-to-date. Thirty two patients have been excluded from analysis for one reason or other and 114 patients comprising 60 in group A and 54 in group B have been included in this analysis.

Table 2 shows the extent of disease and cavitation in the 114 cases included in the analysis. It would be seen that the groups were comparable, by and large, except that patients with involvement of more than 3 lung zones were a little more predominant in group A₁. Eighty three patients were males and 31 were females. Nearly two-thirds were in the age group 15-25 years (Table 2A).

TABLE I

Cases included in the Interim Analysis

	Group A	Group B	Total
Total Intake	74	72	146
Excluded from main analysis:			
Initial Culture Negative	4	3	7
Initial Culture not put up (Lab. mistake)		1	1
Protocol violated by mistake	1		1
Initial Drug Resistance	3	6	9
Not yet completed 4 weeks/ initial sensitivity result not yet available	6	8	14
INCLUDED IN PRESENT ANALYSIS	60	54	114

Two cases, both from group A, had to be withdrawn from the trial because of major toxic reaction. One of these had treatment for less than 4 weeks and the other between four and eight weeks. There has been no death.

Table 3 shows the results of sputum conversion in the two groups at each 4 week interval upto 12 weeks. It would be seen that the results are more or less comparable in both regimens.

An interesting feature of this table is the large number of cases who were positive by direct smear but negative by culture. In accordance with the protocol, patients who were sputum positive by direct microscopy at 8 weeks were to be continued on Rifampicin and INH for another 18 weeks. Of the 11 such cases in group A, 6 were direct smear negative & culture negative at 26 weeks, 2 have yet not completed 26 weeks and 3 cases either dropped out or were removed from the trial for inadvertent breach of protocol. Out of the 11 such cases in group B, 7 have been converted by direct smear and culture at 26 weeks, 2 have yet not completed 26 weeks (though they are already negative by smear and culture examination and 2 have dropped out).

It may also be mentioned that amongst the

TABLE 2
Extent of disease and cavitation in 114 cases included in the analysis

	Group A			Group B		
	A1	A 2	Total	B1	B2	Total
<i>Extent of Disease</i>						
1 Zone	5 10%	1	6	2	3	5 9 %
2 Zones	14 62%	23	37	21	18	39 72 %
3 Zones	11	6	17 28%	4	6	10 19 %
<i>Sides involved</i>						
U	14 52%	17	31	12	18	30 56 %
B	16 48%	13	29	15	9	24 44 %
<i>Cavitation</i>						
Nil	8 30%	10	18	8	7	15 28 %
Single	17 58%	18	35	17	14	31 57 %
Multiple	5 12%	2	7	2	6	8 15 %
	30 100%	30	60	27	27	54 100 %

TABLE 2 A
Age and sex distribution of 114 patients included in the analysis

	Group A	Group B	Total
Males	45	38	83
Females	15	16	31
15—25 Years	42	33	75
26—35 Years	10	16	26
36—45 Years	8	5	13
Total	60	54	114

Patients who continued drugs beyond 12 weeks (groups A2 and B2), there was only one who could technically be considered as unconverted in group A2 at the end of 26 week's treatment. However, he too was marked as such by mistake. In other words, the sputum conversion at 26 weeks in groups A2 and B2 was virtually 100%

All patients who were smear positive at 8 weeks in both groups and were therefore put on RMP+INH for 18 weeks, had converted by smear and culture at the end of chemotherapy for 26 weeks.

Table 4 shows the radiological results at 12 weeks and table 5 shows the results at 26 weeks in groups A₂ and B₂ who were given anti-tuberculous drugs upto 26 weeks. Even here the results are more or less comparable in the two groups. It is worth pointing out that many cases in group A₁ and B₁ who were on placebo from 12—26 weeks also showed continued radiological improvement during the period 12—26 weeks.

TABLE 3

Bacteriological Assessment at 4, 8, and 12 weeks

		Group A			Group B		
		4W	8W	12W	4W	8W	12W
Direct Microscopy	Number Assessed	60	56	53	54	50	44
	Sputum Neg. %	48.3%	80.4%	85.0%	57.4%	78.0%	90.0%
Culture	Sputum Neg. %	75.0%	98.2%	98.2%	75.9%	94.0%	100.0%

TABLE 4

Radiological Assessment at 12 weeks

	+2 +3	+1	No Change	Worse	Total Assessed
Group A	20% 36%	28% 50%	7% 12%	1% 2%	56% 100%
Group B	24% 50%	17% 35%	4% 8%	3 6%	48 100%

TABLE 5

Radiological Assessment at 26 weeks among patients continuing treatment (Groups A2 and B2)

	+2 +3	+1	Worse	Total Assessed
Group A ₂	21 78%	5 18%	1 4%	0 27 100%
Group B ₂	18 90%	1 5%	0	1 5 % 20 100%

TABLE 6

Bacteriological reversions (12—26 weeks) among patients attaining sputum conversion by culture at 12 weeks

		Groups A ₁ (Placebo)	Group A ₂ (R & H)	Group B ₁ (Placebo)	Group B ₂ (R & H)
Number followed		16	19	15	14
Relapses	Bacillary	1	-	2*	-
	Only Radiol	1	-	-	1
	Total	2	-	2	1

* One case DS positive at 16 weeks wrongly marked as reversion (Culture was negative)

TABLE 7

Relapses during 26 weeks' follow up after completing 26 weeks' treatment

		Group A ₁ (Placebo)	Group A ₂ (R & H)	Group B ₁ (Placebo)	Group B ₂ (R & H)
Number followed		11	7	9	7
Relapses	Bacillary	3	-	4*	-
	Only Radiological	1	-	-	1
	Total	4	-	4*	1

* One case DS positive at 16 weeks wrongly marked as reversion (Culture was negative)

Since the treatment after 12 weeks was different in the four sub-groups, the bacteriological results for the period 12-26 weeks are shown separately in Table 6 for those who were sputum negative by culture at 12 weeks. It would be seen that two reversions were noticed in group A₁ (one bacteriological and one only radiological) whereas both the reversions in group B₁ were bacteriological. There were no bacteriological reversions in groups A₂ and B₂.

Table 7 shows the relapses among patients in all the groups who have completed 26 weeks' follow-up after completing 26 weeks' treatment. Although no valid conclusions can be drawn at this stage because of small numbers, the table tends to show that the relapses among those whose treatment was stopped at 12 weeks were pretty high. There have so far been no bacteriological relapses among those treated for 26 weeks.

A noteworthy feature is that the bacilli in all relapses so far have been sensitive to all the drugs with which they were treated.

The 9 cases (3 in group A and 6 in group B) where the bacilli were initially resistant to one or other of the drugs tried in this study (table 1) were also followed. Of these 9, 7 have completed 26 weeks' treatment and they are all converted.

Conclusions

The only tentative conclusions that are possible at this stage are:

- (1) Addition of Streptomycin does not seem to influence at all the results obtainable from RMP+INH-PZA regimen in respect of speed of sputum conversion and reversions during the first 26 weeks of follow-up.
- (2) 12 weeks' treatment even with these potent regimens does not seem to be enough for the type of patients included in the trial.
- (3) All relapses so far have been caused by sensitive bacilli.

ORGANIZATIONAL EFFORT IN A CLINICAL TRIAL AND ITS RELEVANCE TO APPLICABILITY OF SHORT-COURSE CHEMOTHERAPY IN NATIONAL TUBERCULOSIS PROGRAMME

K.S. ANEJA¹ and G.E. RUPERT SAMUEL²

Summary : The high rate of treatment completions and the regularity of treatment achieved in clinical trials of Short-Course Chemotherapy, could possibly be attributed to efficient organizational set-up, careful selection of cases and all-out effort to control defaulters. The organizational effort put forth to achieve the regularity is relevant to the applicability of Short-Course Chemotherapy in the existing set-up of District Tuberculosis Centres under National Tuberculosis Programme. First 300 patients admitted to a Short-Course Chemotherapy trial to assess the efficacy of three drug regimens of 3/5 months duration under fully supervised conditions, being carried out jointly by the Tuberculosis Research Centre, Madras and National Tuberculosis Institute, Bangalore, have been analysed for that purpose. To keep up the regularity, 1/3 of the patients required home visits—some of them repeatedly. If the same type of defaulter retrieval actions are envisaged to be taken in the normal working conditions of a District Tuberculosis Centre catering to 500 patients in any one observation month. 350 to 300 home visits will have to be made in a month. This may not be feasible in the existing set-up of National Tuberculosis Programme. A new strategy of defaulter retrieval actions for programme conditions may have to be devised. Further, selection of drug regimen which has the maximum potential of being given on self-administered basis may reduce the work-load to a considerable extent.

Drug toxicity/side-effects and the cost of drugs may not be major handicaps. However, the only way to understand various operational problems is to undertake scientific operational studies in actual working conditions of National Tuberculosis Programme,

Introduction

In the management of pulmonary tuberculosis, emergence of Short-Course Chemotherapy is considered to be an event of major importance in patient management. From the operational point of view, however, its value lies in the feasibility of its application on a wider scale.

The applicability of Short-Course Chemotherapy in Programme conditions mainly depends upon patients' acceptability in terms of regularity of treatment and organizational effort in terms of work-load on the Health Care Delivery System within the available resources. No studies in this regard seem to have been reported so far.

It was therefore thought to be of interest to know the treatment completions, the default pattern, the factors contributing to irregularity and the organizational effort put forth for keeping the patients regular throughout a clinical trial, so as to generate thinking on the modalities of applying Short-Course Chemotherapy, in the existing organizational frame-work of National Tuberculosis Programme (NTP).

Material

A clinical trial of Short-Course Chemothe-

rapy was started in September, 1978, jointly by the Tuberculosis Research Centre (TRC), Madras, the National Tuberculosis Institute (NTI), Bangalore, and the Lady Willingdon Tuberculosis Demonstration and Training Centre, Bangalore, to assess the efficacy of 3 drug regimens namely, Rifampicin + Streptomycin + INH + Pyrazinamide daily for 3 months (RSHZ); RSHZ followed by Streptomycin + INH + Pyrazinamide twice a week for another 2 months (RSHZ/SHZ TW) and Streptomycin + INH + Pyrazinamide daily for 3 months followed by the same drugs twice a week for another 2 months (SHZ/SHZ TW). First 300 of the 381 patients admitted to the study, were analysed. The patients were supposed to take 91 doses to complete daily phase of 3 months and 18 doses to complete the biweekly phase of next 2 months. If a patient fell short of the stipulated doses, compensatory doses were given in each phase within a specified period.

The information relevant to the objectives was collected from the case-sheets of these patients. The analysis pertains to all the 3 groups combined but has been presented separately for the daily and biweekly phase. Compensatory periods were not considered.

From National Tuberculosis Institute, Bangalore

¹ TB Specialist

² Statistical Assistant

TABLE 1
Number of Patients Completing Various Stages of Treatment

	Regimens			Total
	RSHZ	RSHZ/SHZTW	SHZ/SHZTW	
No. Allocated	101	101	98	300
No. Completed 3 Months	96 (95.0)	95 (94.1)	96 (98.0)	287 (95.7)
No. Completed 5 Months	—	90 (89.1)	93 (94.9)	183 (92.0)
No. Completed Prescribed No. of Doses	95 (94.1)	89 (88.1)	93 (94.9)	277 (92.3)

Numbers in brackets indicate percentages out of the total numbers allocated to the regimen.

Findings

Treatment Completion

Patients completing various stages of treatment in each drug regimen are given in Table 1. The completion rates were very high. Only about 8 % did not complete the prescribed treatment.

Table 2 shows that of the 287 patients who completed 3 months of treatment, for 146 (51 %) patients, the daily phase period was extended to complete the prescribed number of doses. The number of doses compensated per patient ranged from 1 to 36. Similarly, during the biweekly phase; of the 183 patients, for 66 (36 %) patients treatment period was extended. The number of doses compensated per patient ranged from 1 to 10. Seventeen per cent of the patients missed 5 or more doses in daily phase and 7% in biweekly phase.

Of the 23 patients who did not complete the chemotherapy, 8 stopped it at the first month itself and 17 did not complete the daily phase of treatment.

Default Pattern

If a patient failed to attend for any dose in either phase of the chemotherapy, he was considered to have made a default. A continuous default, irrespective of the number of days or the doses missed as a result of it, was considered as one default.

In the daily phase, 141 (49.1%) patients did not make any default and 32 (11.1 %) made 4 or more defaults. The mean number of defaults made was 1.4.

Ind. J. Tab., Vol. XXIX, No. 1

TABLE 2

Distribution of Patients by the Number of Doses Missed Due to Default

No. of Doses Missed	Daily Phase		Biweekly Phase	
	No.	%	No.	%
0	141			63.0
	44			19.7
	22			4.9
	20			3.3
	12			1-6
	48			6.6
	287		183	
Doses Missed	770		178	

In biweekly phase, the corresponding figures were 34.4%, 13.1% and 1.5% respectively. The proportion of the patients making various number of defaults was more in biweekly phase.

The mean number of defaults for different categories of patients was compared and found to be significantly more in males, age group 25

TABLE 3
Distribution of Patients by the Number of Defaults Made

Phase of Chemotherapy	Total Patients	No. of Defaults					Mean
		0	1	2	3	4+	
Daily	287	141 (49.1)	69 (24.0)	28 (9.8)	17 (5.9)	32 (11.1)	1.4
Biweekly	183	63 (34.4)	52 (28.4)	30 (16.4)	14 (7.7)	24 (13.1)	1.5

Number in brackets indicate percentage out of total patients.

and above, those engaged in occupations requiring frequent movement, and alcoholics.

It is evident from Table 4 that the proportion of the defaulters progressively increased with each successive month. However, there was not much difference between 4th and 5th month.

Reasons for Default

Irrespective of the phase of chemotherapy, the reasons for defaulting as told by the patients were classified in broad headings and are given

below:

1. Appearance of new symptoms/ aggravation of symptoms .. 27%
2. Out of station .. 22%
3. Family/social obligation or domestic problems .. 14%
4. Difficulties associated with the occupation .. 10%
5. Festivals or religious functions or disturbances in the city .. 9%
6. Confusion in understanding the instructions or visited late .. 9%

TABLE 4
Distribution of Patients by the Number of Defaults Made in Each Month of Treatment

Months	NO. of Patients	No. of Defaults				
		0	1	2	3	4+
<i>Daily Phase</i>						
I	292	232 (79.5)	44 (15.1)	8 (2.7)	5 (1.7)	3 (1.0)
II	288	198 (68.8)	57 (19.8)	18 (6.2)	10 (3.5)	5 (1.7)
III	287	287 (66.9)	56 (19.5)	21 (7.3)	13 (4.5)	5 (1.7)
<i>Biweekly Phase</i>						
IV	185	97 (54.2)	57 (30.8)	19 (10.3)	8 (4.3)	4 (2.2)
V	183	96 (52.5)	54 (29.5)	16 (8.7)	12 (6.6)	5 (2.7)

Numbers in brackets indicate percentages out of number of patients in second column.

TABLE 5

Management of Adverse Symptoms

Month	No. of Patients	No. with Adverse Symptoms	No. Requiring Symptomatic Treatment	No. Requiring Modification of Chemotherapy		
				Regimen Modified	Drugs Withheld	Modified and Withheld
<i>Daily Phase I</i>						
I	292	169 (57.9)	153 (52.4)	2 (0.7)	8 (2.7)	6 (2.1)
II	288	195 (67.7)	158 (54.9)	30 (10.4)	4 (1.4)	3 (1.0)
III	287	166 (57.8)	138 (48.1)	22 (7.7)	3 (1.0)	3 (1.0)
<i>Biweekly Phase</i>						
IV	185	68 (36.8)	66 (35.7)	1 (0.5)	1 (0.5)	
V	183	35 (19.1)	35 (19.1)			

Numbers in brackets indicate percentages to patients in second column.

Adverse Symptoms

The adverse symptoms might have been due to reactions to the drugs, aggravation of disease or coincidental super added ailments. Month-wise occurrence of adverse symptoms, symptomatic treatment given and modifications of chemotherapy affected has been shown in Table 5. Nearly half the number of patients needed special attention and symptomatic relief during daily phase of the treatment. Intensive actions were required for a much smaller number of patients. The maximum adverse symptoms requiring modification of treatment, were observed in the second month. In the biweekly phase, the adverse symptoms observed and the actions taken were considerably less.

Organizational efforts*(a) Staffing Pattern*

To keep up the regularity of the patients in terms of default prevention and default retrieval,

the 2 Medical Officers (MO) responsible for the day to day work were assisted by a Public Health Nurse (PHN), 6 Health Visitors (HV) and 3 Social Workers (SW). In addition, there was 1 Senior MO provided for overall supervision of the study. Further, a supervisory team of senior officers consisting of an MO and a PHN from TRC supervised the study once in every 2 to 3 months for 3 to 4 days regularly.

(b) Selection of Patients

A strict criteria for admission into the study was laid down. The patients living outside Bangalore Corporation area, below the age of 12 years who had previous anti-tuberculous treatment for more than 14 days, judged to be non-co-operative having other concomitant diseases which might lead to difficulties in the management of the patient and those who were not fit to undergo domiciliary treatment, were excluded.

Suitability of the patient was methodically assessed by an MO, an SW and an HV for 5 to 7 days. Apart from that, the close relatives of the patient were also interviewed to ensure co-operation. An initial home visit was made by an HV and an SW to assess domiciliary stability, family set-up, socio-economic background including employment, income, details regarding previous treatment and patients co-operation with regard to treatment, follow-up and home visits.

During the period of intake, a total of 1,221 patients were registered but only 300 were admitted into the study. Considerable effort was thus put forth in careful selection of patients and elimination of nearly 3/4 of the cases who could have been a source of irregularity in treatment during the trial.

(c) Management of Default

If a patient failed to attend for any dose, a home visit by an HV was arranged either on the same day, if possible, or the next day. Repeat visits were continued each day till the patient reported. In case of special social problems or other difficulties, a visit by an SW and/or an MO was also undertaken. A weekly meeting was held to discuss about the defaulter actions for

problematic patients who failed to attend for a long time. It can be seen from Table 6 that the proportion of patients making various number of defaults increased with each successive month; so also the work-load in terms of home visits and clinic motivations done.

(d) Follow-up During Treatment Phase

Follow-up examinations were done monthly. At each month, 2 overnight collection and one spot specimens of sputum were examined. A full plate X-ray of the chest was taken at the end of 1 and 3 months and 5 months for those who were in the 5 months' regimens. Intensive organizational effort was put in to achieve maximum coverage at each follow-up.

(e) Adverse Symptoms

If a patient made a spontaneous complaint of an untoward symptom to any staff member, he was referred to an MO. Careful questioning and clinical examination was done. Laboratory tests like blood sugar, liver function test, etc., if necessary, were undertaken by referring the required specimens to other suitable institutions for which a rapport was created. Symptomatic treatment/modification regarding reduction of doses/temporary withdrawal or termination of

TABLE 6

Number of Defaulters and Total Number of Actions Taken in Each Month

Month	No. of Patient	No. Making Various Nos. of Defaults	Total No. of Home Visit Made	Total No. of Clinic Motivations Done
<i>Daily Phases</i>				
I	292	60 (20.5)	73	118
II	288	90 (31.2)	104	214
III	287	95 (33.1)	145	213
<i>Biweekly Phase</i>				
IV	185	88 (47.6)	139	157
V	183	87 (47.5)	134	167

Numbers in brackets indicate percentage out of the number of patients.

drug (s) was made according to the individual patient requirements.

Other efforts

Apart from careful selection of the patients at the initial stages and the organizational effort put during the treatment, a good relationship was maintained between the staff and patients to achieve regularity of high order during the treatment. To meet this end, some financial assistance in the form of bus fare was given to the patients. Likewise, a liaison was made with TB and general hospitals to meet with the eventualities requiring hospital admission. Thus, 8% of the patients were given financial assistance and for 5 patients, TB hospital admission was arranged for varying periods. Had these efforts not been made, probably their regularity would have been affected.

Organizational set up for Defaulter Control in NTP¹

(a) Man-power

In the District Tuberculosis Centre (DTC), the matching organization for default prevention and retrieval consists of a District Tuberculosis Officer (DTO), who is assisted by a second MO and only 2 HVs. There is no provision for a PHN or an SW. Further, the DTO and 1 HV remain on tour for nearly half the time in a month in connection with implementation and maintenance of District Tuberculosis Programme.

(b) Patients

In the DTC, all patients diagnosed to be suffering from tuberculosis, irrespective of their clinical conditions presence of concomitant diseases and previous treatment are put under treatment. There is no selection made by the organization. No effort is made to assess the domiciliary stability or patients' co-operation for treatment, follow-up and home visits. There is no provision for any financial assistance to keep up the regularity.

(c) Default Prevention and Retrieval

At the initiation of the treatment, the patient is motivated by DTO/MO and an HV in the Clinic, wherein emphasis is laid on treatment completion. Repeat motivation is done at each collection every month. However, if a patient does not come for drug collection within 3 days of the due date under the self-administered drug regimen or misses 2 consecutive injections under supervised regimen, he is considered to have made a default. Only two defaulter actions are recommended for each treatment default. The first action is taken by posting a letter to the pati-

ent soon after he is declared a defaulter. The second action is taken by a home visit for motivating him/family members on the 8th day after the first action.

(d) Follow-up

A new patient put on treatment becomes eligible for first follow-up examination 6 months after initiation of treatment by sputum examination on direct smear, X-ray examination being optional. The second follow-up examination becomes due 12 months after initiation of treatment when both X-ray and sputum examinations could be ordered.

For TB patients who continue beyond the limit of optimum treatment, there are no fixed recommendations for follow-up examinations. Each case is decided by DTO on individual circumstances.

(e) Management of Adverse Symptoms

In the supervised drug regimen, there is an opportunity for the MO to know about the adverse symptoms and take necessary actions whereas in self-administered oral drug regimens, patients are seen only once in a month except when he reports on his own for any unexplained symptoms. Further, very few ancillary drugs are provided in a DTC to tackle with the adverse symptoms.

No assistance is provided to seek admission for any untoward happenings in TB/general hospital except for giving reference letter if asked for.

Discussion

The feasibility of the application of Short-Course Chemotherapy on a wide scale is expected to usher a new era of tuberculosis treatment service. The anticipated advantages are lower failure or relapse rates, higher probability of permanent sputum negativity in drug defaulters, exposure to toxicity of drugs for lesser duration, better acceptability of treatment and less work-load on the Health Care Delivery System.

The cost of the drugs, however, is considered to be a major handicap. The cost of the drug regimens used in this trial is much more than the cost of the regimens widely used in NTP (Table 7)².

There is, however, already a sharp fall in prices, particularly that of Rifampicin, and with the large scale use of these drugs, the prices are expected to come down further. There is also a recommendation of the establishment of a

TABLE 7
Cost of Drugs for 45 Kg Patient at Current Prices

	I Phase	II Phase	Total Duration (Months)	Total No. of Doses	Cost (Rs.)
Clinical Trial	3 Months	2 Months			
	RSHZ	-----	3	91	880
	RSHZ	SHZ TW	5	109	1010
	SHZ	SHZ TW	5	109	510
N.T.P		TH	12	365	55
		PH	12	365	535
		SHTW	12	104	160

SOURCE : Tuberculosis Research Centre, Madras.

Regional Revolving Fund (3rd Regional Seminar on TB Chemotherapy, 1979) in collaboration with international agencies for the supply of drugs used in Short-Course Chemotherapy in developing countries. It is, therefore, likely that the drugs will be available in NTP.

In the absence of any study of the applicability of Short-Course Chemotherapy in operational conditions of NTP, the envisaged advantages listed above may or may not be real. A comparison of the staffing pattern in the clinical trial and the existing organizational set-up of NTP shows a wide gap. The organization for the management of default in NTP is at a level of about 30% of that of a clinical trial. On the contrary, 3/4 of the total registered cases not admitted in the clinical trial who were definitely more prone to irregularity will also have to be treated in programme conditions, as there is no selection of patients for treatment in a DTC—a situation conducive to more irregularity and default.

Treatment completions and the pattern of drug default cannot be compared in a clinical trial and operational conditions of NTP as the situations are entirely different. Even so, such a comparison may help in better understanding of the factors responsible for the gaps. A retrospective analysis of the Treatment Cards for one calendar year in Bangalore, (Seetha *et al* 1976)

showed that if collection of 80 % of the total treatment is considered as a satisfactory level of treatment completion, 37 % of the patients completed 12 months' treatment within 15 months. In an operational study (Baily *et al*, 1974), to assess the efficacy of self-administered Thioacetazone + INH regimen and supervised biweekly Streptomycin +INH regimen for 12 months in programme conditions, treatment completions were 31 % in the former and 56 % in the latter regimen. On the other hand, in the clinical trial, with the permissible extension period of treatment, the completion was as high as 92 %. The duration of treatment here, however, was 3 to 5 months only. Presuming 5 months to be the dead end of chemotherapy in programme conditions, the treatment completions in both the studies quoted above were around 60%. Thus, there is a wide gap of treatment completions between the clinical trial and operational situation, although strict comparison cannot be made. The gap could possibly be attributed to heavy organizational set-up, careful selection of cases and all out efforts to control default in clinical trial situation. Similarly, the comparison of default pattern in different situations (Table 8), shows that the defaulting is more common in the programme than in the clinical trial situation.

Further, in the programme, the loss due to default was much more in the first 2 to 3 months

TABLE 8

Default Pattern in Different Situations

	No. of Patients	Proportion of Patients Making Various Number OF Defaults			Range
		0	1	4+	
Trial					
Daily Phase – 3 months	287	49.1	24.0	11.1	0-13
Biweekly Phase – 2 Months	183	34.4	24.8	13.1	0-8
Operational study-12 Months					
Biweekly Supervised Regimen	134	9.7	29.1	38.1	0-17
Self-Administrated Daily Regimen – Months Collection	189	11.1	45.0	16.4	0-8
Programme Condition-15 Months					
Self-Administrated Daily Regimen – Months Collection	522*	20.1	19.3	32.0	0-10

NOTE ; *Patients Completing 15 Months Period without Interruption of 2 or More Months.

of treatment, whereas in the clinical trial, defaulting increased with each successive month. The timing of the default is relevant as the intensity of retrieval actions in the programme could be manoeuvred accordingly.

Defaulter retrieval effort is another important aspect. Some of the defaulters did not require home visit as they reported of their own on the next day and some required repeat home visits before they could be retrieved. For example, in the first month, of the 60 defaulters, 45 required home visits; 73 home visits were made and 118 clinic motivations were done. Thus, in the clinical trial, home visits for 15% of the patients had to be made for reasons of default in the first month. This proportion increased thereafter and in the 4th and 5th months, 1/3 of the patients required home visits. Further, each defaulter required 2 home visits on an average before he could be retrieved. In an average DTC, there may be about; 500 patients on treatment in any one month of observation. 65 % of the patients collect the drugs on due date leaving 35% for defaulter retrieval actions. Thus, if the

defaulter retrieval actions taken in the clinical trial are envisaged to be taken in a normal working condition of a DTC, 250 to 300 home visits have to be made in a month. Under the existing organisational set-up of NTP, this may not be

required to be taken for defaulter retrieval are actually not taken. In the analysis of Treatment Cards quoted above, no action was taken for 23% of the defaulters and for those for whom action was taken, delay was observed for a considerable proportion of the defaulters. Moreover, the defaulter actions as recommended under NTP for standard chemotherapy may not be strictly applicable for Short-Course Chemotherapy. A new strategy may have to be developed.

An important basis of the acceptability of a drug regimen is its toxicity/side effects. Major toxicity requiring modification or withdrawal of drugs for Short-Course Chemotherapy, is shown to be 3% to 6% (Third East African/BMRC 1978). In this trial, such modifications were effected in 2.9% to 12.8% of the patients,

the maximum being in the second month. However, side-effects which although they may not require termination of the therapy, may be troublesome enough for the patients to discontinue the treatment under programme conditions, particularly if the regimens are given on self-administered basis. In a clinical trial in Singapore (Singapore/BMRC Study 1978), such side-effects were 20 %. In this trial, adverse symptoms due to drugs alone have not been analysed separately, but all the adverse symptoms caused by various factors including side-effects to drugs were reported by 50% of the patients in the first 3 months. The reporting of such complaints was much less thereafter. The side-effects to Thioacetazone and PAS widely used in the NTP are also reported to be about 30% (TB Chemotherapy Centre, Madras, 1966). It is, therefore, expected that the patients receiving Short-Course Chemotherapy in NTP may not be at an excessive disadvantage. Even so, they will require medical attention and additional drugs for symptomatic treatment.

Thus, there are multiple factors which interact and influence the out-come of chemotherapy in programme conditions and there could be a gap between what the regimens are potentially capable of achieving and what in fact could be achieved under programme conditions. A drop in efficacy is inevitable. In case of standard chemotherapy, this drop is 30% (Baily, 1974). The extent of this drop for Short-Course Chemotherapy is not known. The question is how to minimise this drop? One of the solutions could be to select the drug regimen(s) which has the maximum potential of being given on self-administered basis. Such drug regimens will not only be comparatively cheaper, but the home visits for defaulter retrieval could also be limited to the initial intensive phase followed by less intensive efforts in the continuation phase wherein drugs could be issued on monthly basis thereby reducing the work-load of the home visits to a considerable extent. Optimization of the drug regimens suitable for application in programme conditions is therefore absolutely necessary. Another possibility would be to continue with the existing procedures of defaulter retrieval as are advocated in NTP. In that case, the duration of treatment has to be extended to accommodate the prescribed number of doses. For this trial, if the compensatory doses were not permitted in the extended period, the completion of treatment would have been 34.7 % against the 92 %. In the retrospective study mentioned earlier, the average period taken by a patient to make 12 collections was 14.4 months. How much extension could be permitted without affecting the treatment in programme conditions for Short-Course Chemotherapy, is not known.

Sputum smear examination is a standard method for the assessment of the progress during treatment in NTP. With Short-Course Chemotherapy regimens, especially those which contain Rifampicin as one of the drugs, there is appreciable occurrence of smear-positive culture-negative specimens in the early months of treatment (TB Research Centre, Madras 1979). This possibly is due to the fact that the healing process does not keep pace with the rapid killing of the bacilli. Thus, dead bacilli continue to be excreted for an appreciable period of time, though such a smear positivity is of no consequence. The positive smear results during Short-Course Chemotherapy may, therefore, not always indicate failure of chemotherapy. The use of sputum smears for monitoring the progress of patients on Short-Course Chemotherapy, therefore, may not be dependable. A change in follow-up methodology may be required.

Thus, for deciding about the feasibility of application of Short-Course Chemotherapy in operational condition of NTP, the available knowledge based on the clinical trials, is just not enough. The conceptual thinking about some of the operational problems has already been brought out by NTI (Aneja, 1977 and 1979), but the only rational way to get the answer to various operational problems posed in the discussion above, is to undertake scientific operational studies in actual working condition of NTP.

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AGRA STUDY OF SHORT-COURSE CHEMOTHERAPY IN PULMONARY TUBERCULOSIS PATIENTS

M.L. MEHROTRA*

Summary : The efficacy of five short course chemotherapeutic regimens, is compared. In two 4.5 month regimens and in one 3 month regimen the four most potent anti-tuberculous drugs, isoniazid, rifampin, pyrazinamide and Streptomycin were given daily for the initial 3 months of treatment. In another 4.5 month regimen and 3 month regimen a fifth drug, ethionamide, was given along with the above four drugs for the initial 3 months. After initial 3 months, the subsequent 1.5 month treatment in two 4.5 month regimens consisted of isoniazid, pyrazinamide and streptomycin intermittently twice weekly. Bacillary conversion was achieved in 96 percent patients at 2 months and in 99 percent at 3 months, and it was of a similar order at each stage of treatment both in 4 and 5 drug regimens. Drug compliance in 4 drug regimens was substantially higher (91 percent) as compared to 5 drug regimens (81 percent).

A relapse rate of 5 percent followed the 3 month regimen during 12 month follow-up period after completion of treatment as against 3 percent in 4.5 month regimens.

Introduction

Chemotherapeutic regimens of 12 month duration that include an initial intensive phase with standard anti-tuberculous drugs, isoniazid, streptomycin, thiacetazone and pyrazinamide, have shown promise in the treatment of pulmonary tuberculosis in controlled clinical trials (Mehrotra *et al*, 1970). The most important finding in these trials was that the disease relapsed in only a few cases, and relapses occurred with drug—susceptible strains.

Encouraged by these results, attempts were made to shorten the duration of treatment to 9 months with similar regimens. Nine months' treatment with regimens not including rifampin were quite effective (Mehrotra *et al* 1979 and Hong Kong Chest Services/BMRC 1977).

Introduction of rifampin, a bactericidal anti-tuberculous agent, increased the hope of decreasing the duration of treatment even further. Controlled trials by the British Medical Research Council and others (Hoag Kong Chest Services/BMRC, 1977 and Dorous *et al*, 1970) established the possibility of decreasing the duration of anti-tuberculous chemotherapy to 6 months. *In vitro* studies (Mitchison 1978 and Grosset 1978) showed that rifampin was the most useful drug for bacillary sterilization. The work of Pretet and colleagues (Patel *et al* 1978) indicated the success of 4.5 month treatment, with a daily regimen of isoniazid, rifampin, pyrazinamide and streptomycin.

Thus, there is experimental and clinical evi-

dence that daily, and daily plus intermittent short course 4 to 6 month regimens consisting of the four most potent drugs have great efficacy in the treatment of pulmonary tuberculosis.

Results of various *in vitro* and clinical studies encouraged us to conduct a controlled clinical trial with regimens of as short a period as 3 months. Hence, the present study was designed to determine (1) whether, the duration of chemotherapy with the available bactericidal drugs could be decreased to 3 months: (2) whether four or five of the most potent drugs would be needed for 3 month chemotherapy: (3) if 3 month chemotherapy was not sufficient and further follow-up therapy was required, whether daily therapy with two oral drugs or an economical intermittent regimen without rifampin would be equally suitable : (4) whether ambulatory and domiciliary chemotherapy could be applied from the very first day of treatment.

Methods

A total of 360 bacteriologically confirmed cases of pulmonary tuberculosis were admitted into the study. The following were the criteria of case selection: (1) the pulmonary tuberculosis was bacteriologically confirmed (microscopy positive for acid-fast bacilli) at the time of admission to the study and was later confirmed by positive culture of the same specimen, (2) the patient was 12 or more years of age, (3) the patient was a resident of Agra city, (4) the patient did not have any other concomitant disease or pregnancy that might complicate management of the disease, (5) the patient was available for 2 year follow-up

* Director Professor,
T.B. Demonstration Training Centre & Chest Institute,
Agra 282 002 (U.P.)

TABLE 1

Drug Regimens-Initial

Regimen	Dose months	Duration	Dosage of Doses	Total No.
RSZH		3		78
RIFAMPIN (R) STREPTOMYCIN(S) PYRAZINAMIDE (Z)	10 mg/kg 0.75 gm 35 mg/kg		Each drug given in a single dose 6 days/wk.	
RSZHE		3		78
RSZH ETHIONAMIDE (E)	As above 7— 10 mg/kg		As above The drug given in two divided doses every day 6 days/wk.	
RSZH/S ₂ H ₂ Z ₂		4.5		90
RSZH STREPTOMYCIN ISONIAZID PYRAZINAMIDE	As above 0.75 gm 14 mg/kg (SO mg/kg	(3) (1.5)	As above Each drug given twice weekly in a single dose.	
RSZHE/RH		4.5		115
RSZHE RIFAMPIN ISONIAZID	As above 10 mg/kg 5—8 mg/kg	(3) (1.5)	As above Each drug given daily for 6 days/wk.	

after cessation of chemotherapy, (6) the patient had received no previous treatment for pulmonary tuberculosis or had received no more than 15 days of anti-tuberculous therapy.

Chemotherapeutic regimens. Initially, there were two major 3 month regimens. One consisted of four drugs, rifampin, streptomycin, pyrazinamide, and isoniazid. The second included a fifth drug, ethionamide, in a daily divided dose of 7 to 10mg/kg of body weight. These regimens were followed for 1.5 month with either placebo or extended chemotherapy for a total of 4.5 months of treatment. For the four drug regimen, the 1.5 month follow-up chemotherapy consisted of streptomycin, isoniazid, and pyrazinamide twice weekly. For the 5 drug regimen, the 1.5 month chemotherapy consisted of rifampin and isoniazid daily for 6 days/wk.

Patients fulfilling the criteria for admission to the study were randomly allocated to one of the four regimens (table 1).

After approximately 9 months, by which time 121 patients had been admitted to the study, preliminary analysis showed that the five drug regimen with ethionamide had no superiority over the four drug regimens. In fact, it increased the side effects and default rate. We, therefore, modified the study design by eliminating ethionamide (but patients already initiated on 5 drug regimen remained unaffected), leaving the three regimens summarised in Table 2. (Hereafter, we will refer to these regimens by the abbreviations introduced in the tables 1 and 2). The random allocation of patients to these regimens was continued.

Modification of drug doses: In special circumstances, drug dosages were modified so that fractions of tablets did not have to be given. For example, in patients of low weight (≤ 35 kg), the dose of isoniazid was 200 mg; pyrazinamide, 10 g; rifampin 300 mg; streptomycin 0.5 gm. daily, until the patient achieved a weight of 36 kg. During extended twice weekly intermittent therapy in patients weighing less than 36 kg, the

TABLE 2
Drug Regimens Studied

Regimen	Doses*	Duration months	Dosage	Total No. of doses
RSZH		3		78
Rifampin (R)	10 mg/kg		Each drug given in	
Streptomycin (S)	0.75 gm		a single dose 6 days/	
Pyrazinamide (Z)	35 mg/kg		wk.	
Isoniazid (H)	5-8 mg/kg			
RSZH/RH		4.5		115
RSZH	As above	(3)	As above	
Rifampin	10mg/kg	(1.5)	Each drug given	
Isoniazid	5-8 mg/kg		daily for 6 days/wk	
RSZH	As above	(3)	As above Each	
Streptomycin	0.75 gm	(1.5)	drug given	
Isoniazid	14 mg/kg		twice weekly	
Pyrazinamide	60 mg/kg			

*For modification of doses to meet special conditions, see text.

dose of pyrazinamide was decreased from 2.5 to 2.0 g-

Pre-treatment investigations: Before start of any therapy, the patients underwent the following test (1) a tuberculin skin test with 1 TU of purified protein derivative RT XXVII with Tween (R) 80 read at 48 to 96 hours; (2) Postero-anterior roentgenograms of the chest, including a full size, large film and a 70 mm small film; (3) Examination of 3 sputum specimens by direct microscopy, by culture, and by drug-susceptibi-

count and estimation of haemoglobin concentration; (5) Urinalysis, especially for sugar, albumin and red blood cells; (6) initial weight; (7) personal history of previous treatment for tuberculosis, pregnancy, and any other relevant factors, such as smoking; (8) clinical examina-

Management. All patients were ambulatory from the very first day. They were motivated to attend the institution for 2 hours in the morning on week days (Monday through Saturday) for supervised administration of drugs and any necessary investigations, according to the protocol.

During the initial 3 month phase, the patients were first administered rifampin capsules on an empty stomach, followed 1 hour later by 0.5 L of milk and subsequent injection of streptomycin and administration of isoniazid and pyrazinamide pills. They were then allowed to return home to continue their normal duties and work, and required to return to the clinic the next morning.

During the 6 week continuation phase after completion of 3 month administration of RSZH were called on two fixed days every week. Patients receiving a 6 week follow-up regimen of RH received the drugs daily for 6 days every week.

Patients were called at monthly intervals for 2 years. During this period, patients in all regimens were given placebo tablets consisting of calcium lactate.

Investigations during treatment. During treatment, patients were observed for toxic and adverse symptoms and signs daily during initial intensive phase. Every week, two sputum specimens were examined by microscopy, by culture

and by drug susceptibility tests. Postero-anterior chest films (a large film and 70 mm film) were obtained 3 months after start of chemotherapy. Weight and haemoglobin concentration were recorded, and urine specimens were analysed. Any other investigations required were also carried out. Patients were questioned about previous therapy with antituberculous drugs. Each patients' progress was carefully assessed.

Investigations during follow-up period. All patients in the study were to be followed for 2 years after completion of chemotherapy. During the follow-up phase, patients were offered the following investigations: Sputum Examination by microscopy, culture, and drug-susceptibility testing every month; a 70 mm chest film at 6 month intervals and a large film at 12 months; any other investigations required. Each patient's progress was assessed every 6 months.

Intake of patients. During a period of 39 months from July 1977 to October 1980, a total of 360 patients fulfilling the criteria of case selection were admitted to the study; 91 received the RSZH regimen; 30, the RSZHE regimen; 89, the RSZH/RH regimen; 30, the RSZHE/RH regimen; and 120, the RSZH/S₂H₂Z₂ regimen (table 3).

Exclusion of patients. A total of 67 patients

(20 in the RSZH, 4 in the RSZHE, 12 in the RSZH/RH; 8 in the RSZHE/RH; and 23 in the RSZH/S₂H₂Z₂) were excluded from the study for various reasons: 20 were initial culture negative or had contaminated cultures; 42 had previous history of anti-tuberculous treatment for pulmonary tuberculosis; one had diabetes, one had atypical infection, and the remaining 3 continued to take anti-tuberculous treatment even after scheduled period of chemotherapy (Table 3).

Study population. After these initial exclusions, 293 patients remained in the study: 71 in the RSZH regimen; 26 in the RSZHE regimen; 77 in the RSZH/RH regimen; 22 in the RSZHE/RH regimen; and 97 in the RSZH/S₂H₂Z₂ regimen (table 4)

The patients in the three treatment series were comparable in respect of age, sex, extent of disease, and bacillary content of the sputum.

Defaulters. Patients who took less than 90% of the allocated chemotherapy were classified as defaulters. According to this definition, interruption of treatment for more than 10 days of a 4.5 month regimen and more than 7 days of a 3 month regimen was treated as a default.

The defaulters are shown in table 4 for various regimens. The default rate was substantially

TABLE 3

Admissions and Exclusions

Patients	RSZH	RSZHE	RSZH/RH	RSZHE/RH	RSZH/ S ₂ H ₂ Z ₂
Admitted	91	30	89	30	120
Excluded					
initial culture negative or contaminated	5	2	4	4	5
Previous anti-tuberculous treatment.	13	2	7	2	18
Concomitant disease	—		1	—	—
Atypical infection	1		—		
Extension of treatment against advice	1			2	
TOTAL	20	4	12	8	23

For description of drug regimens, see tables 1 and 2.

TABLE 4
Patients remaining in the Study

Patients	RSZH	RSZHE	RSZH/RH	RSZHE/ RH	RSZH/ S ₂ H ₂ Z ₂	Total
Completed treatment	58	19	68	18	88	251
Defaulter	8	5	7	4	7	31
Withdrawn because of toxicity	5	2	2		2	11
TOTAL	71	26	77	22	97	291

For description of drug regimens, see tables 1 and 2.

higher when ethionamide was included in a regimen of same duration. Default rates were comparable in all regimens without ethionamide, ranging from 7 to 11 %. The default rates in regimens containing ethionamide were 18 and 19%. Furthermore, during subsequent 1.5 month phase after initial 3 months' treatment in regimens of 4.5 month duration, the absence on due dates for drug administration was a rare event.

Interruption of regimen because of toxicity. Patients were withdrawn from the study if the entire regimen or some constituent drug of the regimen had to be stopped for a period which otherwise classified the patient as a defaulter. The criteria used to identify drug toxicity were extreme intolerance, challenge, and clinical observation of toxic reactions. As shown in table 4, in 7 % of patients in RSZH regimen, in RSZHE regimen 3% in RSZH/RH regimen, and 2% in RSZH/S, H₂Z₂ regimen, toxicity necessitated withdrawal.

Analysis: Data for all patients including defaulters, and those whose chemotherapy was interrupted because of toxicity were included in the analysis. However, data for patients, with interrupted therapy (by default or toxicity) were not included in calculations of rates of culture conversions, relapse, and radiographic improvement.

Results

Radiographic appearances: All 58RSZH patients assessed at 3 months after start of chemotherapy showed regression of the pulmonary lesions: 26 % regressed markedly, and 74 % regressed moderately. AH 19-RSZHE patients asses-

sed at 3 months showed regression of pulmonary lesions: 16% marked and 84% moderately. Of 68 RSZH/RH patients assessed at 3 months, 97% showed regression of pulmonary lesions (28% marked, and 69% moderate) and 3% showed no change. Of 18 RSZHE/RH patients assessed at 3 months, 89 % showed regression of pulmonary lesions (17% marked, and 72% moderate) and 11 % showed no change. Of 88 RSZH/S₂H₂Z₂ patients assessed at 3 months, 97% showed regression of lung lesions (22% marked and 75% moderate) and 3% showed no change (Table 5).

At 6 months, all patients in RSZH, RSZHE and RSZH/RH regimens showed regression of pulmonary lesions. Of 64 RSZH/RH patients 98 % showed regression of pulmonary lesions; and 2 % showed no change. Of 18 RSZHE/RH patients, 94% showed regression of pulmonary lesions and 6 % showed no change. Of 86 RSZH/S₂H₂Z₂ patients, 98 % showed regression of pulmonary lesions and 2% showed no change. At 12 months, of 45 RSZH patients, 98% showed regression of pulmonary lesions and 2% showed deterioration. Of 18 RSZHE patients, 95% showed regression of pulmonary lesions and 5% showed deterioration. Of 18 RSZHE/RH patients 94% showed regression of pulmonary lesions and 6% showed no change. Of 56 RSZH/S₂H₂Z₂ patients, 98 % showed regression of pulmonary lesions, 2% showed no change and 2% showed deterioration.

Thus, the regression of pulmonary lesions at different stages of treatment and follow-up was of a similar order in all the five regimens. The regression of pulmonary lesions continued even after the cessation of chemotherapy (Table 6).

TABLES
Radiographic Appearance

Months after start of treatment	No. Assessed	Radiographic Appearance, %			
		Marked Regression	Moderate Regression	No. Change	Deterioration
<i>3 Months</i>					
RSZH	*58	26	74		
RSZHE	19	16	84		
RSZH/RH	68	28	69	3	
RSZHE/RH	18	17	72	11	
RSZH/S ₂ H ₂ Z ₂	88	21	75	3	
TOTAL	251	23	74	3	
<i>6 Months</i>					
RSZH	55	43	57		
RSZHE	19	42	58		
RSZH/RH	64	37	61	2	
RSZHE/RH	18	33	61	6	
RSZH/S ₂ H ₂ Z ₂	86	38	60	1	

TABLE 6

Correlation of regression of Pulmonary lesion with period after start of Chemotherapy in Patients followed to 18 Months

Regimen	No. assessed	% with marked regression of Pul. lesions			
		3m	6m	12m	18m
RSZH	35	31	49	54	57
RSZHE	16	19	50	56	56
RSZH/RH	27	30	37	56	59
RSZHE/RH	17	18	35	59	59
RSZH/S ₂ H ₂ Z ₂	39	18	49	61	61

Culture Conversions:

At 1 month, 72 % of RSZH, 97 % of RSZHE, 81% of RSZH/RH, 72% of RSZHE/RH and 82% RSZH/S₂H₂Z₂ patients had negative cultures. Because the regimens contained either 4 drugs (RSZH) or 5 drugs (RSZHE), the pooled culture conversion rate was 79% for patients receiving RSZH and 76% for patients receiving RSZHE regimen during the initial month.

At 2month, 93% of RSZH, 100% of RSZHE 94M of RSZH/RH, 94% of RSZHE/RH, and 98% of RSZH/S₂H₂Z₂ patients had negative cultures. The pooled culture conversion rate was 95% for patients receiving RSZH and 97% for patients receiving RSZHE regimen during 2 months.

At 3 months, all patients in each regimen had negative culture. At 4.5 months, all patients in the rive treatment series had negative cultures (table 7).

Relapse. Relapse was denned as culture reversal observed for 4 consecutive months with radiographic lesions showing deterioration after the successful completion of prescribed chemotherapy which was defined as administration of more than 90% of prescribed chemotherapy along with negative cultures and radiographic lesions showing no deterioration at the time of cessation of prescribed chemotherapy.

During first year of follow-up after successful completion of chemotherapy 1 (2.5%) of 40 RSZH patients who completed one year of

follow-up, 2 (10.5%) of 19 RSZHE, 1 (2.9%) of 34 RSZH/RH, 1 (5.6%) of 18 RSZHE/RH, and 1 (2.4%) of 42 RSZH/S₂H₂Z₂ patients relapsed. Of these 6 relapses, 5 had susceptible strains and one had strain resistant to isoniazid and streptomycin (table 8)

The relapse rate during first year of follow-up was of a similar order for all the regimens. The pooled relapse rate was 5% for regimens of 3 month duration, and 3.2% for regimens of 4.5 month duration.

Adverse reactions: In all the five regimens, adverse reactions to anti-tuberculous drugs were observed mainly during the initial 2 months period. Interestingly, with the regimens containing ethionamide, adverse reactions occurred during the first month only. With the remaining regimens without ethionamide, adverse reactions occurred with maximum frequency during the second month. The overall rate of adverse reactions was 17.4% for regimens without ethionamide and 23.4% for regimens containing ethionamide.

In regimens without ethionamide, arthralgia though transient attained the highest frequency: 24 (10%) of 241 patients complained of arthralgia, vomiting occupied second place with 2% patients, jaundice occurred in 1.7% patients, giddiness in 1.2%, peripheral neurities in 1%, and skin rash, vertigo, itching and flu syndrome in 0.4% patients each. In regimens containing ethionamide, vomiting was the major complaint which occurred in 23.4% patients, and skin rash occurred in only 2.1 % patients (Table 9).

TABLE 7

Culture conversion in 251 Patients completing treatment

Months after start of treatment	Culture negative %				
	RSZH	RSZH	RSZH/RH	RESHE/RH	RSZH/S ₂ H ₂ Z ₂
	n-58	n-19	n-68	n-18	n-88
0	0	0	0	0	0
1	72	79	81	72	82
2	93	100	94	94	98
3	100	100	100	100	100
4.5	100	100	100	100	100

TABLE 8

Bacteriological relapse within first year after completion of chemotherapy

Regimen	First Year follow-up			
	No. Assessed	Patients relapsed		
		Total	With susceptible strain	with resistant strain
RSZH	40	1	1	—
RSZHE	19	2	1	1
RSZH/RH	34	1	1	—
RSZHE/RH	18	1	1	—
RSZH/S ₂ H ₂ .Z ₂	42	1	1	—

TABLE 9

Type and frequency of adverse effects

Type of adverse effects	No. with adverse effects				
	5*		6		13*
2. Vomiting	1	8	2	3**	2+
3. Jaundice	1	—	—	—	—
4. Sensation of Heat	2	—	—	—	—
5. Giddiness	2	—	—	—	—
6. Peripheral Neuritis	1*	—	—	—	—
7. Skin rash	—	—	—	1**	1
8. Vertigo	1	—	—	—	—
9. Itching	—	—	—	—	1
10. Flu syndrome	—	-	1	-	-
TOTAL	12	8	13	3	17

*One patient in common

**One patient in common

†One patient in common

Drug Toxicity leading to withdrawal from the study

With regimen containing ethionamide 4.3% of patients had to discontinue ethionamide because of gastro-intestinal toxicity. With regimens containing isoniazid, rifampin, pyrazinamide and streptomycin for initial 3 months, 3.7 percent of patients had to discontinue treatment because of toxicity (table 10).

Gastro-intestinal toxicity was experienced by 4.3% patients on regimens containing ethionamide and by 0.4% patients on regimens without ethionamide. In the former group of patients, ethionamide was completely withdrawn and in

the latter group of patients, all drugs had to be discontinued for 2 weeks. Hepatic toxicity occurred in 1.2% of patients receiving RSZH, In all these patients all drugs had to be discontinued for more than one month. Vestibular toxicity necessitating discontinuation of treatment occurred in 1.2% of patients treated with RSZH during the initial 3 months. Excessive sensation of heat occurred in 1.2% patients on RSZH during the initial 3 months and treatment was discontinued for 2 or 3 weeks because of toxicity.

Acceptability of the regimens: As seen in table 4, the default rates were substantially higher for patients receiving regimens containing ethionamide. Thus, regimens containing isoniazid.

TABIF 10

Drug toxicity leading to withdrawal from the regimens

Type of toxicity	No. with toxicity				
	RSZH n-69	RSZHE n-26	RSZH/RH n-76	RSZH/RH n-21	RSZH/ S ₂ H ₂ Z ₂ n-96
Gastro- intestinal	-	2	-	-	1
Hepatitis	1	-	2	-	-
Vestibular	2	-	-	-	-
Skin Rash, Hypersensitivity	-	-	-	-	1
Vascular	2	-	-	-	1

TABLE 11

Influence of shortening duration of Ambulatory Chemotherapy on success rate and drug coat

Study	Year	Regimen	Duration months	Success rate	Cost US \$
Singapore (BMRC)	1979	(2m) RSZH/RH	6	99	113
Chemotherapy Centre, Madras	1979	(2 m) RSZH/SHZ	7	100	84
Agra	1 979	(3 m) RSZH	3	95	53
		(3 in) RSZH/RH	4.5	97	79
		(3 m) RSZH/S ₂ H ₂ Z ₂	4.5	97	97

rifampicin, pyrazinamide and streptomycin during the initial 3 month-phase were probably more acceptable.

Cost. The findings of the present study at Agra as well as studies at Madras and Singapore (Fox *et al* 1979) are set out in table 11. Regimens including a follow-up phase with rifampin are costly compared to regimens consisting of intermittent phase without rifampin, yet the two regimens are of nearly equal efficacy.

Discussion

One of the main objectives of our study was to determine whether short-course (3 month) chemotherapy with rifampin, isoniazid, streptomycin and pyrazinamide would be effective or whether addition of a fifth drug would be required. We used ethionamide as the fifth drug but it did not improve the regimen; instead, it increased the default rate, adverse effects and withdrawal rate from the regimen because of toxicity. Therefore, the plan of the study was modified by dropping ethionamide. Three regimens, one of 3 months' duration, and two of 4.5 months' duration were continued.

The intake of patients has been a bit slow because the protocol required admitting only untreated patients from the city of Agra.

All three short-course regimens in the present study were successful in achieving 100% bacillary culture conversion within 3 months. In another limited clinical trial by Kreis *et al* (Pretet *et al* 1976) in France, daily administration of high-dose isoniazid, rifampin and streptomycin for 3 months, resulted in a bacteriological conversion in all patients within 3 months.

First year follow-up after cessation of chemotherapy in patients who successfully completed prescribed treatment indicated a 5% relapse rate for regimens of 3 months' duration and 3% relapse rate for regimens of 4.5 months' duration. Thus chemotherapy seems to be relatively short of the ideal duration. A subsequent clinical trial of a 5 month short course regimen at Madras (Tripathy 1979) using RSZH for 2 months followed by SZH for 3 months was followed by a 3% relapse rate. Another study by Pretet and colleagues (Pretet 1978) using RSZH daily for 18 weeks did not show any relapse in 6 to 18 months of follow-up.

In the East African and British Medical Research Council Short Course Study (Aluoch 1978) in which RSZH was given for 2 months, followed by HRZ or HR for 2 months, the relapse rate was 11 to 14%. The Singapore/British

Medical Council trial (Singapore T.B. Service/BMRC 1979) using this same regimen showed a 5 to 10% relapse rate. Furthermore, the East African/BMRC study (Aluoch 1978) showed a considerable decrease in the relapse rate from a range of 28% to 41% to a range of 11% to 14% when the regimens included rifampin along with other drugs for the entire 4 months rather than just 2 months. *In vitro* studies by Grosset (1978) indicated that for bacillary sterilization, a duration of 3 months was enough and rifampin was the most useful drug.

Streptomycin was also found to play an important role in the short course regimens, as indicated by the fact that a short course regimen without streptomycin had 11% more relapses (Aluoch, 1978).

Of 6 patients experiencing relapse in the present study at Agra, 5 had susceptible strains at the time of relapse. The Madras study also showed that all cases of relapse occurred with strains susceptible to isoniazid and streptomycin. Other studies have yielded similar findings. Thus, retreatment of relapse cases is no problem and standard drugs can be used.

Acceptability of four drugs daily by the patients was very good. In the present study, the default rate was 9 to 11%. Thus, approximately 90% of patients could tolerate the allocated chemotherapy.

Adverse reactions to anti-tuberculous drugs were mild and transient. Few toxic reactions necessitated stopping chemotherapy (4%) in 4-drug regimens. A study of the side effects of short course regimens by Zierski and Bek (1980) detected side effects in 16% of patients, compared to 16% in the present series.

In our earlier study (Mehrotra *et al* 1970) of a regimen containing pyrazinamide along with the other three drugs but without rifampin, arthralgia occurred in 24% of patients. Surprisingly, the complaint of arthralgia by the patients in the three regimens of the present study at Agra was of the order of only 10%. In the Madras study, 14% of patients receiving regimens containing rifampin and 34% of patients receiving regimens without rifampin complained of arthralgia. Rifampin might be responsible for prevention of the accumulation of uric acid in the serum. In the study by Zierski and Bek (Zierski *et al* 1980), there were very few complaints of arthralgia.

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**INTERMITTENT SHORT-COURSE CHEMOTHERAPY OF PULMONARY
TUBERCULOSIS
(52 Doses in 26 Weeks)**

K.V. KRISHNASWAMI,* N. SETHDRAMAN** and R.PARTHASARATHY***

Summary : Two six months' short course twice weekly intermittent regimens of chemotherapy comprising Streptomycin, Isoniazid and Pyrazinamide with the addition of Rifampicin for the initial two months in the first regimen (RI) and a non rifampicin regimen (RII) with Ethambutol administered throughout, were studied. Considering the patients' acceptability, efficacy (bacteriological and radiological), the incidence of relapse and cost factor, RI has been found to be better.

Introduction

Several controlled clinical trials, throughout the world, have confirmed the efficacy of short course chemotherapy. There is however no universal agreement on the optimum duration of shortened chemotherapy yet. In Hong Kong it is 9 months, in East Africa it is 6 months and in India it may be 6 months or less. Besides shortening the duration, it will be desirable to reduce the number of doses given for each patient. To evaluate a regimen with the fewest number of doses administered in shortest duration and commensurate with efficacy, as shown by immediate satisfactory bacteriological conversion and least relapse rate, a study was undertaken with a total number of 52 doses, administered twice weekly, without an initial daily phase, for a period of 26 weeks.

Plan and Conduct of the Study

Criteria for selection

1. Persons over 12 years of age;
2. Radiological evidence of pulmonary tuberculosis confirmed bacteriologically by sputum smear examination of two spot and one home collections;
3. No previous treatment for tuberculosis;
4. No evidence of any complication, extra pulmonary tuberculosis or concomitant diseases like diabetes, hepatic or renal dysfunction;
5. Permanent residents of the area served by the clinic.

Regimen of Chemotherapy

The two regimen studied were: RI
2 S₂H₂Pz₂R₂/4S₂H₂Pz₂

Streptomycin, Isoniazid and Pyrazinamide administered as single dose twice a week for 6 months with the addition of Rifampicin for the first 2 months.

RII 6 S₂H₂Pz₂E₂

Streptomycin, Isoniazid, Pyrazinamide and Ethambutol administered as single dose twice a week for 6 months.

Dosage

S Inj.	Streptomycin	I.M.	1 gm.
H Tab.	Isoniazid	—oral	650 mg.
Pz Tab.	Pyrazinamide	— oral	3 gm.
R Cap.	Rifampicin	— oral	600 mg.
E Tab.	Ethambutol	— oral	2 gm.

The drugs were administered under full supervision at the clinic in all cases.

Investigations

Pre-treatment

Full plate postero-anterior chest radiograph was taken. Two sputum examinations for tubercle bacilli by smear and culture and drug sensitivity tests complete haemogram and liver function tests (including SGOT&SGPT) were done, besides routine urine examination.

During treatment

Two sputum specimens, one spot and another home, were examined bacteriologically by smear and culture for Mycobacterium Tuberculosis and drug sensitivity tests were carried out every

*Professor and Head of the Department of Tuberculosis and Chest Diseases, Madras Medical College; Chest Physician, Government General Hospital; Director, Institute of Tuberculosis and Chest Diseases, Chetput, Madras—600 031.

**Tutor in Tuberculosis and Chest Diseases and Asst. Surgeon.

***Statistician.

month. Radiograph of chest, haematological and urine examinations were done at 2 and 6 months.

During Follow-up

Once every 2 months after completion of chemotherapy, bacteriological examination of two sputum specimens, one spot and one home, was done by smear and culture and drug sensitivity tests were carried out. Chest radiograph was also taken. The follow-up was for a period of 24 months.

Study Subjects

Newly diagnosed cases, from among the chest symptomatics, attending the clinic formed the pool from which cases were selected based on the criteria vide supra. After the radiological stratification as "Limited or Less" or "Moderate or More" (Tuberculosis Chemotherapy Centre, 1960) and matching, 100 patients were randomly allocated to the two regimens.

5 patients in the RI and 2 in RII prematurely discontinued treatment and for one case in each of the regimens treatment had to be changed because of initial drug resistance. The number of cases analysed were 44 in RI and 47 in RII.

in-patient care, if need arose, on account of side effects or complications. However, none of the patients needed in-patient care.

Results of the Chemotherapy

Over 90% drug collections were made by over 95% and 85% of patients in the limited or less and moderate or more disease respectively in both regimens.

Bacteriological Conversion

The results of the monthly culture of patients in the RI and RII regimens showed :

- (a) Proportionally less conversion rates were seen in RII, although differences do not attain statistical significance.
- (b) Maximum of 98 % and 94 % sputum conversion was attained in RI and RII groups from 3rd month and 4th month respectively. However, the difference was not statistically significant.
- (c) At 6 months, 1 case in RI and 3 in RII regimens were treatment failures respectively.

TABLE I

Distribution of Cases

Regimen	Radiological Extent						Total
	Limited or Less			Moderate or More			
	M	F	T	M	F	T	
RI	15	5	20	15	9	24	44
RII	10	4	20	21	6	27	47
Total	31	9	40	36	15	51	91

20 patients in each regimen had limited or less and 24 and 27 had moderate or more extent of disease radiologically in RI and RII respectively.

The entire course of treatment and follow-up

(d) In the one case under RI regimen, the bacilli were still sensitive to the drug at the end of chemotherapy. Among the failure cases under RII regimen, 2 showed resistance to Isoniazid and in the other the bacilli were found sensitive to all the drugs.

TABLE 2

Bacteriological Conversion

Regimen	No. studied		Month of review					
			1	2	3	4	5	6
R I	44	No. Neg.	30	40	43	43	43	43
		%	68	91	98	98	98	98
R II	47	No. Neg.	27	39	42	44	44	44
		%	57	83	89	94	94	94

TABLE 3

Bacteriological Conversion According to initial Radiological Extent

Review at	Regimen	Total	Initial Radiological Extent					
			Limited or Less			Moderate or More		
			No.	Converted	%	No.	Converted	%
2nd	RI	44	20	18	90	24	22	92
Month	R II	47	20	18	90	27	21	78
6th	RI	44	20	20	100	24	23	96
Month	R II	47	20	20	100	27	24	89

Proportionately higher conversion rates were observed in RI regimen than in RII regimen in the moderate or more group.

Though the limited or less group showed higher proportions of conversions both in the RI and RII regimens at the 6th months, in the moderate or more group the differences were not statistically significant. Nor did the higher proportion of conversions in the moderate or more

group under RI regimen and the higher proportion of conversions in the limited or less group, at the 2nd month review, have any statistical significance.

Comparing the rates of conversion between those allocated to RI regimen and those to RII regimen also did not show any statistical significance both in the limited or less and moderate or more groups.

Radiological Assessment

The X-rays were read independently by two Medical Officers with an umpire reading in case of disagreement.

Complete cavity closure was seen among those who completed 6 months' chemotherapy in 21 (48%) in the RI regimen and 25(53%) in the RII regimen, the difference being not statistically significant.

TABLE 4

Radiological Assessment

			Limited or Less		Moderate or More	
			RI	RII	RI	RII
2nd Month	No.		20	20	24	27
	Ext. Reg. (%)		80	65	88	59
	Cav. Reg. (%)		75	65	92	41
6th Month	No.		20	20	24	27
	Ext. Reg. (%)		90	90	96	78
	Cav. Reg. (%)		95	90	96	82

Radiological Assessment

It is observed that RI regimen ensured a higher proportion of regression of extent as well as cavity in both limited or less and moderate or more groups.

The limited or less group had not shown any statistically significant difference in the regression in the extent of disease proportionately between RI and RII regimen, both at 2nd month and 6th month review.

In the moderate or more group at the 2nd month the difference between the proportions of regression of the extent of the disease in the RI and RII regimens was statistically significant ($0.01 < P < 0.02$) and the proportions of cavity regression also had a statistically significant difference ($P < 0.0n$).

At the 6th month, in the Moderate or More group, the proportions of regression in extent was different, the difference verging on statistical significance ($.05 < P < 0.1$); but the proportions of a cavity regression did not show a statistically significant difference between the two regimens.

The radiological lesion (extent) was stationary in 2 patients in the RI regimen and 6 in the RII regimen.

Side effects of Drugs

The patients were closely monitored with adequate laboratory investigations during treatment. The liver function tests did not show any abnormal variations during chemotherapy. There was also no abnormal change in the haemogram.

TABLE 5
SIDE EFFECTS

	RI		RII	
	M	F	M	F
Nausea and Vomiting	3	3	1	6
Arthralgia	4	3	1	7

A few patients with minimal side effects were equally distributed in both the regimens. However, under RII regimen more women were seen to have side effects than men.

In none of the cases was there any need to withdraw any drug in view of drug toxicity.

Follow-up

Follow up investigations were done every two months upto 24 months after completion of treatment. The criterion for relapse was taken as eversion to bacillary status of two sputum specimens by culture taken at an interval of two weeks.

the effectiveness of intermittent regimens have been furnished by *in vitro* and *in vivo* studies (Grumbach *et al*, 1964, Dickenson and Mitchison, 1966 (a), 1966(b), Grumbach *et al*, 1967, Mitchison, 1970). Studies on Isoniazid dosage and rhythm of administration led to the observation that a higher peak concentration of Isoniazid in the serum was essential for the response to treatment rather than its continuous inhibitory level in the serum (Gangadharan *et al*, 1961; Tuberculosis Chemotherapy Centre, 1964, 1970).

The efficacy of a drug depends not only on its bactericidal activity but also principally on the length of time that bacterial multiplication

TABLE 6

Relapse

Months	RI (43 patients)			RII (44 patients)		
	No.	Cumulative	%	No.	Cumulative	%
0 — 6	-	-	-	4	4	9.2
6 — 12	-	11	2.3	2	6	13.6
12— 24	-	1	2.3	6	13	13.6

9 % of the RII cases had relapsed during 0—6 months of follow up against no instance of relapse among RI cases, a statistically significant ($P < 0.02$) difference.

The single instance of relapse under the RI regimen was observed at the 12th month of follow up, against there having been 2 more relapses in RII regimen during 6—12 months of follow-up. The difference between the cumulative proportions was found to be statistically significant ($0.02 < P < 0.05$).

No further relapse was observed in both the regimens during 12—24 months of follow up.

Discussion

Intermittent Chemotherapy besides being therapeutically efficacious has lower toxicity and cost. It lends itself to full supervision and eliminates concealed irregularity; detection of drug default and prompt correction is easier.

The rationale of, and the explanation for

is inhibited after exposure to the drug (Dickenson & Mitchison, 1966).

In the Guinea pig studies by Dickenson & Mitchison (1970), Rifampicin has been found to be the most suitable drug for intermittent administration and has given better results than daily treatment even when the interval between the doses was increased to 8 days. Similar results were reported by Batten (1969).

Intermittent chemotherapy with Streptomycin 1 gram and Isoniazid 650 mg. twice weekly was found to be as efficacious as daily Paraminosalicylic acid and Isoniazid in standard primary chemotherapy (Tuberculosis Chemotherapy Centre, 1964). Oral intermittent chemotherapy with PAS and Isoniazid (Tuberculosis Chemotherapy Centre, 1973), Ethambutol and Isoniazid (Krishnaswami, K.V. *et al* 1974, 1977; Tripathy, S.P., 1974) have also been found efficacious in the standard primary chemotherapy.

Based on the above reports, intermittent Short Course Chemotherapy has been considered an effective mode of therapy. Such a therapy will

have the added advantage in the form of lower toxicity and cost, besides rapid bacterial conversion and lower failure and relapse rates. Several studies in East Africa, India and other parts of the world have established six months as optimal duration for a highly efficacious Short Course Chemotherapy, restricting the relapse rate to 5% or less.

Studies in East Africa (1976) and Madras (1978) show that, where full supervision of an intermittent regimen in the continuation phase is possible, Streptomycin with Isoniazid and Pyrazinamide thrice a week can give 100% favourable results in 7 months, and 95% in 6 months, (n Hong. Kong, Streptomycin, Rifampicin, Isoniazid and Pyrazinamide given 3 times a week for 4 months followed by twice weekly Streptomycin, Isoniazid and Pyrazinamide was found 99% efficacious at 8 months and 95 % at 6 months. Another regimen with Streptomycin, Isoniazid and Pyrazinamide thrice a week for 9 months cured 95% of patients. The relapse rates were 24 % and 21 % at 6 months and 6 % and 6 % at 9 months in the thrice weekly and twice weekly regimens respectively.

In a pilot study in France (1976) regimens of Streptomycin with 900 mg. of Isoniazid and 1200 mg. of Rifampicin given either daily or 3 times a week, for only 3 months to patients with bacteriologically confirmed pulmonary tuberculosis, gave a relapse rate of 13 %.

In the Singapore/BMRC study (1979) after two weeks of daily chemotherapy with Streptomycin, Isoniazid and Rifampicin the patients received one of the 4 regimens, namely, Rifampicin 900 mg. or 600 mg. with high dose of Isoniazid (15 mg/Kg) twice a week or 900 mg, or 600 mg. with high dose of Isoniazid once week. At 1 year both twice weekly regimens were uniformly successful and in the once weekly regimen the overall quiescence rate was 95%. Relapses were very few.

In the Bucharest Tuberculosis Research Institute study of Intermittent Short Course Regimen (1977), two regimens were tried. After an initial phase of 3 months with Rifampicin and Isoniazid, twice a week in one regimen and with Streptomycin, Isoniazid and Ethambutol twice a week in the other, either Ethambutol plus Isoniazid or Streptomycin plus Isoniazid twice a week were given in the continuation phase which lasted for 6 months. At the end of 9 months treatment failures were 1.8% out of 112 in the Rifampicin group as against 3.4% out of 88 in the non-Rifampicin group. Relapse rates at 15 months follow up from the end of treatment were 5.6% of 89 in the Rifampicin Group and

8.9% of 79 in the non-Rifampicin group. Relapses were negligible among patients with limited extent of disease and significantly high in those with extensive lesions in the Rifampicin regimen.

In The German Democratic Republic once weekly Rifampicin (1200 mg) with Isoniazid has been tried without any daily phase. There were a few failures and a few relapses. (Lancet, 1976).

In the first short course chemotherapy study at Tuberculosis Chemotherapy Centre Madras, all patients received an initial intensive chemotherapy with Streptomycin, Isoniazid, Rifampicin and Pyrazinamide (for 2 regimen) or Streptomycin, Isoniazid and Pyrazinamide (for one regimen) daily for 2 months, followed by twice weekly Streptomycin for 3 months or 5 months so that the total duration of chemotherapy was 5 months or 7 months. The 7 months Rifampicin regimen had no relapses, reducing the duration to 5 months and absence of Rifampicin in the other regimen resulted in the relapse rates of 3 to 5%. In their Second study a 3 months daily regimen of Streptomycin, Isoniazid, Rifampicin and Pyrazinamide was compared with two other 5 months regimen. In the latter, for the first treatment Streptomycin, Rifampicin, Isoniazid and Pyrazinamide and Streptomycin, Isoniazid and Pyrazinamide were given followed by Streptomycin, Isoniazid and Pyrazinamide twice weekly for 2 months. The 3 months regimen had a relapse rate of 12 %. In the other case, the Rifampicin containing regimen had a relapse rate of 3 %, while the non-Rifampicin regimen had 10 % relapse (Tripathy, S.P., 1981).

In the present study, the intermittent administration of drugs from the beginning has proved highly effective. The regimen was fully supervised at the clinic. The regularity among patients was over 90%. The mouth-wise bacteriological conversion rate is proportionately more in RI regimen and reaches 98% by the 3rd month.

It is also observed that the radiological improvement is seen significantly earlier in the "Moderate or More" cases with RI regime.

Among the patients who were followed up for 24 months subsequent to chemotherapy, only one relapse (2 %) had occurred in RI regimen and 6(14%) in RII regimen.

The patients' acceptability was very good, the side effects in both the regimens being minimal except for Arthralgia occurring in patients on both regimens probably due to Pyrazinamide, a constituent of both the regimens.

The cost of RI regimen works out to

approximately Rs. 407/- per patient whereas the RII regimen costs Rs. 461/-per patient.

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SHORT TERM CHEMOTHERAPY IN CHILDREN : THREE YEARS FOLLOW UP**

H.B. DINGLEY*

Summary : The results of treatment of 134 children suffering from the childhood and adult type of pulmonary tuberculosis randomly allocated to one of the following four drug regimens have been reviewed at the end of three years:

Group A: INH + PAS + Thiacetazone. Group B: INH + Pyrazinamide+Ethambutol. Group C; INH + Pyrazinamide + Rifampicin. Group D : INH + Thiacetazone. Patients in groups A,B,C, received drugs for 26 weeks followed by placebo for 26 weeks. Patients in group D received drugs for 78 weeks. AH patients were kept in the hospital for 26 weeks.

Bacteriological confirmation was obtained in 4, 6, 6 and 3 patients respectively. Radiologically, group C had more patients with extensive, bilateral disease and mediastinal glandular enlargement. Though bacteriological conversion was similar in groups B, C and D, radiological regression was more in group C.

Introduction

Tuberculosis is a chronic disease requiring prolonged treatment. Available drugs are specific and, if given in good regimens regularly and uninterruptedly, are highly effective. Effective treatment is associated with quick relief of symptoms complex though it has its own drawbacks i.e. early stoppage of treatment before the target of therapy is achieved, thus leading to unsuccessful treatment. The reasons for failure of chemotherapy are many e.g. patients stopping the treatment prematurely because of amelioration of constitutional symptoms and feeling of well being or irregularity in taking drugs due to various socio-economic reasons. The result is either more relapses or a clinical situation, where re-treatment is associated with failure. Short course chemotherapy by giving those drugs which can destroy the bacilli in the shortest possible time can overcome such a situation. Studies carried out in our country and elsewhere have shown that the results of short course chemotherapy are very encouraging. Since most of these studies have been carried out in adults, a controlled study was carried out in children to determine whether short course chemotherapy would be equally successful in them as well.

Material

The results of treatment of 134 children suffering from the childhood and adult type of pulmonary tuberculosis randomly allocated to one of the following four drug regimens have been reviewed at the end of three years.

Group A : INH+PAS+Thiacetazone.

Group B : INH+Pyrazinamide+Ethambutol.

Group C : INH+Pyrazinamide+ Rifampicin.

Group D: INH+Thiacetazone.

Patients in groups A, B&C received treatment for 26 weeks and for the following 26 weeks, placebo was given while patients in group D received treatment for 78 weeks. All patients were kept in the hospital for 26 weeks and followed; the subsequent treatment in Group D was domiciliary.

Criteria for the Selection of Patients

Patients included in the study were between the ages of 1 to 14 years. They were residents of Delhi and were likely to stay in Delhi for the duration of the study for three years. Patients admitted in the study had no anti-tubercular treatment before or for not more than 10 days. Their tuberculin test was be positive.

Patients with the following conditions were not included:

1. Markedly marasmic or with haemoglobin less than six grammes.
2. Those suffering from any non-tuberculous complications or with extra pulmonary tuberculosis and with TB meningitis.

* Hony. Associate Professor in Tuberculosis, All India Institute of Medical Sciences. Consultant in Chest Diseases, E.S.I., Delhi. Medical Superintendent;

L.R.S. TB Hospital, Sri Aurobindo Marg, New Delhi-110030.

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Investigations Done

1. Tuberculin test.
2. X-ray P.A. view of the chest at the beginning and repeated at 8, 16, 26, 52, 78, 104 and 156 weeks.
3. Direct Smear Sputum examination wherever available with culture and sensitivity studies for the drugs used in the regimen; bronchial lavage and gastric lavage every month upto 52 weeks and subsequently along with X-ray chest at 78,104 and 156 weeks.
4. Complete haemogram at the start and at the end of treatment.
5. Urine examination at start and as and when required thereafter.
6. Weight record.
7. SGOT, SGPT test before and at the end of the treatment.
8. Ophthalmoscopic examination at the start and end of treatment.

Patients were randomly allocated by opening the envelopes marked serially.

Assessment of the Patients included in the Study

Age and Sex: Table 1 shows the age and sex of the children included in the study.

Mean age of the children included in the study in all the groups was the same. Regarding sex; the groups were alike, except there were less males in group C. This was a chance phenome-

non and had no significant influence on the ultimate results.

Bacteriological Status : Table II shows the result of sputum examination and tuberculin reaction. The number of patients with positive sputum was more in groups B and C than in groups A and D. The average mean tuberculin reaction was similar in all the groups.

Radiological Stains is shown in Table III. Extent of disease and cavitation was more in groups A and C. Involvement of 4 or more lung zones was maximum in group C and similar in groups A and D. The enlargement of paratracheal glands was more in groups B and C. Taking into consideration the radiological status as a whole group C had more patients with cavitary and extensive, bilateral disease and mediastinal glandular enlargement.

Fall Outs : Table IV shows that two patients died in groups A, B and C and two and eight patients in groups B and D respectively left the hospital before completing treatment. These have been excluded from final assessment as their stay was less than one month.

Results: Bacteriological conversion is shown in Table V. In all the patients sputum was converted by the 5th or 6th week of treatment, irrespective of the drug regimen.

In group A (H+P+T) one patient reverted at 52 weeks and was given alternative treatment and for assessment purposes at 78, 104 and 156 weeks has been considered as positive.

Regarding radiological regression in group A, there was clearance in six patients, regression in fourteen patients and there was no change in

TABLE I

Groups	Youngest	Oldest	Mean Age	Male	Female	Total
A. H+P+T	4	13	8.8	20	14	34
B. H+PZA+E	6/12	13	8.2	18	16	34
C. H+PZA+R	8/12	14	9.8	14	22	36
D. H+T	10/12	14	8	20	10	30

TABLE II

Groups	Bacteriological Status		Tuberculin Reaction			
	Positive Reaction	Negative	Total	Weak	Strong	Mean
A. H + P+T	4	30	34	10 m.m.	25 m.m.	14 m.m.
B. H + PZA+E	6	28	34	10 m.m.	30 m.m.	15 m.m.
C. H+PZA + R	6	30	36	10 m.m.	20 m.m.	14 m.m.
D. H+T	3	27	30	10 m.m	22 m.m.	15 m.m.

TABLE: III

Groups	Radiological Status						Paratracheal Glands.		Total		
	Unilateral	Bilateral	Cavity Present	Zones Involved							
				1	2	3	4	5		6	Present
A. H + P + T	12 35.4%	22 64.6%	16 47.1%	4	12	6	8	—	4	2	34
B. H + PZA + E	14 41.2%	20 58.9%	10 29.4%	6	10	10	8	—	—	10	34
C. H + PZA + R	13 36.1%	23 63.9%	19 52.8%	2	12	6	10	—	6	7	36
D. H+T	12 40%	18 60%	8 26.7%	4	8	6	6	—	6	6	30

twelve patients at 26 weeks. (Table VI). At 52 weeks, 6 patients who cleared maintained status quo; in 10 there was further regression, eight showed no change and eight patients deteriorated. At 78 weeks, 6 remained clear and in 26 there was no change. At 104 weeks, two patients out of six who had cleared, left the locality and of the 26 who were stationary, one died and five left locality. At the end of 156 weeks, there was complete clearance in two and of the 14 patients

who remained stationary two more left the locality.

Table VII shows that twenty one patients in group B had complete clearance and there was regression in nine. At the end of 52 weeks there was clearance in 24 and regression in six. At the end of 78 weeks, of the twenty four patients with complete clearance, three left the locality and six with regression showed no

SHORT TERM CHEMOTHERAPY IN CHILDREN : THREE YEARS' FOLLOW UP

Table IV
Fall Outs

Group	Died	Left the hospital	Total Assessed
A. H+P+T	2	-	32
B. H+PZA+E	2	2	30
C. H+PZA+R	2	-	34
D. H+T	-	8	22

Table V
Bacteriological Conversion

	A		B		C		D	
	+	-	+	-	+	-	+	-
26 Weeks.	4	4	6	6	6	6	3	3
52 Weeks	-	3	-	6	-	6	-	3
78 Weeks	-	3	-	6	-	6	-	3
104 Weeks	-	3	-	6	-	6	-	3
156 Weeks	-	3	-	6	-	6	-	3

TABLE VI

Radiological Assessment (Group A)

	26 wks.	52 wks.	78 wks.	104 wks.	156 wks.
Cleared	6	6	6	4 (two left locality)	2
Regression	14	10	-	-	—
No Change	12	8	26	20 (one died; five left locality)	14 (two left locality)
Deterioration	-	8	-	-	—

TABLE VII

Radiological Assessment (Group—B)

	26 wks.	52 wks.	78 wks.	104 wks.	156 wks.
Cleared	21	24	21 (three left locality)	18	18
Regression	9	6	—	—	—
No Change	-	-	6	5 (one left locality)	4
Deterioration	—	—	—	—	—

further change. At the end of 104 weeks, 21 who had cleared remained stationary and of the six who showed no change, one left the locality. At the end of 156 weeks, in 18 there was complete clearance. There was no further change in four patients.

In group C, there was complete clearance in twenty seven patients and in seven there was regression (Table VIII) At the end of 52 weeks, there was complete clearance in thirty one patients and three showed further regression. At the end of 78 weeks, of the 31 in whom there was complete clearance one left locality and there was no further regression in two patients. At the end of 104 and 156 weeks, in thirty patients there was complete clearance and there was no further change in two patients.

In group D, there was complete clearance in

eight patients, regression in 10 and no change in four patients at 26 weeks. (Table IX). At 52 weeks, complete clearance was seen in fifteen patients, regression in five patients and there was no change in two patients. At the end of 78 weeks, of fifteen patients who had completely cleared, two left the locality, there was further regression in one and six remained stationary. At 104 weeks, of the 11 with complete clearance, one left locality and of the six who remained stationary, two more left locality. At 156 weeks, in 10 there was complete clearance and five remained stationary.

In group A at the end of 26 weeks, of the sixteen patients with cavitory disease the cavity closed in ten patients (Table X). In two, the cavities became bigger. At 52 weeks, cavities remained closed in eight patients, but reopened in two others. At the end of 78 weeks there

TABLE No. VIII

Radiological Assessment (Group—C)

	26 wks.	52 wks.	78 wks.	104 wks.	156
Cleared	27	31	31 (one left locality)	30	30 wks.
Regression	7	3			
No. Change			2	2	2
Deterioration	—	—	—	—	—

TABLE IX

Radiological Assessment (Group—D)

	26 wks.	52 wks.	78 wks.	104 wks.	156 wks.
Cleared. (two left locality)	8	15	13	11 (one left locality)	10
Regression.	10	5	1	1	—
No Change	4	2	6	6 (two left locality)	5
Deterioration.				—	—

TABLE X
Cavity Closure (Group—A)
(Total cases 16)

	26 wks.	52 wks.	78 wks.	104 wks.	156 wks.
Cavity closed	10	K (two left	8	6	4
				locality)	
Present	4	8	8	8	8
Bigger	2	—	—	—	—

was no change. At the end of 104 weeks, two patients in whom the cavities closed left the ocality. At the end of 156 weeks, cavities remained closed in four and were still present in eight patients,

In group B, of the ten patients with cavitory disease, cavities closed in eight at the end of 26 weeks (Table XI). At the end of 52 weeks, cavities closed in one more patient bringing the total

to nine. At the end of 78 weeks, of the nine patients in whom cavities were closed, two left locality. At the end of 104 and 156 weeks, cavities remained closed in five patients.

In group C, cavities closed in seventeen out of nineteen patients at the end of 26 weeks (Table XII), and at the end of 52 weeks cavities closed in all the nineteen patients and remained closed thereafter.

TABLE XI
Cavity Closure (Group—B)
(Total cases 10)

	26 wks.	52 wks.	78 wks.	104 wks.	156 wks.
Closed	8	9	7	5	5
			(two left		
			locality		
Present	2	1	1	1	1
Bigger					

TABLE XII
Cavity Closure (.Group—C)

	26 wks.	52 wks.	78 wks.	104 wks.	156 wks.
Cavity closed	17	19	19	19	19
Present	2	—		—	
Bigger					

TABLE XIII

Cavity Closure (Group—D)

(Total cases 8)

	26 wks.	52 wks.	78 wks.	104 wks.	156 wks.
Closed	26	8	7 (one left locality)	6 (one left locality)	6
Present	2	—	—	—	—
Bigger					

In group D, cavities closed in six patients out of eight at the end of 26 weeks (Table XIII). At the end of 52 weeks cavities closed in all the eight patients. At the end of 78 weeks, one left locality and in the rest six patients, cavities remained closed at the end of 104 and 152 weeks.

Conclusions

1. Sixteen patients were excluded because their stay in the hospital was less than a month. Of these, six patients died, two each in groups A, B and C and 10 left the hospital, two in group B and eight in group D.

2. Irrespective of the drug regimens, bacteriological conversion was obtained in all the patients except one patient in group A who became nega-

tive by the 26th week, but again became positive by the 52nd week. Sputum was converted in all the patients in the 5th or 6th week of treatment.

3. More than 2/3 of the patients showed complete radiological clearing in groups B & C at the end of 26 weeks as against about 1/3 in groups A and D. Some clearing was noted during 26—52 weeks period in the groups B and C.

4. Cavity closure was 50%, 90%, 100% and 100%, respectively in the four groups.

5. Results with Rifampicin, Pyrazinamide, Isoniazid regimen were superior to the other drug regimens.

SHORT COURSE CHEMOTHERAPY IN INDUSTRIAL WORKERS COVERED

A.G. PATEL

Introduction

Employees' State Insurance Scheme was introduced in 1969 in Baroda. Initially there were 45,000 workers covered under Employees' State Insurance Scheme. At present 1,00,000 workers are covered under the scheme. Case detection and case holding in this group is better than in general population. About 40% patients completed conventional chemotherapy as compared to 5% in general population (Patel, 1977). Director of Employees' State Insurance Scheme permitted use of Rifampicin in a pilot study to assess the efficacy, acceptability, adverse reactions and cost of drugs in the management of tuberculosis under programme conditions in this group.

Design of First Study

Material & Methods:

Patients were drawn from referred industrial workers covered under Employees' State Insurance Scheme, Baroda. All patients were smear positive. They were admitted initially for 4 to 6 weeks. Initial X-ray of chest, sputum smear, culture and sensitivity tests were done. Bacteriological examinations were repeated every month for the first two months and thereafter every two months upto 6 months in the first study and 8 months in the second study. X-ray was repeated at 2, 4, 6 months in the first study and 8 months in the second study. Haemogram and urine examination were carried out routinely.

Patients were given streptomycin, isoniazid and rifampicin daily for first 4 weeks in the initial intensive phase. Intermittent rifampicin containing phase started at the end of initial intensive phase of treatment. Streptomycin, Isoniazid and Rifampicin were given once a week for 9 weeks during this Rifampicin containing intermittent phase. After 13 weeks of Rifampicin containing regimen, Streptomycin and Isoniazid once a week were given for 13 more weeks to complete 26 weeks' treatment. Midweek strengthening dose of Isoniazid was given in rapid inactivators during intermittent phase (Tripathy, 1973).

Result

Total patients	50
Completed treatment	41

Sputum conversion was 100% in those who completed treatment. Nine patients did not complete treatment,

2 patients expired.

3 patients migrated-all well

* 4 patients premature stoppage of drugs.

* 1 patient well

1 patient restarted treatment and well

2 patients completed treatment after resuming it later.

TABLE I

Dose and Rhythm of Drugs Used

	SM	INH	RFM
Initial intensive phase			
First 4 weeks	0.75 gm	400 mg.	450 mg.
9 weeks once a week			
Rifampicin containing			
Phase	1.00 gm.	15mg/kg	12mg/kg
		*	600 mg
			total
13 week once a week			
maintenance phase.	1.00 gm.	15 mg/kg	
		*	

* Mid week strengthening dose in rapid inactivators

Patients' compliance in reality was 44 out of 45 patients in Baroda, three having migrated and 2 died after stopping treatment prematurely. One patient is well, sputum negative with radiologically healed lesion in serial examination during follow up period of four years. Thus, all 45 patients in Baroda are sputum negative at the end of four years after stopping the treatment.

Adverse Reactions

One patient developed clinical jaundice on 10th day in the daily phase. It disappeared after stopping rifampicin and did not reappear after restarting it after 10 days.

Medical Superintendent, S.P. Sanatorium, Baroda-390 007.

Relapse Rate

One patient out of 41 who completed treatment committed suicide because of family problem. One patient had bacteriological relapse. Two were smear positive and culture negative. Three had radiological deterioration. Thus, only one patient had bacteriological relapse. Five patients left Baroda after 18 months' follow-up.

Design of Second Study

Encouraged by immediate results in first study, it was decided to design a study to reduce requirement of rifampicin without reducing efficacy of the regimen by giving it once a week from the beginning (Singapore Study, 1977 and Eule, 1977). Streptomycin and Isoniazid daily were considered necessary for first 4 weeks.

Material and Methods

Selection of patients and methodology was the same as in the first study. Patients were given streptomycin and Isoniazid daily for first 4 weeks along with Rifampicin once a week. All three

drugs were given once a week after initial period of first 4 weeks. Patients were divided into two groups, A and B.

Group A received Rifampicin once a week for 13 weeks and group B received it for 16 weeks. After first 4 weeks, once a week, streptomycin and Isoniazid were continued to complete 32 weeks' treatment. Midweek strengthening dose of Isoniazid was given in rapid inactivators. Bacteriological and radiological follow-up was done every 3 months. Patients were advised to report if any symptom reappeared.

There were 61 patients in group A and 58 in group B. Sputum conversion was 100% in both groups. Fortysix patients in group A and 39 patients in group B completed one year's follow up. There was one bacteriological relapse in group A. There was no bacteriological relapse in group B. Of 27 patients who stopped the treatment prematurely, 16 restarted treatment and completed it; 4 migrated and 3 died. Thus, out of 112 patients, 101 (90%) completed the treatment. Cost of drugs of the regimen was 130 rupees (16\$). It is lower than cost of drugs in conventional regimen.

TABLE 2

	SM	INH	Rifampicin
Initial intensive phase	0.75 gm	400 mg	
First 4 weeks			12 mg/kg once a week 600 mg upper limit once a week,
<i>Group A</i> : 9 weeks			
Once a week Rifampicin containing phase	1.0 gm	20 my/kg *	12 mg/kg 600 mg. Total
<i>Group B</i> : 12 weeks			
Once a week Rifampicin containing phase.	1.0 gm	10 mg/kg *	12 mg/kg
<i>Group A</i> — 19 Weeks			
Once a week maintenance phase	1.0 gm	20 mg/kg *	
<i>Group B</i> — 16 weeks			
Once a week maintenance phase	1.0 gm	20 mg/kg *	

*Mid week strengthening dose in rapid inactivators

Results

	GROUP A	GROUP B
Total patients	61	58
Completed treatment	46	39
Expired	2	1
Migrated	1	4
Loss	12	14
Restarted treatment	9	7
Real Loss	3	7

Relapse Rate

In the 46 patients in group A, there was one bacteriological relapse and 4 radiological deteriorations. There was no bacteriological relapse in group B and there was one radiological deterioration during 12 months follow-up.

Adverse Reactions

No adverse reactions either hepatic or immunological were observed in both the groups

Drugs Resistance

No primary drug resistance was detected in these two studies of 169 patients.

Discussion

Twice a week Streptomycin with high dose of Isoniazid under supervision proved very effective in Madras studies. Results of once a week Streptomycin with high dose of Isoniazid are not satisfactory, and are poor in rapid inactivators of INK (Menon, 1980).

First 4 weeks' daily Streptomycin plus Isoniazid improved results of once a week Streptomycin plus Isoniazid to a considerable extent. Increasing dose of Isoniazid did not improve the results to a satisfactory level. It was interesting to note that the culture results of first 8 weeks of Streptomycin plus Isoniazid daily, Streptomycin with Isoniazid twice a week and Streptomycin plus Isoniazid once a week were the same (Tripathy, 1970).

Response in rapid and slow inactivators was the same when ethambutol and Isoniazid were given daily (Table 3). Response in rapid inactivators was marginally inferior when both the drugs were given twice a week. Response in rapid inactivators was 57% and slow inactivators 91% when both the drugs were given once a week. Results in rapid inactivators improved to 91% when mid-week streng-

TABLE 3

Regimen	Response	Relapse	Response		Overall failure
			Rapid	Slow	
* E ₇ H ₇	96%	9%	98%	95%	13%
* E ₂ H ₂	88%	16%	83%	92%	28%
* E ₁ H ₂	93%	19%	91%	95%	26%
* E ₁ H ₁	75%	35%	57%	91%	60%
** R ₁ H ₁	94%	1%	94%	100%	7%
***R ₁ H ₂	100%	0.0%	100%	100%	0.0%

E — Ethambutol

H — Isoniazid

R — Rifampicin (Tripathy, 1973 and Singapore Study, 1975)

* Madras Study

** Singapore Study

***Baroda Study

thening dose of Isoniazid was given in once a week regimen of Ethambutol and Isoniazid.

In Singapore, once a week Rifampicin and Isoniazid regimen was used. Response in rapid inactivators was 94%. This clearly proves excellent bactericidal quality of Rifampicin over poor bacteriostatic quality of Ethambutol. In Singapore study, there were 82% rapid inactivators. In Baroda, proportion of rapid inactivators is 40%. So chances of failure will be half (3%) of Singapore study. When Rifampicin and Isoniazid were used once a week midweek strengthening dose of Isoniazid corrected inadequacy of Isoniazid and produced 100% results.

Fear of immunological reactions had prevented intermittent use of Rifampicin in short course chemotherapy. Intermittent Rifampicin has been very successfully used in Rumania (Anastasatu 1979), G.D.R. (Eule, 1973), Zaire (Verbist *et al.* 1972) and Hong Kong (Hong Kong Chest Services/BMCR, 1979). It is reported from Poland (Zierski, 1979) and Italy (Nitti, 1977) that intermittent Rifampicin preceded by intensive phase of 4 to 8 weeks produced very satisfactory results. Reports from Rumania showed that 3 months' intermittent twice a week Rifampicin regimen followed by 6 months' non-Rifampicin intermittent regimen gave satisfactory results (Anastasatu, 1979). Eule from G.D.R. reported that once a week Rifampicin along with streptomycin and high dose of Isoniazid was a very effective regimen. He states that "Efficacy of Once a Week Rifampicin is Beyond Doubt". (Eule 1973).

Verbist reported successful use of "Intermittent therapy with Rifampicin once a week in advanced pulmonary tuberculosis" (Verbist *et al.* 1972). Nagpaul reported satisfactory results of once a week Rifampicin in T.B. of spine (Nagpaul, 1981). Shukla also reported satisfactory results in lymphnode T.B. with once a week Rifampicin regimen (Shukla 1981). Patel reported that results of twice a week or once a week Rifampicin are similar in pyopneumothorax in a series of 120 patients (Patel, 1981). Patel showed improvement in patient compliance and sputum conversion with marked reduction in number of chronic cases at Navsari with once a week Rifampicin containing regimen applied under programme conditions (Patel 1981).

Table 4 shows the potential effectiveness of a number of short course intermittent regimens in disease with drug sensitive bacilli.

Most of the relapses occurred during first six months after stopping the treatment in short course chemotherapy. This was seen in 2 patients who relapsed, one each in the first study and group A of the second study. There was no relapse in Group B of the second study. This suggests that extra 3 weeks available in 16 weeks' duration of weekly Rifampicin administration was important. In 13 weeks' duration of weekly Rifampicin we observed one relapse. However, the superiority of 16 weeks' regimen over 13 weeks' regimen was not large enough to become statistically significant because number of relapses is small.

Intermittent once a week Rifampicin reduces

TAULE 4

	Regimen	Duration (Months)		
		9	8	6
Hong Kong (Hong Kong Chest Services/BMCR, 1979)	S ₃ R ₃ H ₃ Z ₃ /S ₂ H ₂ Z ₂	-	99%	95%
** Hong Kong (Hong Kong Chest Services/BMCR, 1975)	S ₃ H ₃ Z ₃		95%	
	S ₂ H ₂ Z ₂		90%	
Anastasatu	3 R ₂ H ₂ /6 E ₂ H ₂		97%	
Krishnaswami (Verbist et al, 1972)	2 S ₂ Z ₂ R ₂ H ₂ / 4 S ₂ H ₂ Z ₂		98%	
Eule (Eule 1973)	4 S ₁ H ₁ R ₁ /8 S ₁ H ₁		99%	

the cost of drugs and makes it easy to organise treatment under supervision. Immunological reactions are nil because of low dose of Rifampicin (12 mg. per kg.) and period of administration of Rifampicin is limited to 16 weeks. Cost of drugs will be rupees two hundred and rupees one hundred thirty in the first and the second study respectively. The cost of drugs in second study is lower than in conventional regimens.

Conclusions

- (1) Once a week Rifampicin containing regimen is effective.
- (2) Once a week Rifampicin for 16 weeks seems to be superior to 13 weeks.
- (3) Patient compliance is high (90%).
- (4) Adverse reactions of an immunological nature to Rifampicin are absent.
- (5) The cost of drugs is less than in conventional regimens.

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THE 36TH NATIONAL CONFERENCE ON TUBERCULOSIS AND CHEST DISEASES

The 36th National Conference on Tuberculosis and Chest Diseases was held in the General Education Auditorium of M.S. University, Baroda from 2nd to 5th November, 1981. The Conference was a great success. It was hosted by the Gujarat State TB Association under the joint auspices of the Tuberculosis Association of India and the Gujarat State TB Association and was attended by about 500 delegates from all parts of the country and one delegate from the U.S.A. Dr. G.D. Gothi, Director, New Delhi TB Centre, was President of the Conference.

The Conference was inaugurated by Her Excellency, the Governor of Gujarat on the morning of 2nd November, 1981. The Inaugural Session was presided over by the Hon'ble Chief Minister of Gujarat and was attended by many dignitaries, including Smt. Kokilaben Vyas, Minister of State for Health; Rajmata Smt. Shantadevi Gaekward, Dr. Jatinbhai V. Modi, Mayor of Baroda, Dr. I.D. Bajaj, Director-General of Health Services, Dr. Amubhai Shukla, President of the Gujarat State TB Association and Dr. O.P. Gupta, Director of Health Services, Gujarat.

The Governor in her Inaugural Address exhorted the voluntary agencies and all citizens to join the Government in meeting the challenge posed by tuberculosis. Joint efforts and dedication were necessary to bring the disease under control according to her. She hoped that the Conference would be 'action oriented' rather than 'speech oriented'. The Chief Minister stressed the need for reviewing and revitalising the National Tuberculosis Programme in the light of research and experience gained so far since it has failed to make much of an impact on the problem during the last 18 years that it has been in operation. He also said that the Government of Gujarat was planning a Joint Sector Enterprise to manufacture the much-needed drug, Rifampicin. Smt. Kokilaben Vyas, said that rapid industrialisation and pollution had created problems vis-a-vis tuberculosis control. She pleaded for a bigger central aid for tuberculosis control. Dr. I.D. Bajaj, reviewed the state of tuberculosis control in the country and gave an assurance that very soon the programme will be implemented in all districts of the country.

Dr. G.D. Gothi who presided over the 36th National Conference referred in his Presidential Address mainly to the need for making the National Tuberculosis Programme centrally sponsored with 100% central subsidy; removing the

short-falls and lacunae in the implementation of the programme in the light of the Expert Committee Report of 1975; stepping up the case-finding and case-holding facilities, especially at the periphery so that the Alma Ata Declaration of 'Health for All by 2000 A.D.' could be attained; small longitudinal studies in different parts of the country to determine the epidemiology of tuberculosis. He made a plea for a befitting celebration of the Centenary of the Discovery of Tubercle Bacillus by Robert Koch.

During the Scientific Sessions, 43 papers were presented in addition to an Oration on "Tuberculosis in India—the Prospects" and a Panel Discussion on 'Case-finding'. The Oration delivered by Dr. S. Sivaraman surveyed broadly the epidemiology of tuberculosis in all parts of the world and the extent of the problem in our own country and its likely trends in future.

The Panel Discussion on 'Case-finding' was moderated by Dr. S.P. Pamra and discussed in detail the problems, the short-falls and practical measures aimed at stepping up 'case-finding' in metropolitan cities, other cities and towns and, more specially, rural areas of the country. A plea was made by the Panel for greater attention to the under-served slums of the city and revamping and stepping up the activities of the health workers and health guides in the rural areas as well as involving the general practitioners, not only of the western system of medicine but also of the indigenous systems of medicine since most persons with symptoms suggestive of disease contact these to begin with.

The scientific papers covered a number of subjects including chemotherapy, acute respiratory infections in children, problems of tuberculosis in the geriatric age, Immunology, Smoking, Surgery, operational aspects of 'case-finding' and 'case-holding', non-tuberculous chest diseases, etc. A noteworthy feature of the scientific papers was that most of them were presented by younger workers and the presentations were concise and to the point.

The Scientific Sessions started with discussion on 'Acute Respiratory Infections in Children'. It was reported that of the total sickness in infancy, 8—10% is on account of acute respiratory diseases, most common of which are the upper respiratory infections. The general consensus was that in children the use of tetracycline must be avoided as far as possible. The session also

highlighted the use of bronchoscopy in children in management of foreign body inhalation.

The Session on 'Geriatrics' highlighted the fact that tuberculosis has a relatively higher prevalence in older age groups and is more often associated with other diseases like diabetes. Otherwise, tuberculosis in this age group does not pose any problem, different in any way from tuberculosis in younger age groups except that it is neglected more often.

The Session on 'Smoking' showed that the respiratory functions get reduced in proportion to the amount of smoking. There is need for intensive health education to prevent the harmful effects of smoking and the statutory warning on the cigarette packets is not adequate for discouraging the smoking habits of the people. Wider publicity about the harmful effects of smoking is very essential to prevent the future occurrence of Lung Cancer and heart and chest diseases.

Role of immunological reactions and certain blood groups in influencing the manifestations of disease was brought out in another session.

Interim results of the second trial being conducted by the Research Committee of the Tuberculosis Association of India were reported. It was corroborated that it is possible to reduce the duration of treatment of tuberculosis, both pulmonary as well as extra pulmonary, with the help of newer drugs. However, treatment regimens of a duration shorter than six months would be rather inadequate. Still one has to keep in mind the cost of the treatment with newer drugs. Dr. A.G. Patel demonstrated that newer drugs could be administered intermittently yet effectively thus further lowering the cost of treatment. It was felt that the use of short course chemotherapy in programme conditions still needs some more studies before it could be adopted under the National Programme.

In the management of treatment failures, the previous standard drugs were reported to be of limited value. Therefore, either one has to use expensive drugs or all efforts have to be made to prevent the treatment failures, the latter being more economical as well. Most important aspect in the control of tuberculosis is the 'case holding'. In this respect, Shri Mankodi of Surat suggested the involvement of Private Practitioners in the programme to reduce the distance between the drugs and the patients and also to improve the referral system so that the patients could avail of the governmental facilities.

A simple test to detect the consumption of Rifampicin by examining urine was also suggested by a study undertaken at Tuberculosis Research Centre, Madras.

Lack of awareness of the problem of tuberculosis on the part of patients in hospitals, clinics, etc. which was a big deterrent in 'case-finding' and 'case-holding' was reported by some workers.

Dr. Thomas Moulding of Denver (USA) reported on a device evolved by him for monitoring the regularity in self-administration of drugs by patients.

The papers on surgery dealt mainly with Empyema and plural biopsy. A study based on nearly 200 autopsies in children and young adults was reported from the J.J. Group of Hospitals, Bombay. The preponderance of haematogenous manifestations in children and isolated pulmonary tuberculosis in young adults was highlighted. The localized manifestations in the central nervous system, abdomen and other organs were more or less equal in children and young adults. A study from the TB Institute, Madras reported on the high prevalence of tuberculosis among beedi workers.

A paper each from Tuberculosis Research Centre, Madras and the New Delhi Tuberculosis Centre dealt with operational aspects of the National Tuberculosis Programme. The paper from Madras reported that sputum specimens collected at the periphery could be stored for 7 days for microscopy and 3 days for culture without any appreciable loss of efficiency and the paper from the New Delhi TB Centre showed that microscope slides could be used 20 times, irrespective of whether the previous specimens were positive or negative for AFB.

An innovation during this Conference was the 'open session' lasting one hour on the last day during which a panel of 10 senior workers answered the queries from delegates on all aspects of Tuberculosis. Large number of questions showed the aptness and popularity of this new feature.

The scientific programme was followed by the usual closing and business session. Dr. Gothi reviewed briefly the entire session. Drs. H.V. Bahulkar, V.K. Arora, R.B. Patel, and A. Chakrapani Rao were elected by the delegates as members of the Central Committee for the ensuing year. Dr. Jaswant Singh moved the Vote of Thanks.

The hosts had arranged two cultural programmes. One was a ballet based on Ritu Samharam (of Mahakavi Kalidasa) compered by

Professor C.V. Chandrasekhar, Principal and Head of the Department of Dance, College of Indian Music, Dance and Drama and the other consisting of a ballet Leel-Hari Leela and Folk Dances of Rajasthan and Gujarat compered by Kum. Pratibha Pandit, Principal of the Arya Kanya Lalit Kala Vidyalaya, Baroda. Both programmes were superb and were immensely enjoyed and appreciated by the delegates. The Hon'ble Minister of Finance, Gujarat addressed the delegates after the first Cultural Programme.

A meeting of the Standing Technical Committee was held immediately after the closing session. The Committee noted with relief and appreciation that the proposal of the Indian

Medical Council to bifurcate the speciality of MD (Tuberculosis and Respiratory Diseases) into two separate specialities dealing with tuberculosis and chest diseases has been abandoned and *status quo* will continue. It was reaffirmed that the 1982 Conference will be held in Delhi during September/October next year. A list of 12 tentative subjects for discussion at the next Conference was drawn up. Since the Centenary of the Discovery of Tubercle Bacillus is also being celebrated next year, an International Symposium would also be arranged as apart of the National Conference. The members suggested a list of eminent foreign workers who may be invited to participate in the International Symposium.

Third Zonal Conference of the East India Chapter of the International Academy of Chest Physicians and Surgeons of the American College of Chest Physicians will be held in Hotel Oberoi Grand, Calcutta, from 19th to 21st February, 1982. Symposia, Panel Discussion, Oration and Free Papers shall cover the three day programme. For further details please feel free to write to Dr. S.K. Sharma, Honorary Secretary, 54, Chowringhee Road, Calcutta-700071.

NEWS AND NOTES

CENTENARY DAY CELEBRATIONS — DISCOVERY OF TUBERCLE BACILLUS

The year 1982 will mark the Hundredth Anniversary of the monumental discovery by Robert Koch of the Tubercle Bacillus, a discovery which heralded the opening of a new era in the diagnosis, management and control of tuberculosis. Robert Koch announced the discovery of the tubercle bacillus on the 24th of March, 1882. The World Health Organisation, the International Union Against Tuberculosis and National TB Associations all over the world are organising special programmes during the Centenary Year to honour the eminent scientist who made this epoch-making discovery and also to utilise the occasion for high-lighting the tuberculosis problem, and intensifying the case-finding programme and health education activities. The Tuberculosis Association of India has also drawn up a special programme to observe the Centenary in a befitting manner.

The Association is organising a special function to celebrate the Centenary Day of the Discovery of Tubercle Bacillus by Robert Koch at 9.30 A.M. on Wednesday, the 24th March, 1982 in the Association's premises at 3, Red Cross Road, New Delhi. The Hon'ble Shri M. Hidayatullah, Vice-President of India will be the Chief Guest and the Hon'ble Shri B. Sankaranand, Minister for Health & Family Welfare will preside over the function. A special commemorative stamp on Robert Koch which is being brought out by the Posts & Telegraphs Department will be released on the occasion by Hon'ble Shri C.M. Stephen, Minister for Communication, who will present the commemorative stamp to the Chief Guest.

ANNUAL MEETINGS OF THE T.A.I.

The 43rd Annual General Meeting of the Tuberculosis Association of India will be held at 11.00 A.M. on Wednesday, the 24th March, 1982 in the Association's premises at 3, Red Cross Road, New Delhi. The Technical Committee of the Association will meet at 9.30 A. M. on Tuesday, the 23rd March, 1982 and the Conference of Secretaries of State TB Associations will be held in the afternoon of 24th March, 1982.

KOCH'S CENTENARY CONFERENCE

The 37th National Conference on Tuberculosis & Chest Diseases which is being designated as "KOCH'S Discovery of TB Centenary Conference" will be held in the Mavlankar Auditorium, Rafi Marg, New Delhi, for five days, *i.e.*

from Wednesday, the 6th to Sunday, the 10th October, 1982 under the joint auspices of the Tuberculosis Association of India and the Delhi TB Association and in collaboration with the Vallabhbai Patel Chest Institute, Delhi and the National College of Chest Physicians. One day of this Conference will be set apart for an International Symposium on Tuberculosis (the emphasis will be on 'Microbiology' and 'Immunology') in which leading specialists both "from India and abroad will be invited to participate. The Technical Committee of the Tuberculosis Association of India has tentatively selected the following subjects for discussion at this Conference :

1. Chemotherapy
2. Immunological aspects of TB
3. Tuberculosis and associated Chest Diseases
4. Fate of smear positive and culture negative cases
5. Tuberculosis Meningitis
6. Occupational Chest Diseases
7. Pulmonary Suppuration
8. Surgery in non-tuberculous Chest Diseases
9. Microbiology and drug resistance
10. Panel discussion on 'Operational aspects of Case holding'
11. Symposium on C.O.P.D./Cancer Lung/Respiratory Emergencies

Those who wish to present papers at the Conference may kindly send an abstract of their paper on the above mentioned subjects or on any other subjects of their choice to the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-1, latest by the 1st March, 1982.

INAUGURATION OF THE 32ND TB SEAL CAMPAIGN

The 32nd TB Seal Campaign under the auspices of the Delhi TB Association was inaugurated by the President of India, Shri Neelam Sanjiva Reddy on 2nd October, 1981. He made a token purchase of TB Seals worth Rs. 100/-. The Campaign was inaugurated the same day in various States. In *Andhra Pradesh*, the Campaign was inaugurated by Prof. G. Ram Reddy, Vice-Chancellor of the Osmania University. Sri A. Madan Mohan, Minister for Medical & Health, Andhra Pradesh, presided over the inaugural function. In *Goa*, the campaign was inaugurated by Hon'ble Minister for Health & Family Welfare, Dr. Wilfred D'Souza, in the Municipality Hall, Mapuca. The function was presided over by Shri Shamsunder Neuguh M.L.A. In *Jammu & Kashmir*, Begum Shiekh

Mohamed Abdullah inaugurated the campaign in Srinagar. In *Karnataka* the Hon'ble Health Minister Sri A.K. Abdul Saraad inaugurated the Campaign and the function was presided over by the Hon'ble Sri P. Venkataraman, Minister for Social Welfare and Backward Classes. In *Kerala*, the campaign was inaugurated by Shri E.K. Nayanar, the Chief Minister at Malappuram Dist. The Dist. Collector and President of the Dist. Association presided over the function. In *Maharashtra*, the campaign was inaugurated by the Hon'ble Dr. A.U. Memon, Mayor of Bombay. Dr. N.C. Puri, Vice-Chairman of the Association presided over the function. They also organised a Symposium on "The Proposed Tuberculosis Control Programme for Bombay City as part of the Centenary Celebrations of the Discovery of Tubercle Bacillus by Robert Koch". In *Madhya Pradesh*, His Excellency the Governor inaugurated the Campaign in Raj Bhawan, Bhopal. In *Meghalaya* Sri Prakash Mehrotra, Governor of Assam and Meghalaya, inaugurated the Campaign at Raj Bhawan, Shillong. The function was presided over by the Hon'ble Shri D.D. Lapang, the Minister for Health & Family Welfare. In *Orissa*, the Minister of State for Health & Family Welfare, inaugurated the Campaign at Raj Bhawan by purchasing Seals worth Rs. 880/-. In *Pondicherry*, the campaign was inaugurated by Shri P. Shanmugam, M.P. in the Mahatma Gandhi Government Leprosy Hospital, Dubavapet, Pondicherry. Sri. D. Ramchandran, Hon'ble Chief Minister of Pondicherry, presided over the function. His Excellency Shri R.N. Haldipur, Lt.-Governor, declared open the Leprosy Rehabilitation Centre on the same occasion. In *Tamil Nadu*, the campaign was inaugurated by the Hon'ble Dr. H.V. Hande, Minister for Health & Family Welfare. In *Uttar Pradesh*, the campaign was inaugurated by Dr. R.V. Singh, former Vice-Chancellor, Lucknow University, in Vigyan Bhawan of the Balrampur Hospital, Lucknow. Dr. B.N. Sinha, President, Medical Council of India; presided over the function.

HEALTH VISITORS COURSE

The 1982-83 TB Health Visitors' Course will commence in July, 1982. The course will be of nine months' duration and will be held at the New Delhi TB Centre (including two weeks in a rural centre). The minimum qualification for admission to this course is Higher Secondary/Pre-University with Science or Hygiene and Physiology in Matriculation. Application forms for admission to this course can be had from the Secretary-General, Tuberculosis Association of Delhi, 3, Red Cross Road, New Delhi-110 001. The last date for receipt of application is 30th April, 1982.

Ind. J. Tub., Vol. XXIX, No. 1

CHANCHAL SINGH MEMORIAL AWARD—1982

The Tuberculosis Association of India, will award a Cash Prize of Rs. 500/- to a TB Worker, below 45 years of age, for an original article not exceeding 30 double spaced foolscap typed pages (approximately 6,000 words) excluding charts and diagrams on a subject relating to tuberculosis. Papers may be sent, in quadruplicate to reach the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110 001, before 31st of July, 1982.

ESSAY COMPETITION—1982

The Tuberculosis Association of India will award a cash prize of Rs. 300/- to a final year medical student in India for an original essay on Tuberculosis, adjudged best by a special committee of the Association. The subject selected for the 1982 competition is Contributions of Robert Koch in the Field of Tuberculosis. The essay should be written in English, typed in foolscap size, double-spaced and should not exceed 15 pages (approximately 3,000 words excluding tables, diagrams, etc.) Four copies of the manuscript should reach the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110 001, by not later than 31st July, 1982, and should be forwarded through the Dean or Principal of College/Univeristy.

SHORT FILMS ON TB

The Tuberculosis Association of India is producing three short films, in colour, of about 4 minutes duration each, on Diagnosis, Treatment and Preventive Measures of Tuberculosis. These films are being produced by M/s. Karashree, Bombay, and directed by the famous Film Director Shri M.S. Sathyu. The films are expected to be ready in time for the Centenary Day Celebrations of the Discovery of Tubercle Bacillus by Robert Koch on 24th March, 1982.

STATE CONFERENCES

Rajasthan: The 2nd Rajasthan Conference on TB & Chest Diseases was held on 10th and 11th October, 1981 at Sanwali (Sikar). The Conference was held under the joint auspices of the Rajasthan State Tuberculosis Association and Shree Kalyan Arogya Sadan, Sanwali. It was inaugurated by the Hon'ble Minister for Health and Family Welfare, Rajasthan and the function was presided over by the Hon'ble Justice Shri P.D. Kudal; Judge, of the Rajasthan High Court. Dr. S.P. Pamra, Honorary Technical Adviser, TB Association of India, participated in the Conference. About 110 delegates from various parts of Rajasthan attended the Conference.

Tamil Nadu: The 3rd Tamil Nadu Conference on TB & Chest Diseases was held at Lakshmi Simdaram Hall, Madurai, on the 16th and 17th October, 1981. The Conference was sponsored by the Tamil Nadu TB Association and hosted jointly by the Dist. TB Association, Madurai and Madurai Medical College. The Conference was inaugurated by Hon'ble Dr. K. Kalimuthu, Minister for Agriculture and the function was presided over by the Hon'ble Dr. H.V. Hande, Minister for Health. The Conference was presided over by Dr. S. Muthuswami and it was attended by about 300 specialists and experts on TB and Chest Diseases, private and general practitioners and social and TB workers. Thiru R. Poornalingam, IAS, Collector and President of the Dist. TB Association of Madurai, welcomed the gathering.

REFRESHER COURSES

Pondicherry: A one-day refresher course in pulmonary tuberculosis was held, under the joint auspices of the TB Association of Pondicherry and I.M.A., Pondicherry Branch, on 27th October, 1981 at JIPMER. The course was inaugurated by Dr. Bhargava, Dean, JIPMER and Dr. V. Sambasivam, Director of Health and Family Welfare Services, welcomed the delegates. About 185 doctors including some faculty members of JIPMER attended the course. Dr. S.P. Pamra, Honorary Technical Adviser, TB Association of India, participated in the Refresher Course.

Andhra Pradesh: Under the joint auspices of the TB Association of Hyderabad and Andhra Pradesh State Faculty of I.M.A. College of General Practitioners and I.M.A. North Hyderabad Branch, a Refresher Course in Tuberculosis and Chest Diseases and General Medicine was organised in the premises of the Hospital for Diseases of Chest and TB, Irramnuma, Hyderabad on 29th November, 1981. Dr. P.S.R.K. Harnath, Director of Medical Education, inaugurated the Course. Dr. B. Pulliah, President, I.M.A. Andhra Pradesh State Branch, presided over the function. About 100 doctors including general practitioners and medical officers of some of the public sector undertakings attended the Refresher Course.

DACCA CONFERENCE

The XII Eastern Region TB Conference of the International Union Against Tuberculosis was held under the joint auspices of the National Anti-TB Association of Bangladesh, People's Republic of Bangladesh and the Eastern Region of the IUAT in Dacca (Bangladesh) from the 7th to 12th December, 1981. The Hon'

ble Justice Abdus Sattar, President of the People's Republic of Bangladesh, inaugurated the Conference. About 360 delegates, 300 from Bangladesh and 60 from twelve other countries in the Region namely, Australia, Hong Kong, India, Indonesia, Japan, Malaysia, Nepal, Pakistan, Korea, Singapore, Sri Lanka and Thailand attended the Conference. Dr. K. Styblo, Director, Scientific Activities of the Union represented the IUAT, Paris. The delegation from India consisted of Dr. S.P. Pamra, Sri P.N. Raman, Dr. H.B. Dingley, Dr. M.L. Mehrotra and Dr. M.S. Agnihotri.

The Scientific Sessions of the Conference were spread over five days. In all about 55 scientific papers were presented and discussed in eleven separate sessions. A special session was devoted to the report of the WHO/IUAT Study Group presented by Drs. T. Shimaō and K. Styblo.

The Executive Committee and Council of the Eastern Region met on the 7th December, 1981. Dr. T. Shimaō, Chairman of the Executive Committee of the IUAT and Vice-Chairman, Eastern Region, chaired these meetings. Shri P.N. Raman attended the meeting of the Executive Committee while at the Council Meeting Inida was represented by Dr. S.P. Pamra and Shri P.N. Raman as Councillors and by Drs. H.B. Dingley, M.L. Mehrotra and M.S. Agnihotri as Observers. The Council decided that the next Conference of the Region be held at Djakarta (Indonesia) sometime in September-October, 1983. The Council also elected new office-bearers for the Region for the next two years. Shri P.N. Raman was re-elected as a member of the Executive Committee of the Region.

OBITUARY

We regret to report that Dr. K.N. De, former Honorary General Secretary, Bengal Tuberculosis Association, passed away in Calcutta on 23rd December, 1981. Dr. De was actively associated with the anti-TB movement in our country for the past several years and has rendered yeoman service to the suffering humanity. He was closely connected with the Tuberculosis Association of India for some years as a member of its Central and Technical Committees. He was also Chairman of the Technical Committee during 1971-72 and President of the 27th National Conference on TB & Chest Diseases held in Patna in November 1972. The Tuberculosis Association of India offers its sincere condolences to the bereaved family.

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ABSTRACTS

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Controlled Clinical Trial of four Short-Course regimens of Chemotherapy for two durations in the treatment of Pulmonary Tuberculosis

Third East African/British Medical Research Council Study, Tubercle, 1980, 61, 59.

Four short-course chemotherapy regimens for pulmonary tuberculosis were compared: (1) streptomycin, isoniazid, rifampicin and pyrazinamide daily for 2 months followed by daily thiacetazone plus isoniazid; (2) the same 4 drugs daily for 1 month followed by thiacetazone plus isoniazid; (3) the same 4 drugs daily for 1 month followed by twice-weekly streptomycin, isoniazid and pyrazinamide; (4) the first regimen but without pyrazinamide in the initial intensive phase. Each regimen was given for 6 and 8 months and patients were followed up to 30 months.

When given for 6 months, regimen with a 2-month 4-drug intensive phase had a bacteriological relapse rate of 13% and when given for 8 months, there were no relapses. When pyrazinamide was omitted in the first 2 months the relapse rates were 18% for the 6-month and 6% for the 8-month series. The regimen with the 4-drug initial phase shortened to 1 month had relapse rates of 18% and 7% respectively, if the continuation phase was thiacetazone plus isoniazid. However, the relapse rates were lower, 9% and 2% respectively, when the continuation phase was twice-weekly streptomycin, isoniazid and pyrazinamide.

Six months Chemotherapy in Pulmonary Tuberculosis : A Controlled Trial by the British Thoracic Association

L.A. Campbell; Br. J. Dis. Chest (1980) 74, 415,

In this study of patients with culture-positive pulmonary tuberculosis isoniazid and rifampicin were given daily for six months, with an initial two-month intensive phase of streptomycin and pyrazinamide (SHRZ 6 regimen) or ethambutol and pyrazinamide (EHRZ 6 regimen). These were compared with a regimen of isoniazid and rifampicin for nine months supplemented by ethambutol for the first two months (EHR 9).

Of 511 patients starting chemotherapy 444 completed treatment according to the protocol. Significantly, more patients receiving the pyrazinamide-containing regimens were culture-negative at two months (77%) than in the EHR 9 group (64%). A difference was still evident at three months (98% vs. 88%). The conversion rates of the SHRZ and EHRZ groups were virtually identical. All patients in the three groups were culture negative by the end of the fifth month of treatment. Hepatitis occurred in 4% of the patients in each group. Other adverse reactions were commoner in the pyrazinamide-containing regimens. In the three groups between 0.6% and 2% of patients have relapsed after the end of treatment.

Controlled Double-blind study of the effect of Rifampin on Humoral and cellular immune responses in patients with pulmonary tuberculosis and in tuberculosis contacts

D.P. Humber et al, Amer. Rev. Resp. Dis. 1980, 122, 425—436

The effect of rifampin on humoral and cellular immunity was investigated in a double-blind comparison in which 33 patients were treated with streptomycin, isoniazid and rifampin or with streptomycin, isoniazid and pyrazinamide, and 41 healthy control subjects (all contacts of cases of pulmonary tuberculosis) were given chemoprophylaxis with rifampin or a placebo. Treatment was given for 6 months, and all subjects were followed for a further year. On admission, the patients had lower concentrations of plasma albumin and elevated concentrations of globulin, IgG, IgA, IgM, and C3 compared with the control subjects. The patients also had lower T cell concentrations and reduced lymphocyte transformation to PPD and suboptimal dosages of PHA. During chemotherapy, the concentrations of globulin, IgG, IgA, IgM, and C3 in the patients returned within 6 to 11 wk to that of the control subjects. The primary antibody responses to tetanus toxoid and pneumococcal polysaccharide, injected at 5 wk, and the antibody titres to *E. coli* were greater in the patients than in the control subjects. Subsequent responses to secondary and tertiary challenges at 21 and 36

wk, to E. coil after 21 wk, and to blood group antigens were similar in patients and control subjects. The depressed T cell concentrations and reduced lymphocyte responses to purified hemagglutinin (PHA) and purified protein derivative (PPD) also returned within the first 6 wk of therapy to that of the control subjects. No difference between patients and control subjects was found in their skin test reactions to *Candida*, trichophyton, varidase, or PPD. No effect of rifampin could be demonstrated on any of the measures of humoral or cellular immunity studied.

A service program of antituberculosis chemotherapy with five drugs for four months in the treatment of drug addicts and prisoners with pulmonary tuberculosis in Hong Kong

Hong Kong Chest Service/British Medical Research Council; Amer. Rev. Res. Dis., 1980, 122, 417-424

The results are reported of a service program in Hong Kong of intensive antituberculosis chemotherapy with 5 drugs given daily for 4 months, or until discharge from hospital or release from prison if earlier, in the treatment of male Chinese drug addicts and prisoners who had pulmonary tuberculosis positive for acid-fast bacilli on microscopic examination of the sputum. Of 69 patients who received 4 months of chemotherapy, all those with sputum cultures negative for *M. tuberculosis* initially, and more than 80% of those with positive cultures, 41 % of whom had strains resistant to isoniazid, streptomycin, or both drugs, achieved quiescent disease, which was maintained for a year of follow-up. Some of the patients who received less than 4 months of chemotherapy also responded well. Despite the 5 drugs, the frequency of adverse reactions to the regimen was low.

Short-Course (6 Month) Cooperative Tuberculosis Study in Poland: Results 18 months after completion of treatment

Marian Zierski, et al; Amer. Rev. Resp. Dis.; 1980, 122, 879.

The efficacy and toxicity of 4 drug regimens containing rifampicin, isoniazid, and ethambutol administered both daily and intermittently for a total duration of 6 months (26 wk) have been compared. There were 411 patients with newly diagnosed, previously untreated, pulmonary tuberculosis admitted to the study, 49 patients received isoniazid, rifampicin, and ethambutol daily in a hospital for the first 8 wk of treatment. One group continued to receive these 3 drugs daily as outpatients for an additional 18 wk; a second group received the same drugs

twice weekly, and a third group received the 3 drugs once weekly during the 18-wk "continuation phase." A fourth group of patients received 2 drugs, isoniazid and rifampicin, twice weekly during the continuation phase. Drug toxicity was not a major problem; drugs were permanently discontinued in only 1 % of the patients. All 4 regimens were highly effective in achieving sputum negativity. By the fifth month, 100% of the patients had become culture negative. However, the relapse rate was found to be relatively high for all regimens (12, 7, 20 and 17% respectively in the four groups. The difference was, however, significant only between groups 3 and 4. Patients with extensive disease, large cavities, heavy growth on pretreatment cultures, slow sputum conversion, persistent cavities, heavy use of alcohol, and concomitant diseases were more likely to relapse. In order to achieve relapse rates acceptable in developed countries, regimens containing rifampicin and isoniazid must either be given for longer than 6 months or strengthened by the addition of supplemental drugs during the initial phase.

Results of Short-Course Chemotherapy in Extra-pulmonary Tuberculosis

A.K. Dun, et al; Amer. Rev. of Res. Diseases: 1981. 123 (4 Supple), 255.

109 patients of extra-pulmonary tuberculosis were treated with short-course chemotherapy consisting of INH and Rifampicin daily to begin with and twice weekly subsequently with a total duration of treatment of 9 months. Diagnosis was confirmed bacteriologically and/or histologically in 84 cases; 70 were males and 39 females. Average age was 57.8 years (range 17-92). Bones and joints were involved in 23 cases, urogenital 11, pericardial 7, abdominal 6, lymph nodes 11, miliary and meningitis 14, pleural 30, laryngeal 3, miscellaneous 4. Major side effects were hepatitis in two, one due to INK and one due to Rifampicin and 'Flu syndrome' in one due to Rifampicin after 5 months of twice weekly treatment. Four cases of minor intolerance were mainly gastrointestinal. Length of follow-up ranged from 1 month to 47 months. The results have been favourable in all except 2 who died during the course of treatment due to non-tuberculous causes. There have been no relapses.

Controlled Clinical Trial of Five Short-Course (4-Month) Chemotherapy Regimens in Pulmonary Tuberculosis

Amer. Rev. of Res. Dis; 1981, 123,165.

Bacteriological relapse rates between during follow-up (5 and 28 months) in five 4-month

chemotherapeutic regimens for pulmonary tuberculosis have been compared. The regimens were: (1) Streptomycin plus isoniazid plus rifampin plus pyrazinamide daily for 8 wk followed by isoniazid plus rifampin plus pyrazinamide daily for 9 wk; (2) the same 4 initial drugs for 8 wk followed by isoniazid plus rifampin daily for 9 wk; (3) the same 4 initial drugs for 8 wk followed by isoniazid plus pyrazinamide daily for 9wk; (4) the same 4 drugs for 8 wk followed by isoniazid daily for 9 wk; (5) the same as regimen 4; but without streptomycin for the first 8 wk. The first 2 regimens, in which rifampin was given for 4 months, had relapse rates of 16 and 11%, respectively, but the rates were much higher for the regimens in which rifampin was given for only 2 months (32 and 30% respectively). The addition of pyrazinamide in the continuation phase had no effect on relapse rate. Removal of streptomycin (regimen 5) resulted in a relapse rate of 40%, but this was not significantly higher than that (30%) after regimen 4 ($p=0.2$).

Side-effects of drug regimens used in Short-Course Chemotherapy for Pulmonary Tuberculosis. A controlled clinical study

M. Zierski, et al ; Tubercle; 1980, 61, 41-40.

An analysis is presented of the side effects which occurred in 530 patients treated with 6 months' chemotherapy for newly detected pulmonary tuberculosis. Five treatment regimens were used. The initial phase of treatment consisted of daily isoniazid rifampicin and ethambutol (HRE) or isoniazid, rifampicin, streptomycin and pyrazinamide (HRSZ) given for 2 months. The second phase of treatment consisted of isoniazid and rifampicin given twice weekly (H.R.) or isoniazid, rifampicin and ethambutol given daily (4HRE) or intermittently (H.R.E. or H.R.E.) for 4 months.

Side effects were detected in 66 (12.4%) patients. Hepatotoxic reactions occurred in 48 (9%) patients, mainly of a mild and transient nature and the majority were attributable to isoniazid. The 'flu like' syndrome occurred in only 2 patients both during the daily phase of treatment and it was not encountered in patients taking rifampicin intermittently (dose 600 mg).

Inclusion of pyrazinamide in the initial phase of 1 regimen did not result in an increase of frequency of side effects. In 56% of patients on pyrazinamide the serum uric acid concentration was elevated but there was no arthralgia.

Drug toxicity leading to alteration or withdrawal of treatment occurred in only 10(1.8%) patients. This study shows that with these 6 month regimens the overall risk of drug

toxicity was low, and less than that associated with more conventional treatment regimens.

A case of Rifampicin-Induced Acute Renal Failure and Review of 47 cases with liver dysfunction induced by Isoniazid and Rifampicin

Yukihiko Sugiyama, et al; Kekkaku; 1981, 65, 375.

A case is reported who developed liver dysfunction and renal failure following Rifampicin in a study in Japan. Twelve cases out of 47 who were given Rifampicin 450 mg daily with INH showed slight liver dysfunction. There was no interruption in the treatment and all the patients showed normal liver function subsequently while continuing drugs, except one of these who, in addition, developed acute renal failure after three weeks treatment and the drugs had to be withdrawn.

Histological Characteristics of Tuberculous Cavity Treated with Rifampicin

Issei Tanaka, et al; Kekkaku; 1981, 56, 355.

Histological features of tuberculous cavities in resected lungs from patients treated with rifampicin among other drugs were studied in Japan. The caseous material showed a tendency to be more concentrated and dehydrated. Migration of a large number of macrophages into the caseous lesions was followed by digestion of the necrotic debris and invasion of capillaries into the caseous lesions. There was a suggestion that the caseous material is quickly degraded, ingested and organised as a result of strong bactericidal action of Rifampicin and thereafter it belied as a foreign body.

Short Course (6 months) Co-operative Tuberculosis Study in Poland. Results 30 months after Completion or Treatment.

Marian Zierski, et al., Ameri. Rev. Resp. Dis. 1981, 124, : 249-551,

The results of four 6-months' chemotherapy regimens 30 months after the completion of treatment of all patients, who received isoniazid, rifampin and ethambutol daily for 18 weeks as in-patients have been reviewed. One group received these three drugs daily as an out-patient for an additional 18 weeks, a second group received the same drugs twice weekly, and a third group received these drugs once weekly for 18 weeks. A fourth group received two drugs, isoniazid and rifampin twice weekly. Drug toxicity was negligible in all patients. Drugs were discontinued in 1% of all patients. Bacteriological conversion was very high in all regimens. Relapse rate was high in all regimens (range 8 to 22%).