REVIEW ARTICLE

SHORT COURSE CHEMOTHERAPY OF PULMONARY TUBERCULOSIS

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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 revolutionalised 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 ! 8-24 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 Hast Africa.[1,2] In this study, t 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.

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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 pesist 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 Kong [5] 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 Madres, 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 bacterioststic 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 E – Ethambutol
T – Thioacetazone Z – Pyrazinamide
P – PAS 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 signficant 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, pyra2inamide and streptomycin are drugs with bactericidal and sterilising activity and can be employed in appropriate combinations in short-course chemotherapy.[9,10] Ethambutol, 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, Paris[11], from *In vivo* and *in vitro* laboratory experimental work of Prof. Mitchison's Unit in London[12,13] and from studies in East Africa[14] on the reduction in viable bacterial counts in sputum achiev ed with 2 days of chemotherapy have also provided valuable data on the activity of antituberculosis drugs. On the basis of these findings. Prof. Mitchison[15] 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 finaliy, 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), Fox[10] 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 $EHRZ_3$ 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'

TABLE 4

Bacteriological relapses associated with highly effective 6-month regimens[10,17-21]

Regimen	Dura lion (months)	Study	Bact. relapses (%)
2 SHRZ/HR2	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/SHZ2	7	Madras	0
SHRZ/HR 3	6	Poland	0
$SHRZ/SH2_3$	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 initia-lly 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 iso-niazid 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/SHZ_2 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 study[23] 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 net 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 8 [28] 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

Regimen	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-montb 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, ail the three inexpensive regimens nave 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 $SHRZ_2$, 2 SHRZ/5 SHZ_2, 3 SHRZ, and 3 SHRZ/2 SH_2) and non-rifampicin regimens (2 SHZ/5 SHZ_2 and 3 SHZ/2 SHZ_3).

It will be seen that streptomycin resistance was of no consequence. With the rifampicin regimes, 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 chemo-therapy (%)	Relapses (%)	Patients assessed	Failure during chemo-therapy (%)	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 lymphadeenitis 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, pro vided 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 considera tion 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 involve ment in miliary tuberculosis. In general, intermittent regimens are likely to be less often associated with adverse re actions 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 consi deration logistics of transportation of drugs from central locations to remote rural areas where the bulk of the tuber culosis 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 programe, 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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