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RELAPSE IN TUBERCULOSIS

S.P. TRIPATHY**

At the outset I would like to express my sincere gratitude to the Tuberculosis Association of India for having bestowed upon me the coveted Wander-TAI Oration Award. When I think of the illustrious personalities who have preceded me I begin to have doubts as to whether I will be able to do justice to today's occasion. If I fail to come up to your expectations it will not be because of lack of honest efforts on my part–it is because I neither have the scientific stature nor the grey hairs which my predecessors had. I sincerely hope you will view it in the proper spirit and condone any lapses in my presentation.

We are about to celebrate the centenary of the discovery of the tubercle bacillus by Robert Koch. It is less than 4 decades since we have had the benefits of chemotherapeutic agents with specific activity against tuberculosis. Nevertheless, the decades following the discovery of streptomycin by Waksman in 1943 have seen spectacular achievements in the chemotherapy of tuberculosis. We now have several antituberculosis drugs–isoniazid, rifampicin, streptomycin, pyrazinamide, PAS, ethambutol, thiacetazone, ethionamide and a few other drugs. Isoniazid is by far the most potent and most effective drug with a bactericidal activity, with rifampicin being a close second. Streptomycin and pyrazinamide also have bactericidal activity, and like isoniazid and rifampicin, cause death of tubercle bacilli. Drugs such as PAS, ethambutol and thiacetazone have a bacteriostatic activity, that is, they prevent the multiplication of the bacilli, so that the elimination of the bacilli would depend upon the defence mechanism of the host; their utility is limited to their being companion drugs given in combination with isoniazid with the object of preventing the multiplication of isoniazid-resistant mutants. The present day management of tuberculosis consists of treatment with a combination of isoniazid with at least one other drug in appropriate dosages and rhythms for periods upto 24 months. With a judicious choice of drug regimens containing isoniazid and other drugs it is possible to produce rapid sputum conversion to negativity and to eliminate the possibility of emergence of drug-resistance ; further, patients attaining bacteriological quiescence continue to have quiescent disease even after stopping chemotherapy. With inadequate chemotherapy, on the other hand, failures may manifest in one or more ways-sputum may fail to become culture negative, drug-resistance may emerge, or sputum conversion occurs during treatment but culture becomes positive again after treatment is discontinued, that is, the patient has a bacteriological relapse. With the advent of highly effective chemotherapeutic regimens with practically 100 % efficacy, bacteriological relapse has become the most crucial factor in determining the relative merits of chemotherapeutic regimens. I have, therefore, chosen the subject of relapse for today's oration.

Antituberculosis drugs have two major roles-they are required to kill dividing bacilli, so that the patient becomes sputum negative and non-infectious; they are also called upon to kill bacilli which have a tendency to persist during chemotherapy and give rise to bacteriological relapses later on. The speed of sputum conversion and relapse rates are thus good measures of the bactericidal and sterilising activity of regimens and drugs. Table 1 summarises findings from patients in East Africa[1] and Hong Kong[2] and presents the bactericidal activity of various regimens measured in terms of proportions of sputum positive cases who converted to negativity by the end of 2 months of chemotherapy.

TABLE 1

Bactericidal activity on dividing bacilli in sputum positive patients

Regimen	Percent culture negative at 2 months
SH	49 –
SHT	49 –
SHZ	66 –
SHZR	95 –
SHER	81 –

S–Streptomycin H–Isoniazid
T–Thiacetazone Z–Pyrazinamide
R–Rifampicin E–Ethambutol

*Wander - T.A.I. Oration, 1980.

**Director, Tuberculosis Research Centre, Madras-31.

The regimen SH produced sputum conversion in 49 per cent of patients. The addition of thiacetazone, a bacteriostatic drug, to the SH regimen, made no difference to the bactericidal activity of the regimen. Pyrazinamide, however, made a substantial contribution raising the proportion to 66 per cent. Rifampicin further enhanced the bactericidal activity, with 95 per cent of the patients becoming culture negative. Ethambutol, another bacteriostatic drug, was clearly inferior to rifampicin.

Table 2 presents data on the ability of the drug regimens to kill persisting bacilli and thus produce sterilisation of lesions and prevent the occurrence of bacteriological relapses after stopping chemotherapy.

Table 2

Sterilising activity on persisting bacilli

Regimen	Duration of chemotherapy (months)	Relapses 1-2 years after stopping therapy (%)
6 SH*	6	*29*
6 SHT	6	*22*
6 SHZ	6	*8*
2 SHRE/4$S_2H_2E_2$**	6	*21*
2 SHRZ/4$S_2H_2Z_2$	6	*7*
2 SHRE/6$S_2H_2E_2$	8	*10*
2 SHRZ/6$S_2H_2Z_2$	8	*4*

* The prefix indicates the number of months of chemotherapy with the regimen

** The suffix indicates the number of doses of the drug during the week.

The addition of thiacetazone (T) to SH did not significantly bring down the relapse rates; pyrazinamide, on the other hand, brought the relapse rate down from 29 per cent to 8 per cent. The contrast between pyrazinamide and ethambutol clearly shows that pyrazinamide is more effective than ethambutol in killing persisting bacilli and thus preventing relapses.

Bacteriological relapses have been investigated extensively in the various chemotherapy studies conducted at the Tuberculosis Research Centre, Madras, under the auspices of the Indian Council of Medical Research in collaboration with the British Medical Research Council, the World Health Organisation and the Government of Tamil Nadu. In addition, the British Medical Research Council has also participated in collaborative studies in East Africa, Hong Kong, Singapore and other countries. Consequently, we now have a wealth of information on relapses, why they occur and how they can be prevented. We shall discuss the findings, separately in tuberculosis patients who were initially bacteriologically positive, and those who were initially bacteriologically negative but had active pulmonary tuberculosis requiring treatment.

Sputum positive cases

Most of the controlled clinical studies in pulmonary tuberculosis have been carried out on patients who were bacteriologically positive. Since its inception in 1956, the Tuberculosis Research Centre in Madras has carried out a series of controlled clinical trials in newly diagnosed previously untreated bacteriologically positive cases of pulmonary tuberculosis residing in Madras City. Most of them were treated with drug-regimens on an ambulatory basis for durations of 1 year in the earlier studies, and 3 to 7 months in the recent studies. All these patients had culture-positive tuberculosis, with over 90 per cent having positive smears; nearly all had cavities, with about 70 per cent of them having moderate or extensive cavitation and moderate or gross disease as assessed radiologically. Thus, most of the patients in these studies had extensive pulmonary pathology. The pretreatment characteristics of these patients have remained more or less same during the past 25 years.

These patients were treated with drug regimens for the scheduled durations and were classified as having quiescent disease if all cultures during the last 2-3 months were negative for tubercle bacilli, and the response was considered as favourable. Patients having quiescent disease at the end of chemotherapy were followed upto 60 months-by monthly sputum examination upto 24 months from the start of treatment and at 3 monthly intervals, thereafter, in order to determine the stability of bacteriological quiescence and the relapse rates. A patient was classified as having had a bacteriological relapse if 2 or more positive cultures were obtained during a 6-month period. A culture was considered to be an isolated positive culture if there was no other positive culture in the previous 6 months or in the succeeding 6 months.

Table 3

Bacteriological Relapses following Chemotherapy with conventional 12 *Month Doily Regimens*

Regimen	Total patients	Culture negative at 2 months (%)	Favourable response at 1 year (%)	Total patients in relapse study	Relapse (%)	Overall efficacy (%)
H 100 mg b.d.	129	*35*	*45*	32	*12*	*40*
or						
H 200 mg b.d.						
H 400 mg o.d.	207	*44*	*70*	50	*12*	*62*
or						
H 650 mg o.d.						
H + T o.d.	72	*44*	*82*	21	*19*	*66*
H + P b.d.	454	*42*	*85*	143	*17*	*71*
H + E o.d.	107	*49*	*96*	43	*16*	*81*

P-PAS

Table 3 summarises the results of chemotherapy with conventional daily regimens of isoniazid alone, isoniazid plus thiacetazone, isoniazid plus PAS or isoniazid plus ethambutol, for a duration of one year. The regimens had efficacies ranging from 45 per cent to 96 per cent.

The regimens of isoniazid alone were associated with relapses in 12 per cent of cases. It is significant that the two-drug combinations of isoniazid plus thiacetazone, PAS or ethambutol were associated with equally high relapse rates– 16-19 per cent. Thus, ethambutol, PAS and thiacetazone did not contribute to the killing of persisting bacilli which give rise to relapses. This is also seen in the proportions of patients who were culture negative at 2 months– namely, 44 per cent with regimens of isoniazid alone (450 mg or 650 mg daily), compared with 42-49 per cent with the two drug regimens.

Table 4 summarises similar findings in Madras patients treated with supervised intermittent regimens for a duration of 12 months, Even these regimens did not have high bactericidal activity: less than 50 per cent became culture negative by the end of 2 months and 9-15 per cent of the patients with quiescent disease had a relapse. As a consequence of the relapses the overall efficacy of the regimens was considerably reduced, to 81 per cent with the best daily regimen, ethambutol plus isoniazid, and to 86 per cent with the best intermittent regimen, streptomycin plus isonianid twice a week.

As stated earlier, nearly all the patients had cavitated disease at the start. In many, the cavities disappeared during treatment; there were also patients who had a favourable response to treatment but were left with residual cavities lined by fibrous tissue or epithelial cells, i.e., 'open negative syndrome'. Data on the frequency of relapses in those with residual cavitation and in those without are presented in Table 5. There is evidence that with conventional regimens, the relapse rates were higher in patients with residual cavitation, with roughly a fifth of the patients having a relapse before the end of 5 years.

Table 6 summarises the findings of several studies on relapse in Madras patients 3-6. It will be seen that 18 per cent of 296 patients treated with 12-month regimens had a relapse; in about two-thirds of them the relapse occurred

Table 4
Bacteriological Relapses following Chemotherapy with intermittent 12 *Month Regimens*

Regimen	Total patients	Culture negative at 2 months (%)	Favourable response at 1 year (%)	Total patients in relapse study	Relapse (%)	Overall efficacy (%)
SHOW or SHZOW	224	*41*	*70*	30	*19*	63
SH/SHOW	261	*47*	*88*	197	*15*	*75*
SPH/SPHOW	174	*49*	*89*	47	*13*	*77*
SHTW	199	*42*	*94*	55	*9*	*86*

Table 5
Relationship between Residual Cavitation at the end of Chemotherapy and Relapse

Regimen	Cavitation			No cavitation		
	Total	Relapse No.	%	Total	Relapse No.	%
Isoniazid alone	11	2	*18*	44	3	*7*
PH, EH or TH	70	14	*20*	138	21	*15*
Intermittent S+H regimens	160	30	*19*	169	10	*6*

Table 6
Bacteriological relapses daring 4 + Years after Chemotherapy for 1 *Year in Madras Patients*

Report	Total patients	Total relapses in 4 year period		Year of relapse		Relapse with H sensitive cultures
		No.	%	2nd	3rd, 4th and 5th	
Dawson et al (1966)	61	8	*13*	5	3	6
Evans et al (1969)	87	15	*17*	*9*	6	13
Ramakrishnan et al (1969)	54	11	*20*	5	6	9
Nazareth et al (1966)	94	20	*21*	14	6	18
ALL	296	54	*18*	33	*21*	46(86)

during the second year i.e., during the first 12 months after stopping chemotherapy. In all, 86 per cent of the patients relapsed with cultures sensitive to isoniazid, so that they could be retreated with regimens of conventional chemotherapy such as streptomycin plus isoniazid.

Isolated Positive Cultures

We have seen that among patients who had attained bacteriological quiescence following 1-2 years of chemotherapy with standard regimens, about 18% had a bacteriological relapse, i.e., they excreted 2 or more cultures during a 6-month period. In addition, several patients excreted isolated positive cultures. Thus, 73 (17%) of 434 patients excreted 1 or more isolated positive cultures during 3-4 years after completion of chemotherapy (Table 7).

Table 7

Isolated postive cultures during 4 years after chemotherapy for 1-2 *Years in Madras*

Report	Total patients	Patients with isolated positive cultures		Isoniazid sensitive
		No.	%	
Dawson et al (1966)	126	18	*14*	10[a]
Evans et al (1969)	180	29	*16*	18[b]
Ramakrishnan et al (1969)	128	26	*20*	16
ALL	434	73	*17*	44 65%

a 3 cultures were not tested
b 2 cultures were not tested

Taking into consideration the finding that about 18 % patients had a bacteriological relapse (with at least 2 positive cultures) it would seem that about a third of the patients who had attained quiescence following standard chemotherapy excreted tubercle bacilli in their sputum on at least one occasion during the 3-4 year period of follow-up.

In our studies at Madras, a proportion of patients were given maintenance chemotherapy after 12 months of the scheduled chemotherapy. The results showed that maintenance therapy with isoniazid alone daily or isoniazid plus streptomycin once a week for 1 year completely prevents the occurrence of relapses, Thus, if chemotherapy with standard drugs were to be continued for 24 months it would be possible to completely eliminate relapses. This however poses logistic problems and also problems of patient compliance. Under field conditions in India and other developing countries only about 50 per cent of the patients complete their chemotherapy-it would be impossible to organise an effective treatment programme with a 24-month regimen because of lack of patient compliance. For any modification in the Tuberculosis Programme to be meaningful one should be thinking in terms of reduction in the duration of chemotherapy, rather than increasing the duration, without compromising on the efficacy of the regimens. With the bactericidal antituberculosis drugs now available, it is possible to evolve effective short-course regimens with high efficacy and no relapse rates. Question is : Which drugs, and how long should they be given.

Table 8 summarises the relative bactericidal properties of four antituberculosis drugs as assessed by their activities in laboratory studies *in vitro* against cultures of tubercle bacilli, and *in vivo* against experimental tuberculosis in mice and in guinea-pigs.

Table 8

Relative bactericidal activity of 4 main drugs used in Short–Course Chemotherapy

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

*H 5.2–5.6

**Drugs given in very high dosages

It is clear that all the four drugs have bactericidal activity; isoniazid and rifampicin have very high activity, while that of streptomycin and pyrazinamide is relatively less.

We now have a wealth of information on the relative efficacy of these drugs in treatment of tuberculosis in man, and the clinical results are generally in conformity with the laboratory findings. These four drugs have now been regargarded as the drugs of choice in the formulation of short course regimens.

Relationship between Drug action and Physiological state of Bacilli

The available data indicate the existence of at least three types of bacterial populations according to their anatomical location.[7] The first is a population of actively growing tubercle bacilli present in the liquefied caseous material. This is by far the largest fraction of the total bacterial population and contributes to practically the entire bulk of bacilli excreted in the sputum in untreated patients and in the early months of treatment. These bacilli are acted upon by isoniazid, and, to a smaller extent, by rifampicin and streptomycin. By virtue of the largeness of the bacterial population, drug-resistant mutants are usually present in this fraction. Combinations of 2 or more bactericidal drugs are therefore, necessary to effectively prevent the survival and selection of drug-resistant mutants.

The second is the population of bacilli situated within the macrophages in an acidic milieu; they grow very slowly, and escape the action of all anti-tuberculosis drugs except pyrazinamide. The third population consists of small numbers of bacilli which are present extra-cellularly in solid caseous lesions and multiply slowly and intermittently; rifampicin is the only drug which acts on this population. There is possibly a fourth population of dormant bacilli not killed by any drug. Since all these populations exist in the lesions, it is necessary to give at least 3 drugs, isoniazid, rifampicin and pyrazinamide, and possibly streptomycin as well to ensure that relapses do not occur. Regimens which do not contain rifampicin and pyrazinamide may still produce sputum conversion by eliminating the first bacterial population but will be associated with persistence of the remaining populations with their subsequent multiplication, giving rise to positive cultures; these tend to be only single positive cultures (isolated) in many patients if the host defence is able to limit the bacterial multiplication. In a proportion of patients the defence mechanism might fail, in which case the patient excretes bacilli repeatedly, and is classified as a bacteriological relapse. Since the persisting bacilli in the special populations have escaped the action of drugs, there has not been the requisite 'elimination' of the drug-sensitive members of the population for the emergence of drug-resistance. Tubercle bacilli isolated from patients who have bacteriological relapses, therefore, are usually sensitive to the drugs with which the patients have been treated.

We have seen that many patients treated with full courses of standard regimens occasionally excrete tubercle bacilli, i.e., isolated positive cultures. As we will see later, such isolated positive cultures occur with almost similar frequency in patients who have been treated with effective short course regimens containing the four bactericidal drugs. The exact significance of such cultures is not yet known. They possibly arise from the persistence of dormant bacilli in the fourth population referred to earlier. At the moment such cultures do not appear to have any clinical significance, since they tend to be limited to single cultures.

Relapses in Short Course Chemotherapy

Combinations of bactericidal drugs administered to patients with drug-sensitive cultures are highly effective with practically no bacteriological failures during treatment, so that virtually 100 per cent of the patients have a favourable response at the end of chemotherapy with rifampicin plus isoniazid or similar potent combinations. Hence, a criterion of a favourable response to treatment cannot discriminate one regimen from another. The crucial question is whether the quiescence attained is stable, i.e., the patient does not have a bacteriological relapse. A close and intensive follow-up during the past-treatment phase is thus an essential part of any controlled clinical trial of short course chemotherapy.

A regimen of rifampicin plus isoniazid daily for 9 months, with an initial daily supplement of streptomycin or ethambutol during the first two months, is associated with a 0 per cent relapse rate during 2 years of follow-up and is now standard short-course chemotherapy in technically advanced countries. This regimen, however, is expensive because of the cost of rifampicin. Controlled clinical studies in East Africa, Hong Kong, Singapore and other countries have shown that with a proper choice of drugs the duration of chemotherapy can be reduced to 6 months without increasing the risk of relapse. Initial intensive chemotherapy with 3 or 4 drugs for 2 months effectively eliminates the bacterial populations so that thereafter

maintenance chemotherapy with two drugs for a further 4 months ensures sputum conversion in all patients and a virtual freedom from relapse.

The First Madras Short Course study was based on the results of studies in East Africa, Hong Kong and Singapore. In this study, (Table 9) all patients received an initial intensive chemotherapy with SHRZ (for 2 regimens) or SHZ (for one regimen) *daily* for two months, followed by *twice-weekly* SHZ for 3 months or 5 months, so that the total duration of chemotherapy was 5 months or 7 months[8]. All the 3 regimens were associated with low relapse rates (Table 10). The 7-month rifampicin regimen had no relapses; reducing the duration to 5 months or the removal of rifampicin from the regimen carried a small penalty in the form of 3-5 per cent relapses. The findings of the non-rifampicin regimen, in particular, are of considerable interest since this regimen is relatively inexpensive and, therefore, can be useful. in developing countries.

The Second Madras Short Course Study[9] investigated the efficacy of a 3-month daily regimen of SHRZ in comparison with two other 5-month regimens (Table 9). The 3-month regimen had *a* relapse rate of 12 per cent, so that the overall efficacy of the regimen is over 85 per cent. This result is highly encouraging, since the duration of the regimen is only 3-months and hence patient compliance is likely to be high. The conventional 12-month daily regimens of Thiacetazone plus isoniazid (TH) or PAS plus isoniazid (PH) are associated with 15-20 per cent. failures during treatment, about 20 per cent relapses afterwards, and a low patient compliance. There is thus *a priori* reason to believe that the results of the 3-month MSHZ regimen will be better than with the 12-month PH or TH regimens under field conditions.

Table 9

Madras Short Course studies-Drug Regimens

	Regimen	Total duration
FIRST STUDY	2 SHRZ/3 $S_2H_2Z_2$	5 Months
	2 SHRZ/5 $S_2H_2Z_2$	7 months
	2 SHZ/3$S_2H_2Z_2$	7 months
SECOND STUDY	3 SHRZ	3 months
	3 SHRZ/2$S_2H_2Z_2$	5 months
	3 SHZ/2$S_2H_2Z_2$	5 months

Table 10

Results of Madras Short Course Studies

(Patients with drug sensitive cultures)

	Daily phase (months)	Twice weekly phase (months)	Total patients	Favourable response at the end of treatment (%)	Relapse during 18 months (%)
FIRST STUDY	RSHZ (2)	SHZ (3)	129	*100*	*5*
	RSHZ (2)	SHZ (5)	132	*100*	*0*
	SHZ (2)	SHZ (5)	269	*100*	*3*
SECOND STUDY	RSHZ (3)	–	139	*98*	*12*
	RSHZ (3)	SHZ (2)	137	*100*	*3*
	SHZ (3)	SHZ (2)	153	*100*	*10*

Isolated positive cultures

Earlier, it had been stated that many quiescent patients who had been treated with standard chemotherapy excreted isolated positive cultures during the follow-up phase. This was also true of patients who attained quiescence following short-course chemotherapy. Thus, in the First Madras Short Course study, 135, i.e. 25% of the 530 patients followed up excreted isolated positive cultures-they included 38 (30 %) patients on the 2SHRZ/3 $S_2H_2Z_2$ regimen, 38 (29%) on the 2SHRZ/5 $S_2H_2Z_2$ regimen, and 59 (22%) on the 2SHZ/5 $S_2H_2Z_2$ regimen. Their exact clinical significance is as yet uncertain.

Role of individual drugs in the prevention of relapse

Relapse rates associated with short-course regimens of varying durations and containing different combinations of drugs provide valuable information on the role of each drug in the prevention of relapses.

It is generally accepted that isoniazid is the drug par excellence. Given alone in high dosage, it leads to sputum conversion in about 70 per cent of patients, and most of the patients who convert remain free from relapse. Because of ethical reasons it is not possible to establish the relative efficacy of isoniazid and any other antituberculosis drug by conducting controlled clinical trials with regimens with and without isoniazid. There is no such limitation in the case of other drugs. Results of controlled trials with short-course regimens provide clear evidence of the role of several antituberculosis drugs in the prevention of relapse.

Role of pyrazinamide

Table 11 summarises the findings on 6 pairs of regimens studies in East Africa[1,10,11] and Singapore.[12] The addition of pyrazinamide daily to a 6-month regimen of streptomycin plus isoniazid (SH) substantially reduced the relapse rate from 29 per cent to 8 per cent. Such a beneficial effect was noted when the administration of pyrazinamide was limited to the first two months. The data on 4-month regimens suggest that the continued administration of pyrazinamide beyond 2 months does not influence the relapse rates.

In summary, pyrazinamide administered during the first 2 months effectively reduces relapse rates but continued administration beyond 2 months does not confer any additional benefit.

Table 11

Role of pyrazinamide in Short Course Chemotherapy

Place of study	Regimen	Duration (months)	Relapses (%)
East Africa	6SH	6	29
	6SHZ		8
East Africa	2SHR/TH	6	18
	2SHRZ/TH		13
East Africa	2SHR/TH	8	6
	2SHRZ/TH		0
East Africa	2SHRZ/HRZ	4	14
	2SHRZ/HR	4	11
East Africa	2SHRZ/HZ	4	28
	2SHRZ/H	4	30
Singapore	2SHRZ/HRZ	4	10
	2SHRZ/HR	4	5

Role of streptomycin

Data on the role of streptomycin in the prevention of relapse are summarised in Table 12. The high relapse rate of 29 per cent associated with the 6SH regimen in East Africa shows that streptomycin is a poor companion drug to isoniazid, unlike rifampicin. The contrast between the 2HRZ/H and 2SHRZ/H regimens[11] as well as that between 6 HR and 6SHR regimen[13] however, suggests that the addition of streptomycin reduces the relapse rates, but only marginally.

Role of rifampicin

Data on the role of rifampicin in short-course regimens are summarised in Table. 13. The addition of rifampicin to SH or SHZ reduces the relapse rates. The contrast between the regimens 2SHRZ/H and 2SHRZ/HR clearly shows that, unlike pyrazinamide, rifampicin continues to make an important contribution in the continuation phase. This suggests that the special bacterial population on which rifampicin

Table 12

Role ofstreptomycin in Short Course Regimens

Regimens	Duration (months)	Relapses (%)
2HRZ/H	4	41
2SHRZ/H		30
6 H R	6	8
6 SHR		4
6 S H	6	29

Table 13

Role of rifampicin in Short Coarse Regimens

Place of study	Regimen	Duration (months)	Relapses
East Africa[1]	6 S H	6	29
	6 SHR		4
Madras[8]	2 SHZ/$S_2H_2Z_2$	7	3
	2 SHRZ/$S_2H_2Z_2$		0
Madras[9]	3SHZ/$S_2H_2Z_2$	5	10
	3SHRZ/$S_2H_2Z_2$		3
East Africa[11]	2SHRZ/H	4	29
	2SHRZ/HR		4

acts exclusively requires a longer period of exposure to ensure its elimination.

Role of bacteriostatic drugs

Data from East Africa and Hong Kong, already presented in Table 2 indicate the role played by bacteriostatic drugs such as thiacetazone and ethambutol in short-course chemotherapy. The addition of thiacetazone to SH did not reduce the relapse rate significantly, while the addition of pyrazinamide did so substantially. The ethambutol regimen studied in Hong Kong was associated with a relapse rate of 21 per cent, while the corresponding pyrazinamide regimen had a relapse rate of 7 per cent. There is thus clear evidence that bacteriostatic drugs such as thiacetazone and ethambutol are associated with high relapse rates, and have no place in short-course regimens.

Rhythm of administration of drugs

Intermittent chemotherapy has several advantages over conventional daily regimens. Firstly, the drugs can be given under full supervision, and this eliminates concealed drug-irregularity; secondly, adverse reactions due to drugs occur less frequently when drugs are given intermittently, and finally, intermittent regimens often less expensive than the corresponding daily regimens, particularly in the case of regimens which employ rifampicin.

Table 14 presents data from a controlled trial in Hong Kong[14], comparing the results of daily, twice-weekly and thrice-weekly administration of drugs. The results show that there is little change in the relapse rates when the interval between successive doses is increased from one day to two days or to three days.

Influence of the duration of short-course chemotherapy on the relapse rates

There is evidence from many studies that

Table 14

Rhythm of administration of drugs in Short Course Chemotherapy

Regimen	Duration (months)	Unfavourable response at the end of treatment (%)	Relapse (%)
SHZ	6	0	18
$S_3H_3V_3$		1	24
$S_2H_2Z_2$		4	21
SHZ	9	0	5
$S_3H_3V_3$		0	6
$S_2H_2Z_2$		1	6

the relapses associated with some short-course regimens can be prevented by continuation of the regimen by a further 2 or 3 months (Table 15). The two 4-month regimens studied in Singapore[12] had relapse rates of 5 % and 10 %; extending the duration of the continuation phase by another 2 months virtually eliminated the occurrence of relapses. While the near-sterilising effect of 6-month chemotherapy stands out clearly, there is an important message for a developing country like India-reducing the duration of chemotherapy from 6 months to 4 months has resulted in only a small penalty-the over-all efficacy of the 4-month regimen is still high enough for application in routine chemotherapy.

Relapse in patients who had drug-resistant cultures initially

In the two short-course studies reported from Madras there were 214 patients with resistance to Streptomycin or to isoniazid or to both drugs. Their response to treatment, as well as the relapse rates in those who had a favourable response, are presented in Table 16. It will be seen that the relapse rates were low and similar in patients treated with the rifampicin and the non-rifampicin regimens, even though the response to treatment was substantially inferior in the case of the non-rifampicin regimen. Whether resistance was to one drug or both drugs or whether resistance was to streptomycin or to isoniazid did not also have any influence on the relapse rates.

Table 1.5

Duration of short-course chemotherapy

Place of Study	Regimen	Duration of Chemo-therapy (months)	Bacterio-logical relapse (%)
Singapore[12]	2 SHRZ/HRZ	4 6	10 0
	2 SHRZ/HR	4 6	5 1
Madras[8]	2 SHRZ/$S_2H_2Z_2$	5 7	5 0
Hong Kong[14]	$S_2H_2Z_3$	6 9	25 9
Hong Kong[2]	$4S_3H_3T_3Z_2/S_2H_2Z_2$	6 8	6 1

Relapse in patients with smear-negative pulmonary tuberculosis

Patients with smear-negative pulmonary disease in general have less extensive disease and less number of bacilli in their lesions than patients with smear-positive disease. One may

Table 16

Response of patients with initial drug-resistance in the two Madras Short-Course Studies

Resistance	Non-rifampicin regimens			Rifampicin regimens		
	Total	Favourable response	Relapse	Total	Favourable response	Relapse
S only	17	16	1	32	32	4
H only	25	16	1	48	43	2
SH	33	7	0	59	44	2
Either drug	75	39	2(5)	139	119	8(7)

Table 17

Relapse in smear-negative-patients

Culture result on admission	Group	No. of patients assessed	Bacteriological relapses by 12 months (%)
Negative	Selective chemotherapy	181	*34*
	2 SHRZ	175	*1*
	3 SHRZ	168	*1*
	SPH/S_2H_2	167	*1*
Positive,	2 SHRZ	73	*14*
drug-sensitive	*3* SHRZ	74	*1*
	SPH/S_2H_2	83	*0*

expect that sterilisation of their lesions could be achieved with less intensive chemotherapy and for shorter durations. There is, however, very little scientific evidence in support of this contention. The Tuberculosis Research Centre participated in a cooperative study in collaboration with the Hong Kong Chest Services and the British Medical Research Council.[15] Symptomatic patients with smear-negative, radiologically active pulmonary tuberculosis were admitted to a controlled clinical trial and randomly allocated to 4 groups –

(a) A selective chemotherapy group-the patients were placed under observation and carefully followed up by periodic bacteriological examination. Treatment was started only if the patient's sputum yielded tubercle bacilli on culture or if there was clinical or radiographic deterioration warranting initiation of chemotherapy; such patients were prescribed a standard 12-month regimen of SPH/S_2H_2.

(b) 2 SHRZ group: The patients received SHRZ daily for a period of 2 months

(c) 3 SHRZ group: The patients received SHRZ daily for 3 months; and

(d) SPH/S_2H_2 (Control Group) : The patients received PH daily for 12 months with a supplement of Streptomycin daily for the first 3 months.

Of 1072 patients with negative smears, 64 % had all cultures negative, while the remaining 36% had at least one culture positive. The patients were followed up by regular monthly bacteriological examination. The results are presented in Table 17 separately for those patients with one or more positive cultures fully sensitive to streptomycin and isoniazid, and for those who were culture negative.

Thirty-four percent of patients in the Selective Chemotherapy Group had a break-down, giving rise to positive cultures, and were started on treatment with SPH/S_2H_2. In contrast, the relapse rate was 1% each of the three groups treated with drugs. Thus, the two short-course regimens had prevented relapse rates of the order of 30 %.

Considering the results in patients who had one or more positive cultures on admission, it is seen that while there were no failures among those treated with the standard SPH/S_2H_2 regimen for 12 months, 14 % of the patients on 2 SHRZ and 7% of those on 3 SHRZ had a bacteriological relapse.

In summary, even 3 months of intensive daily chemotherapy with the 4 drugs SHRZ is inadequate in patients who are smear-negative but culture positive; a longer duration of chemotherapy is necessary for complete prevention of relapse in such cases. However, 2-3 months of chemotherapy effectively prevents the occurrence of relapses in patients with smear-negative culture-negative disease.

General features of relapse

We have by now quite a large body of data on relapses so that we can make some general conclusions.

(1) Relapses generally tend to occur within the first year after stopping chemotherapy.

(2) In the case of patients who had drug sensitive cultures at the start of chemotherapy, relapses occur with drug-sensitive cultures (the so-called relapses occurring *during* chemotherapy are actually not relapses–they are manifestations of a fall and rise phenomenon; such cultures are usually drug-resistant).

(3) Since their cultures are usually sensitive to isoniazid and streptomycin, patients who have a relapse can be successfully retreated either with short-course regimens or with conventional 12-month regimens containing isoniazid.

(4) Relapse rates are higher with regimens which include bacteriostatic drugs than with regimens containing bactericidal drugs.

(5) Relapse rates are similar in patients who have drug-sensitive cultures and in those who have drug-resistant cultures on admission.

(6) It is not clear as to what factors are responsible for relapse occurring in an individual patient. There are indications that the initial bacterial content, the extent of disease initially, the month of sputum conversion and the presence of residual cavitation at the end of chemotherapy have some role. The immunological status of the host may play a major role and may determine which patient will have a relapse and when.

So far, we have been discussing the occurrence of relapses in tuberculous patients who had been successfully treated with full courses of antituberculosis drugs and had attained bacteriological quiescence. Such relapses which occur due to a break-down of the host defence mechanism represent only a small part of the tuberculosis problem in the country. A similar situation exists on a much larger scale in infected, tuberculin-positive, apparently healthy individuals in some of whom, for no apparent reason, the immune mechanism is disrupted and tuberculosis results due to a process of endogenous reactivation. Although such breakdowns are not generally termed relapses, they deserve to be so named since they occur in more or less the same way relapses occur in patients who had attained quiescence following chemotherapy. They pose a much bigger problem, since the bulk of the cases of tuberculosis in our country come from the tuberculin positive individuals. Thus, in the recently concluded BCG trial in Chingleput, the annual incidence of disease was 20 times higher in the tuberculin-positive group than in the tuberculin negative group. The important question is whether anything can be done to activate the host defence mechanism so that it effectively eliminates residual, dormant bacilli from lesions which have apparently healed under the influence of chemotherapy or from healed primary complexes in apparently healthy tuberculin-positive individuals. This issue has now assumed considerable importance in view of the lack of efficiency of BCG in protection against bacillary forms of pulmonary tuberculosis. Research on the immunology of tuberculosis in general, and its relationship with relapses and break-downs in particular, is urgently needed so that the strategy for tuberculosis control can be strengthened.

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