

## THE EFFICACY OF SHORT-COURSE CHEMOTHERAPY FOR TUBERCULOSIS<sup>1</sup>

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*Potentially, shortened courses of drug chemotherapy for tuberculosis have obvious advantages over standard 12-month regimens. Existing data show that certain six-month regimens, and even shorter regimens for culture-negative patients will produce acceptable results.*

### Introduction

Short-course chemotherapy was born in 1956 when McCune, Tompsett, and McDermott (1) demonstrated that mouse experimental tuberculosis could be cured with a combination of isoniazid and pyrazinamide. Despite high drug dosages employed, the experiment yielded very promising results. Mice treated with a combination of isoniazid and pyrazinamide showed negative lung and spleen cultures after only 90 days of therapy. This spectacular result was not recognized at that time, mainly because a high percentage of the animals was again culture-positive 3 months after the chemotherapy ended. Because some bacilli were still living but not cultivable when the treatment stopped, these bacilli were called persisters, and the disease in the animals at that stage was said to be in a latent state. Thus these results were used more to emphasize the persistence of tubercle bacilli despite an apparent negativization of cultures than to emphasize the negativization itself.

It took exactly 11 years to rediscover short-course therapy. This rediscovery was made in 1967 at the Pasteur Institute in Paris, when F. Grumbach and N. Rist (2) used a similar

mouse experimental model to obtain total negativization of spleen and lung cultures in 6 months with a combination of isoniazid and rifampicin, a result that could not be obtained with either drug used alone. The value of the isoniazid-rifampicin regimen emerges even more clearly when this result is compared to those obtained with the combination of isoniazid and streptomycin, a combination that fails to render the organs of all mice negative in even 18 months.

The effectiveness of the isoniazid-rifampicin combination can be assessed by studying the percentage of relapses after treatment stops. Such study shows that 18 months of therapy with isoniazid-streptomycin is far less effective than 6 months of therapy with isoniazid-rifampicin. This is the main conclusion. Another is that in order to preclude relapses in the mouse, the isoniazid-rifampicin combination should be given for 9 months.

### The Bacillary Populations in the Tuberculous Lesions

To understand how each drug in a given combination can affect tubercle bacilli in man, it is worth reviewing the different bacterial populations upon which the drugs have to act (see Fig. 1). The main one is the population of tubercle bacilli that are freely growing at a neutral pH in the liquified caseous layer of the cavities. Because the bacilli are in favorable conditions of growth, the size of this population can be estimated

<sup>1</sup>From a paper presented at the III Regional Seminar on Tuberculosis: Chemotherapy, held at Washington, D.C., on 27-30 March 1979. Also appearing in Spanish in the *Boletín de la Oficina Sanitaria Panamericana*.

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to  $10^8$  ( $10^7$  to  $10^9$ ) organisms. The others are scarce populations that are located either inside macrophages or in solid caseous areas. Because the bacilli are in unfavorable conditions of growth—at an acid pH inside the macrophages and under a low oxygen pressure in the solid caseous areas—the size of these populations can be estimated to  $10^4$ - $10^5$  organisms.

### The Conventional Isoniazid-streptomycin Regimen

Both isoniazid (INH) and streptomycin (SM) have a bactericidal activity on the freely growing tubercle bacilli. If the drugs are given daily, at an adequate dosage (5 mg INH and 15 mg SM per kg of body weight), sputum conversion should be obtained regularly, and no failures with acquired resistance should occur (Figure 1b). But INH is only weakly bactericidal on intracellular bacilli and inactive against the intermittently growing bacilli located inside solid caseous materials, while SM is inactive against both of these different tubercle bacilli populations.

Table 1. Comparison of two regimens, isoniazid-paraaminosalicylic acid and isoniazid-paraaminosalicylic acid-streptomycin, in terms of treatment failures and relapses.

Regimen	Failure at 12 months	Relapses
INH + PAS	16%	22%
INH + PAS + SM	3%	18%

Therefore, in theory these populations must be eliminated mainly (and slowly) by natural host defenses during the long course of prophylactic INH therapy.

As shown in Tables 1 and 2, clinical data fully agree with these theoretical considerations (3, 4). On the one hand, the use of SM prevents the selection of INH-resistant mutants and therefore the failures during therapy, but has no effect on the incidence of relapses. On the other hand, a very long course of INH therapy can prevent the high incidence of relapses.

### Pyrazinamide as a Supplement to the INH-SM Regimen

Because pyrazinamide (PZA) has a strong bactericidal effect on intracellular tubercle bacilli, its addition to the conventional INH-SM regimen should help eliminate the intracellular population of tubercle bacilli (Figure 1c). Since this population is the source of the population of bacilli inside solid caseous material, its destruction should speed up sterilization and reduce the percentage of relapses after stopping chemotherapy.

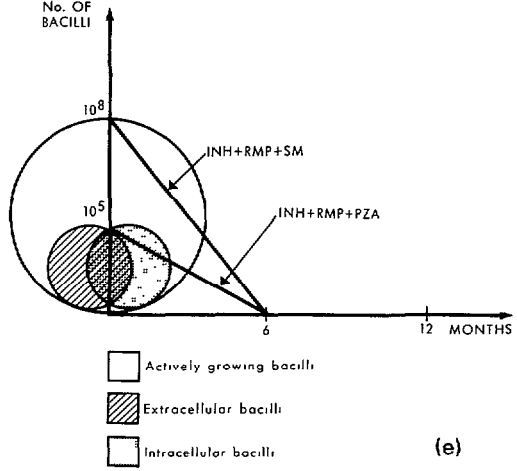
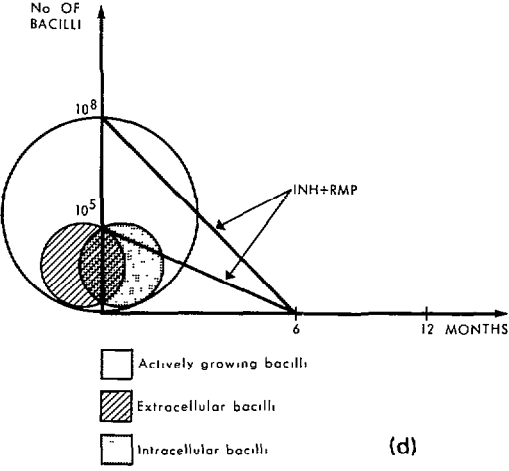
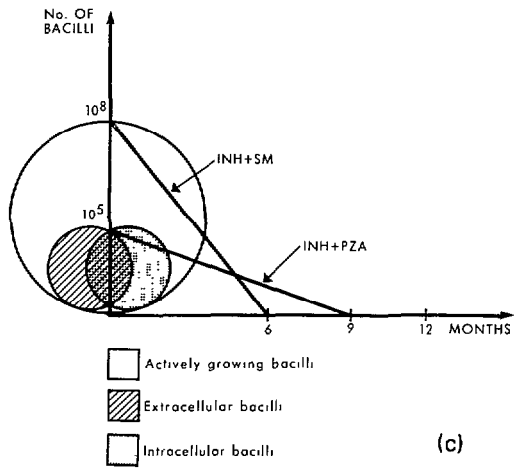
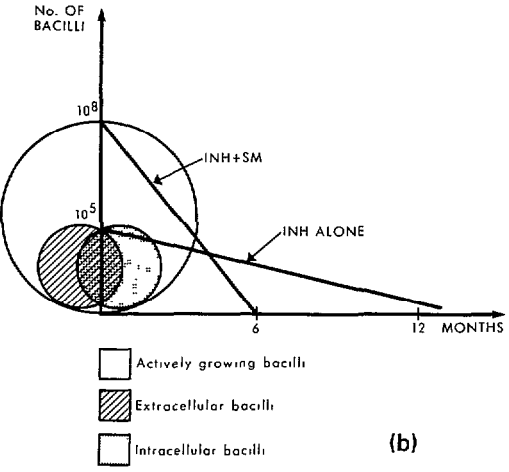
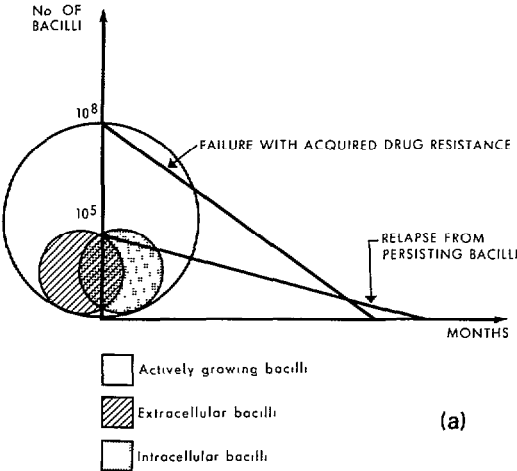
Clinical data (4, 5) are in full agreement with these theoretical considerations. When a six month INH-SM regimen is supplemented with PZA, the percentage of relapses occurring after stopping chemotherapy is considerably reduced (Table 3); and when a nine-month INH-SM regimen is supplemented with PZA, the percentage of relapses is only 3 per cent. This latter figure is similar to the

Table 2. Comparative effectiveness of short-course and long-course chemotherapy with isoniazid-streptomycin.

Regimen	Total patients	Failures at end of treatment	Relapses in 2 years of follow-up
INH + SM (6 months)	112	2	29%
INH + SM + Tb <sub>1</sub> (2 months) followed by INH + Tb <sub>1</sub> (16 months)	102	4	4%

Tb<sub>1</sub> = thiacetazone.

**Figure 1. Tuberculosis chemotherapy with various drug regimens, showing the usual impacts of the different drugs actively growing, intracellular, and intracaseous bacterial populations: (a) a general diagram of various favorable and possible adverse results; (b) impact of INH-SM regimen; (c) impact of INH-SM-PZA regimen; (d) impact of INH-RMP regimen; (e) impact of INH-RMP-PZA regimen.**



**Table 3. Comparative effectiveness of isoniazid-streptomycin and isoniazid-streptomycin-pyrazinamide-regimens.**

Study	Regimen	Duration	Bacteriological failures (%)	Bacteriological relapses (%)
East Africa 1972	INH + SM	6 months	2	29
	INH + SM + PZA	6 months	0	11
Hong-Kong 1975	INH + SM + PZA	6 months	0	13
	INH + SM + PZA	9 months	0	3

percentage of relapses observed in other clinical studies using 18-month INH-SM regimens.

### Short-course Chemotherapy with Isoniazid-Rifampicin

Both INH and rifampicin (RMP) are bactericidal for actively growing tubercle bacilli. Both are also bactericidal, but to a lesser degree, for tubercle bacilli multiplying slowly inside macrophages, while only rifampicin is bactericidal on tubercle bacilli multiplying slowly or intermittently inside solid caseous material (Figure 1d). An INH-RMP regimen should thus produce sputum conversion rapidly and regularly (more regularly than an INH-SM regimen because the risk of selecting resistant mutants is less with RMP than with SM). Furthermore, elimination of

persistent bacilli should be achieved much more rapidly with regimens containing RMP than with regimens not containing RMP.

It is now well-known that clinical results (6-9) have borne out the hopes founded on results of experimental studies conducted with INH-RMP combinations. All studies to date (Table 4) have shown 6 months of therapy with the INH-RMP combination to involve relapse rates of 5 per cent or less. This combination given for 6 months is therefore at least as effective as the triple combination of INH-SM-PZA given for 9 months or the double combination of INH-SM given for 18 months. When given for 9 months, studies have shown the INH-RMP combination to be followed by no relapses at all, even in cases where large cavities were involved.

**Table 4. Effectiveness of isoniazid-rifampicin regimens.**

Study	Total patients	Duration of treatment (months)	Bacteriological failures (%)	Bacteriological relapses in 24 months (%)
East Africa, 1974	170	6	0	5
Brazil, 1973	139	6	0	4.4
	55	6	0	5
France, 1977	62	9	0	0
	60	12	0	0
Great Britain, 1976				
	cav. < 2 cm	160	6	0
		155	12	0
	cav. > 2 cm	135	9	0 (2 <sup>a</sup> )
		127	18	0 (1 <sup>a</sup> )

<sup>a</sup>Patients yielding a single isolated culture.

### Improvement of Short-course Chemotherapy with INH-RMP Combination

Despite its effectiveness, the INH-RMP combination should be given for 9 months to ensure 100 per cent success. The question was therefore whether it would be possible to obtain as good results in less than 9 months by adding other drugs to the combination. The contribution of W. Fox and D. Mitchison in this field research is so excellent that I cannot do better than to try and summarize it. In theory, two drugs can increase the effectiveness of the INH-RMP combination. These drugs (Figure 1e) are SM (highly bactericidal upon actively growing bacilli) and PZA (highly bactericidal upon intracellular bacilli). A clinical trial (10, 11) conducted in East Africa and Zambia (Table 5) has actually proved that the addition of SM and PZA can significantly increase the effectiveness of the INH-RMP combination.

#### *Does PZA Really Contribute to Short-course Chemotherapy?*

Since rifampicin and isoniazid are effective against the bacilli located inside cells, while rifampicin alone is effective against the bacilli inside solid caseous material, one can wonder whether or not pyrazinamide itself makes a real contribution to short-course chemotherapy. Two recent studies (12, 13) afford precise answer to this question (Table 6). Both studies have demonstrated that

pyrazinamide given in combination with INH-SM-RMP plays a well-defined role. In the first study, substitution of ethambutol (EMB) for PZA in a six-month course of chemotherapy appeared to raise the rate of relapses in the year following treatment from a level of 7 per cent to 21 per cent; and the same substitution in an eight-month course of treatment appeared to raise the one-year relapse rate from 1 per cent to 10 per cent. In the second study, the relapse rate was higher (15 versus 9 per cent) among patients whose six-month regimens omitted PZA, and was also higher (4 versus 0 per cent) among patients on eight-month regimens without PZA.

#### *The Nature of PZA, RMP, and SM Contributions to Short-course Chemotherapy*

The fourth East African/British Medical Research Councils Study (14), conducted in Kenya, compared the effectiveness of different four-month regimens. Each regimen entailed an initial intensive two-month phase followed immediately by a two-month continuation phase. The drugs included in each regimen are shown in Table 7. Although none of the regimens was good enough for practical use, the findings of this study are of great interest. For one thing, the study showed RMP to make a major contribution in the continuation phase; for another, it demonstrated the good contribution made by SM

Table 5. Comparative effectiveness of INH-RMP, INH-RMP-SM, and INH-RMP-SM-PZA regimens.

Regimen	Duration (months)	Total patients	% negative at 2 months	No. of failures	Relapses (%)
INH + RMP daily	6	164	64	1	7
INH + RMP + SM daily	6	171	70	0	2 <sup>b</sup>
INH + RMP + SM + PZA daily followed by	2	159	82 <sup>a</sup>	2	4
INH + RMP + PZA twice weekly	4				

<sup>a</sup>A significant increase ( $p = 0.006$ ).

<sup>b</sup>A not significant reduction ( $p = 0.06$ ).

Table 6. The contribution of pyrazinamide to short-course chemotherapy.

Study	Regimen	Duration (months)	Bacteriological relapses (%)
Hong-Kong, 1978	INH + RMP + SM + PZA (2 months), followed by INH + SM + PZA twice a week for 4-6 months	6	7
		8	1
	INH + RMP + SM + EMB (2 months), followed by INH + SM + EMB twice a week for 4-6 months	6	21
		8	10
3d East Africa, 1978	INH + RMP + SM + PZA (2 months), followed by INH + Tb <sub>1</sub> for 4-6 months	6	9
		8	0
	INH + RMP + SM (2 months), followed by INH + Tb <sub>1</sub> for 4-6 months	6	15
		8	4

Table 7. The comparative contributions of rifampicin, pyrazinamide, and streptomycin to short-course chemotherapy.

Initial phase (2 months)	Regimen Continuation phase (2 months)	Total patients	Bacteriological relapses (%)
SM + INH + RMP + PZA	INH + RMP + PZA	102	14
"	INH + RMP	90	11
"	INH + PZA	98	28
"	INH	100	30
INH + RMP + PZA	INH	98	41

during the initial phase; and finally, it indicated that the PZA given in the continuation phase had no effect on the relapse rate. As W. Fox has pointed out, when compared with the findings referred to in Table 6, these data strongly suggest that PZA, at least in combination with RMP, makes its entire contribution during the first two months of chemotherapy.

#### *Minimum Length of Short-course Chemotherapy*

Table 8 makes a tentative comparison of available data on relapses rates following

several chemotherapy regimens of progressively shorter duration. The INH-RMP combination results in a relapse rate of about 5 per cent when the therapy lasts 6 months and leads to no relapses at all when the therapy lasts 9 months. These findings are well-documented.

The findings of the Singapore Tuberculosis Service/British Medical Research Council Study of 1978 (15) suggest that a six-month regimen involving an initial two-month intensive daily phase with the main four drugs (INH, SM, RMP, and PZA), followed by a continuation phase with RMP + INH, may be 100 per cent effective. Until now, contri-

Table 8. The results obtained with progressively shorter regimens including rifampicin.

Regimen	Duration (months)	Relapses (%)
INH + RMP	9	0
INH + RMP	6	5
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INH + RMP + SM + PZA (2 months), followed by 4 months of INH + RMP + PZA	6	0
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INH + RMP + SM + PZA (2 months), followed by 2 months of INH + RMP + PZA	4	10
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INH + RMP + SM	3	13

butions by drugs other than RMP + INH in the continuation phase have not been demonstrated.

Studies using courses of treatment lasting less than 6 months overall have led to unacceptably high relapse rates, the four-month treatment shown involving a 10 per cent relapse rate and the three-month treatment resulting in a relapse rate of 13 per cent (16). Hence, the available data indicate that it is not feasible to use treatment regimens lasting less than 6 months for patients with bacteriologically active tuberculosis.

#### *Minimum Length of Chemotherapy in Smear-Negative Patients*

In most countries a high proportion of tuberculosis patients (50 per cent or more) have smear-negative disease, without extensive or cavitated pulmonary lesions. If we assume these patients have, in general, better host defenses than the smear-positive patients, it might be expected that chemotherapy would cure them more easily than smear-positive patients, and more easily means more rapidly.

Recently, an investigation (17) was undertaken in Hong-Kong on the treatment of smear-negative patients. Short-course SM-

INH-RMP-PZA regimens lasting 2 and 3 months were given to smear-negative culture-positive patients and to smear-negative culture-negative patients. As the data in Table 9 show, neither short regimen lasted long enough to produce acceptable results in culture-positive patients, the relapses rates at 12 months being too high; but both regimens did produce acceptable results in culture-negative patients. This latter finding is of practical importance for national tuberculosis control programs.

#### **Retreatment Regimens**

In most countries, despite careful organization and supervision of treatment, some patients do not receive the prescribed chemotherapy. Hence there will be failure or relapses. Also, in most countries some patients with initial drug-resistant disease will fail to respond to prescribed chemotherapy (Table 10). The majority of these patients will have organisms in their sputum that are resistant to INH, RMP, or both. Therefore, INH and RMP should not be included together in retreatment regimens. The companion drug of INH or RMP should be either paraaminosalicylic acid (PAS) or ethambutol (EMB).

In these retreatment regimens one bactericidal drug is associated with a bacteriostatic drug (Figure 2a). Therefore, these regimens can give neither a rapid sputum conversion nor 100 per cent effective prevention of resistant mutant selection. Consequently, some failures during treatment can be expected. Because the effectiveness of the combination on slowly multiplying bacilli is poor, long-course therapy will be required but will not be able to prevent relapses. As shown in Table 11, INH-PAS, INH-EMB, and RMP-EMB regimens given for 12 months led to failures rates ranging from 4 to 13 per cent and relapses rates ranging from 1 to 9 per cent (18-21). It is worth noting that the relapse rate was less after RMP-EMB than after INH-EMB, a finding that tends to confirm the special sterilizing efficacy of RMP.

Table 9. Results obtained with short-course chemotherapy of smear-negative culture-positive and smear-negative culture-negative patients.

Patient status	Regimen	Duration (months)	Bacteriological relapses (%)
Smear-negative	SM + INH + RMP + PZA	3	7
culture-positive	SM + INH + RMP + PZA	2	14
Smear-negative	SM + INH + RMP + PZA	3	1
5 cultures-negative	SM + INH + RMP + PZA	2	1
	No chemotherapy <sup>a</sup>	0	34

<sup>a</sup>Monthly bacteriology and radiography.

Table 10. Present incidence of primary and acquired drug resistance of *M. tuberculosis* in France.

	Untreated patients		Previously treated patients	
	No.	%	No.	%
Total	1,907	100	370	100
No. resistant	151	7.9	93	25.1
INH-resistant		2.4		18.1
SM-resistant		5.8		17
RMP resistant		—		4.3
EMB-resistant		0.05		1
Others		0.7		0

Table 11. Comparative effectiveness of INH-PAS, INH-EMB, and RMP-EMB 12-month regimens.

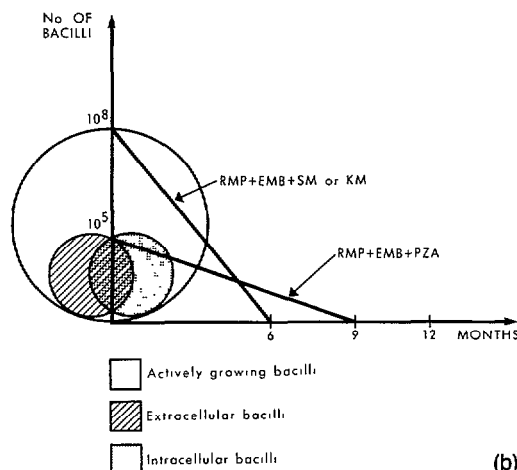
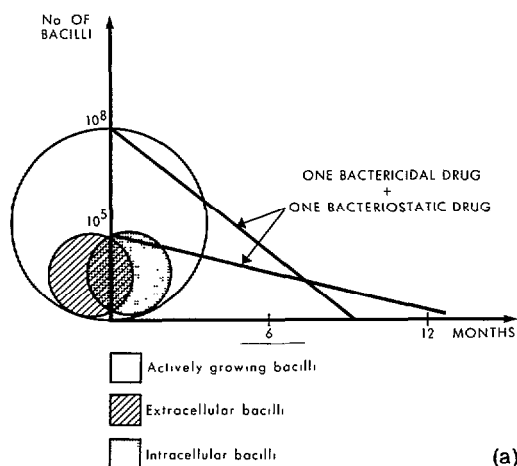
Study	Regimen	Failures (%)	Relapses (%)
Madras, 1960	INH + PAS, daily	9	7
Madras, 1972	INH + PAS, daily	13	—
Madras, 1974	INH + EMB, daily, plus 15 days of SM supplement	4	9
Hong-Kong, 1975	RMP + EMB, daily	13	3
Algiers, 1975	RMP + EMB, daily for 3 months and twice weekly thereafter	4.4	1
Poland, 1975	RMP + EMB, daily for 3 months and twice weekly thereafter	5	3



Consideration of the different bacterial populations involved (Figure 2b) suggests a possible easy way of increasing the total effectiveness of retreatment regimens, especially of the RMP and EMB regimens. To kill the actively growing bacilli more rapidly

and more regularly (that is, to reduce the number of failures), SM, or kanamycin (KM) if SM has been prescribed previously, could be given as an initial supplement. To kill the slow-growing bacilli more rapidly, PZA could be given, also as an initial supplement. Surprisingly, until now no clinical studies directed at bringing scientific data to bear on this subject have been performed. But it is easy to predict on the basis of present knowledge that an initial supplement of SM (or KM) and PZA would strongly increase the effectiveness of the RMP-EMB retreatment regimens.

**Figure 2. Effects of retreatment regimens:**  
(a) general diagram; (b) likely impacts of RMP-EMB regimen supplemented with SM (or KM) and PZA.



## Conclusions

From the foregoing summary of collected data the following conclusions can be drawn:

1) For short-course chemotherapy, RMP is an essential drug, both in the initial and continuation phases.

2) The contribution of INH is still unclear. However, when this drug is not given (or inactive), as in the RMP-EMB regimens, the results are relatively poor.

3) SM and PZA are likely to contribute to the success of short-course chemotherapy as initial supplements, or to the success of alternative regimens in cases where RMP is not available.

4) For patients with bacteriologically active disease, the total duration of a 100 per cent effective short-course regimen cannot be less than 6 months, the optimal duration being somewhere between 6 and 9 months.

5) A daily initial intensive phase appears as essential to the final success of short-course chemotherapy as it is to the success of conventional chemotherapy.

6) Tuberculosis cases involving relatively small bacterial populations may be treated effectively with chemotherapy regimens of less than six months' duration.

## SUMMARY

Short-course tuberculosis chemotherapy regimens generally depend on direct drug action against tubercle bacilli within cells and solid caseous materials that are multiplying only slowly or intermittently. In this they tend to differ from the old, traditional 12-month regimens, which attack actively growing bacterial populations while relying mainly on natural host defenses to reduce the bacilli within cells and solid caseous materials.

The drug pyrazinamide (PZA) has a strong bactericidal effect on intracellular tubercle bacilli, and its addition to the conventional isoniazide-streptomycin (INH-SM) combination considerably reduces the incidence of relapses occurring after a short (6 or 9 month) course of treatment.

In addition, the drug rifampicin (RMP) has a bactericidal effect on tubercle bacilli multiplying slowly or intermittently inside macrophages and solid caseous materials. All studies conducted to date have shown 6 months of therapy with INH-RMP to entail relapse rates of 5 per cent or less, and have shown 9 months of therapy with this combination to produce complete success.

Furthermore, a clinical trial has proven that addition of SM and PZA can significantly increase the effectiveness of this INH-RMP combination,

and the findings of a 1978 study suggest that an initial two-month phase of treatment with all four drugs (SM, PZA, INH, and RMP) followed by a four-month phase of continued treatment with RMP may be 100 per cent effective. So far it has not been demonstrated that any additional drug supplementing INH + RMP can make further inroads against the disease during the four-month continuation phase.

Courses of treatment shorter than 6 months have generally involved unacceptably high relapse rates. However, for smear-negative culture-negative patients, short-course SM-INH-RMP-PZA regimens lasting 2 and 3 months have produced acceptable results.

INH and RMP cannot be given together in all retreatment regimens, because most patients will harbor organisms resistant to one or both. Instead, a companion drug of INH or RMP (either PAS or ethambutol) should be employed. There is not yet any direct proof that addition of SM and PZA to such retreatment regimens would greatly improve the effectiveness of these regimens; but at least in the case of RMP-ethambutol regimens, our present knowledge makes it logical to assume that a marked increase in effectiveness would occur.

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#### TEN NEW MEMBERS FOR WHO EXECUTIVE BOARD\*

The Thirty-third World Health Assembly (May 1980) elected the following 10 Member States entitled to designate a person to serve on the WHO Executive Board for three years: Brazil, Canada, Gabon, Gambia, Guatemala, Kuwait, Mongolia, Romania, United Kingdom of Great Britain and Northern Ireland, and Yemen. These States replaced the following whose term of office expired at the end of the Assembly: Angola, Bolivia, Botswana, Cuba, German Democratic Republic, India, Libyan Arab Jamahiriya, Portugal, Tunisia, and United States of America.

The Executive Board of WHO, which is composed of 30 persons, also includes public health experts designated by: Bahrain, Burma, Burundi, Cape Verde, Chad, China, Colombia, Comoros, Congo, France, Iran, Jamaica, Mexico, Netherlands, New Zealand, Norway, Oman, Samoa, Turkey, and Union of Soviet Socialist Republics.

\*Source: WHO Press Release WHA/7, 12 May 1980.