

Treatment of Tuberculosis

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In Britain tuberculosis is a declining disease, but it still causes over 9,000 new cases each year and the annual number of deaths approaches 1,000. However, in poor developing countries, the prevalence of the disease has shown little change; the impact of its high incidence falls on the adult working population. The treatment of tuberculosis is necessary not only for the 'felt needs' of the patients, but also because it breaks the cycle of infection. Epidemiologists now recognise that the most certain and most rapid means for controlling tuberculosis is the finding of infectious cases and treating them[1]. The prevalence of the disease in Arctic Eskimo populations has been reduced from a very high level to one only a little greater than in mainland Canada largely as a result of intensive case-finding and treatment over a 15-year period[2].

Causes of Failure

Although theoretically it should be possible to treat all cases of tuberculosis effectively, failures occur in practice for several reasons (Table 1). Failure to take drugs

Table 1. Reasons for failure of chemotherapy in patients assumed not to have had previous treatment.

Reason	Estimated failure rate (%)
Failure to take prescribed drugs	2*-50 †
Initial drug resistance	0.2-15
Inadequate regimen	0-8
Drug toxicity	0-6

*Technically advanced country.

† Poor, developing country.

regularly or to continue to attend for treatment are undoubtedly the major cases. In developing countries up to one-third of the patients do not attend at all for treatment after a diagnosis has been made and many more abscond early in treatment. Failures due to drug resistance in the tubercle bacilli isolated before treatment may also be important, particularly if a high proportion of the patients have undisclosed acquired drug resistance; that is failure to disclose treatment received before attending the centres concerned. Among the regimens in common use in developing countries, some may not be capable of curing all patients with initially sensitive

organisms, even if taken regularly. Drug toxicity may lead to abandonment of treatment or the incorrect use of alternative drugs and thus to failure.

Two methods have been used to improve regularity of drug-taking. First, the use of intermittent chemotherapy, in which every dose is fully supervised, makes irregularity in drug-taking immediately evident to treatment staff and is often easier and less toxic for the patient. However, the method can only be applied with ease in an urban population. The second and more modern approach is to shorten the duration of chemotherapy from periods of 1 to 2 years to periods of 6 to 9 months.

Principles of Treatment

We now have 12 or 13 drugs active against *Mycobacterium tuberculosis*, of which six are in use for first-line treatment. In designing regimens, the efficacy of a given drug is assessed in terms of prevention of acquired drug resistance, suitability for intermittent use and sterilising activity. The classical approach is to measure the extent to which it prevents drug resistant tubercle bacilli from emerging when given with another drug. For fully supervised regimens, some drugs are much more efficient than others for intermittent use. For short course chemotherapy, we need to know how rapidly a drug will sterilise the lesions and thus reduce the duration of treatment. In all instances we need to be sure that the regimen has an acceptably low level of toxicity, which must be lower for first-line than for reserve regimens.

Prevention of Acquired Drug Resistance

The best way of grading the efficacy of drugs in preventing the emergence of acquired resistance is to compare results from clinical studies (Table 2). Failure, with the emergence of isoniazid resistance, occurred least frequently when isoniazid was given with rifampicin and most frequently when it was given with PAS or thiacetazone. In these studies treatment with two drugs only was given from the start except for the study with isoniazid and ethambutol in which the failure rate relative to the other drugs is underestimated slightly because streptomycin was given for an initial two weeks. The conclusions to be drawn from these and other clinical studies are summarised in Table 3.

Table 2. Efficacy of anti-tuberculosis drugs in preventing the emergence of resistance to isoniazid in patients with severe disease.

Study	Isoniazid with	No. of patients	Failures of treatment (%)
E. Africa [3-7]	Rifampicin	183	0.5
	Streptomycin	96	2
Madras [8-11]	Ethambutol*	105	4
	PAS	309	12
E. Africa	Thiacetazone	423	16

*With initial supplement of streptomycin daily for 2 weeks.

Table 3. Grading of drugs in preventing the emergence of acquired resistance.

Activity	First line drugs	Reserve drugs
High	Isoniazid	
	Rifampicin	
	Streptomycin	Ethionamide
	Ethambutol	PAS
	Thiacetazone	Cycloserine
Low	Pyrazinamide	Capreomycin

In terms of preventing drug resistance, high activity is obtained when all of the bacilli in the lesions are inhibited in growth throughout treatment and also remain inhibited even if occasional doses are not taken. Lower activity occurs for a number of reasons. Sometimes only part of the bacterial population is inhibited, for instance because streptomycin is inactive against organisms in an acid environment and pyrazinamide against those in a neutral or alkaline environment. In other instances, the concentrations attainable in the lesions with non-toxic doses may be insufficient to ensure complete bacteriostasis, as with ethambutol, cycloserine and capreomycin. PAS does not always inhibit drug sensitive organisms and thiacetazone may be of low activity because bacilli can start growing as soon as the drug concentration becomes sub-inhibitory. Although two drugs are sufficient to prevent the emergence of resistance, three or more drugs may be given, especially in the first 1 to 3 months of treatment, to reduce the chances of isoniazid resistance emerging and to guard against failure due to initial drug resistance.

Intermittent Regimens for Pulmonary Tuberculosis

The feasibility of full supervision of drug dosage is improved if the doses can be given twice-weekly or once-weekly rather than in the usual daily rhythm. Table 4 compares studies, using similar methods, of twice-weekly and once-weekly regimens. In these studies, high dosage isoniazid (15 mg/kg) retained its activity when given twice-weekly, but was much less effective when given once-weekly. The rapid inactivators of isoniazid failed much more frequently when treated with once-weekly regimens than slow inactivators. Indeed, in the more effective regimens, all of the failures were in rapid

Table 4. Efficacy of intermittent regimens with doses given twice- or once-weekly for 12 months.

Study	Duration of initial daily phase (weeks)	Isoniazid with	Failures (%)	
			Twice weekly	Once weekly
Singapore [11-13]	2	Rifampicin †	0	5*
	2	Ethambutol	12	25
Madras [14]	0	Streptomycin	9	29
	4		—	12
	6	Streptomycin	1	—
Czechoslovakia [15]	13		0	4*

*All rapid inactivators of isoniazid.

† With initial supplement of streptomycin daily for 2 weeks.

inactivators. In contrast, rapid and slow inactivators did equally well on daily or twice-weekly regimens.

The patients treated in Singapore and Madras had severe disease. It is evident that the rifampicin regimen was strikingly superior to the ethambutol regimen. Rifampicin in the low dose of 600 mg or 900 mg used in these intermittent regimens produced a low incidence of an immunological type of toxicity, usually characterised by the easily manageable 'flu' syndrome, but very occasionally by more dangerous syndromes, including thrombocytopenic purpura[16, 17]. Such toxicity has discouraged the use of twice-weekly or once-weekly rifampicin-containing regimens in technically advanced countries, but in developing countries the small toxic risk may be outweighed by the operational advantages and the great savings in cost in using a once-weekly regimen that includes only 64 doses of this expensive drug. Although the studies with streptomycin are not strictly comparable to those with rifampicin and ethambutol, the findings suggest that it lies intermediate in efficacy between them. Twice-weekly streptomycin and high dosage isoniazid, with or without an initial daily phase, is a widely used regimen recommended by the WHO Expert Committee on Tuberculosis[18], especially for use in urban communities in developing countries. In parts of Czechoslovakia, where the disease is usually less severe than in Singapore or Madras, rapid inactivators of isoniazid are routinely treated twice-weekly and slow inactivators once-weekly with streptomycin and isoniazid in the follow-up phase. In view of the importance of pyrazinamide in short course chemotherapy it is worth noting that it appears to be slightly more active when given at a high dose thrice weekly than in lower, more frequently administered doses[19].

Short Course Chemotherapy

Short course regimens were developed as a result of clinical need, but guided by promising results in experimental tuberculosis of the mouse and other animal species. These experiments have been summarised by Grosset[20]. The main conclusions are: (1) pyrazinamide and rifampicin are the most potent drugs in sterilising the organs of experimentally infected animals; (2) the most potent sterilising combination is isoniazid given with pyrazinamide or rifampicin; (3) the addition of strep-

tomyacin or ethambutol contributes little or nothing to the sterilising activity of the combination. The conclusions of the animal experiments were confirmed in the first study of short course chemotherapy in man (Table 5). The

Table 5. Sterilising activity of four six-month regimens used in East Africa [6, 7]. Of the 73 relapses, 61 began during months 7-12 and 68 were with drug-sensitive organisms.

Regimen	No. of patients	Culture negative at 2nd month (%)	Bacteriological relapses	
			No.	%
SHR	152	69	4	3
SHZ	153	66	13	8
SHT	104	42	23	22
SH	112	49	33	29

S = Streptomycin H = Isoniazid R = Rifampicin
Z = Pyrazinamide T = Thiacetazone

sterilising activity was measured in this and other studies as the speed with which the last few culturable bacilli were eliminated from the sputum, namely as the percentage of patients with negative cultures at one or two months after the start of chemotherapy, and as the proportion of patients who suffered a bacteriological relapse after chemotherapy has been stopped. Thiacetazone had little or no effect on the rate of sputum conversion at two months or on the eventual relapse rate, but both pyrazinamide and rifampicin caused more rapid sputum conversion and a considerable decrease in the relapse rate after stopping chemotherapy.

Table 6 summarises the role of streptomycin and

Table 6. Streptomycin and ethambutol in short course therapy.

Study	Regimen	Culture negative at 2nd month (%)	Relapses (%)	
			6-month	8-month
E. Africa [7]	HR	64	7*	—
	SHR	70	2*	—
Britain (BT TA) [21, 22]	2EHR/HR	53	6	—
	2SHR/HR	60	2	—
Hong Kong [23]	2SHRE/S ₂ H ₂ E ₂	81	23	10
	2SHRZ/S ₂ H ₂ Z ₂	95	7	3

H = Isoniazid R = Rifampicin S = Streptomycin
E = Ethambutol Z = Pyrazinamide

*The difference is not statistically significant.

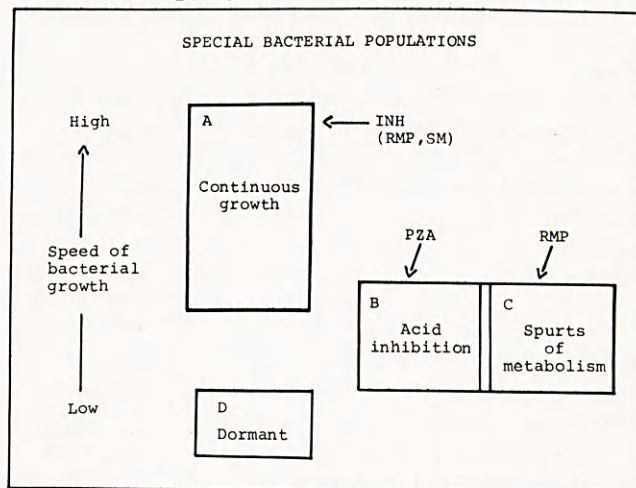
ethambutol in short course chemotherapy. Addition of streptomycin to a six-month regimen of isoniazid and rifampicin only slightly increased the sterilising activity of the regimen. In Britain, a comparison was made between the addition of streptomycin or ethambutol for two months to a daily regimen of isoniazid and rifampicin [21, 22]. Ethambutol may have been slightly inferior to streptomycin, though the difference in sputum conversion rates at 2 months and the eventual relapse rates are not significant. Finally, a study in Hong Kong [23]

compared a two-month initial phase with daily streptomycin, isoniazid, rifampicin and ethambutol followed by twice-weekly streptomycin, isoniazid and ethambutol for a total of either six or eight months with an exactly similar regimen in which pyrazinamide was substituted for ethambutol. The substitution of pyrazinamide for ethambutol increased the sterilising activity of the regimen considerably. The proportion of patients with negative cultures at two months increased from 81 per cent to 95 per cent and the relapse rates after a 6-month treatment period decreased from 23 per cent to 7 per cent and, after an eight-month period, from 10 per cent to 3 per cent; these differences are statistically significant. Thus the results in man are very similar to those in experimental murine tuberculosis. Rifampicin and pyrazinamide play a major role, whereas streptomycin and ethambutol contribute very little to the sterilising activity of the regimens.

Special Bacterial Populations in Short Course Treatment

One might suppose that rifampicin and pyrazinamide were particularly effective in sterilising the organs of mice and man because they were more bactericidal than other drugs used in the treatment of tuberculosis. Bactericidal activity is usually measured as the speed with which actively growing organisms are killed by the drug. However, as measured by *in vitro* experiments, pyrazinamide has little bactericidal activity, while streptomycin is far more bactericidal and isoniazid is at least as bactericidal as rifampicin [24]. We have therefore proposed that rifampicin and pyrazinamide kill special portions of the bacterial population in the lesions that are only metabolising very slowly and are therefore only killed with considerable difficulty by other drugs [25]. This hypothesis is illustrated in Fig. 1, where population A consists of bacilli growing relatively rapidly, populations B and C of slowly metabolising bacilli killed

Figure 1. Hypothesis of the anti-bacterial drugs acting on different bacterial populations within lesions. The populations are defined by the metabolic activity of the bacilli and the pH of their micro-environment.



selectively by pyrazinamide or rifampicin, and population *D* of dormant bacilli not killed by any drug. Pyrazinamide is assumed to act on bacilli inhibited by an acid environment (population *B*), since it shows antibacterial activity *in vitro* only if bacilli are in medium at pH 5.6 or less. Rifampicin is unique among the anti-tuberculosis drugs in the speed with which its bactericidal action starts, though the eventual rate of killing is unexceptional. Population *C* is assumed to consist of bacilli metabolising for brief periods of perhaps a few hours, during which time rifampicin starts killing, but other drugs, such as isoniazid, do not. I will now discuss some of the evidence for this special population hypothesis.

Patients in Nairobi with pulmonary tuberculosis were given a series of unusual regimens for the first 14 days of their treatment[26]. Subsequently, they were given conventional regimens, often with additional drugs that would not usually be available; treatment in all patients was successful. The regimens given in the first 14 days included single drugs at various dose levels, as well as two-drug, three-drug and four-drug combinations. The bactericidal activity of these regimens was studied by doing serial viable counts of tubercle bacilli in the patients' sputum. During the first two days the mean fall in colony counts ($0.42 \log_{10}$ cfu/day) was higher than in the succeeding 12 days ($0.13 \log_{10}$ cfu/day) and there was also more variation from regimen to regimen. We therefore assume that the early (0-2 day) fall in counts was determined mainly by the inherent bactericidal activity of the drug regimen, whereas the 2-14 day fall was determined mainly by the physiological state of the surviving organisms and so was relatively independent of the drug regimen employed. The 0-2 day fall in counts may therefore be thought of as a measure of the bactericidal activity on population *A*. The effects of some of the regimens in the first two days are shown in Table 7.

Table 7. Fall in sputum viable counts during first 2 days of treatment of patients with isoniazid, rifampicin, pyrazinamide or streptomycin alone and the effects of adding isoniazid or rifampicin to other drugs.

Regimen and size of daily dose	No. of patients	Fall in colony counts (\log_{10} cfu/day)
H 150 mg	4	0.57
H 300 mg	4	0.72
H 600 mg	4	0.47
H 300 mg + S 1g	4	0.51
H 300 mg + E 25 mg/kg	4	0.70
H 300 mg + R 10 mg/kg	4	0.71
H 300 mg + Z 2g	4	0.49
R 5 mg/kg	3	0.06
R 10 mg/kg	8	0.19
R 20 mg/kg	8	0.41
R 10 mg/kg + S 1g	4	0.32
R 10 mg/kg + E 25 mg/kg	4	0.56
Z 2g	9	0.04
S 1g	4	0.09

H = Isoniazid S = Streptomycin E = Ethambutol
R = Rifampicin Z = Pyrazinamide

Isoniazid alone was highly bactericidal, irrespective of the size of dose given, suggesting that all doses were well above the minimal effective level. When isoniazid was added to a second drug the bactericidal activity of the combination remained high. The bactericidal activity of rifampicin alone was considerably less than that of isoniazid and was also related to the size of the dose given, a statistically significant association. Thus the usual dose of about 10 mg/kg rifampicin appears to be only just sufficient, a conclusion supported by Long *et al.*[27]. When rifampicin was added to a second drug, the bactericidal activity in the two regimens was less than in the corresponding isoniazid-containing regimens. It therefore seems that rifampicin either alone or in combination was less bactericidal than isoniazid. The bactericidal activity for streptomycin alone and pyrazinamide alone is low. Thus the remarkable sterilising ability of rifampicin and pyrazinamide cannot be explained by particularly high bactericidal activities of these drugs.

A second line of evidence arises from experimental tuberculosis in animals, as in the work of Grumbach *et al.*[28]. Mice were infected intravenously and treatment was started with isoniazid and streptomycin for a total of four months. Rifampicin was given to half of the mice for the first month of treatment only. Counts of viable tubercle bacilli in the lungs at one month, just after rifampicin had been started, showed only a $3\frac{1}{2}$ times lower count in the rifampicin-treated animals than in those not given rifampicin. At four months, the difference was much larger, the count on the animals previously treated with rifampicin being 50 times lower, despite the fact that the treatment of the two groups had been identical during the previous three months. This delayed effect of rifampicin can only be explained as being due to the killing by rifampicin of a special bacterial population that was not easily eliminated by isoniazid and streptomycin.

The final evidence for special bacterial populations comes from two recent studies of short course chemotherapy of pulmonary tuberculosis. The East African study[29] explored the efficacy of four-month regimens. Each started with two months of daily streptomycin, isoniazid, rifampicin and pyrazinamide, and was followed by a further two-month period in which various combinations of isoniazid, rifampicin and pyrazinamide were given in the four treatment series (Table 8). The relapse rates after the four-month treatment period ranged from 11 per cent to 30 per cent, so that one can conclude that acceptably low relapse rates cannot be obtained with only four months of treatment. However, when one examines the results in detail, it is evident that the two regimens containing rifampicin had lower relapse rates (14 per cent and 11 per cent) than did the regimens that did not contain rifampicin in the follow-up period (28 per cent and 30 per cent). In contrast, the addition of pyrazinamide in the second two months of treatment did not appear to influence the relapse rates at all. Thus it appears that pyrazinamide exerts its full effects during the first two months of treatment, whereas rifampicin continues to be effective as

Table 8. Bacteriological relapses after four-month regimens.

Regimen	4-month regimens				6-month regimens	
	East Africa		Singapore		Singapore	
	No. of patients	Relapses (%)	No. of patients	Relapses (%)	No. of patients	Relapses (%)
2SHRZ/HRZ	102	14	80	10	84	0
2SHRZ/HR	90	11	74	5	80	1
2SHRZ/HZ	98	28	—	—	—	—
2SHRZ/H	100	30	—	—	—	—

a sterilising drug in the later phases of treatment. This conclusion is strengthened by the results of the Singapore study[13] which used two of the regimens of the East African study, but also extended the period of treatment in two of the regimens for a total of six months. Again, it is evident that pyrazinamide did not reduce the bacteriological relapse rate after the four-month regimen had been completed and that continuation with the rifampicin-containing follow-up part of the regimen successfully reduced the subsequent relapse rate to a negligible level. The only reasonable explanation for the finding that pyrazinamide stops acting after the first two months of treatment, while rifampicin continues to act for many months thereafter, is that these drugs act on two different portions of the bacterial population in the lesions.

Applications of Short Course Chemotherapy

It has been the policy of the groups co-operating in Medical Research Council studies to evaluate several types of treatment as alternatives for different countries whose needs vary considerably.

Low cost regimens

In many developing countries with poor resources, it is essential to keep the cost of drugs as low as possible and therefore to limit the amount of the especially expensive drug, rifampicin, and to a lesser extent pyrazinamide. Table 9 summarises the results with regimens which include an initial period of intensive treatment with streptomycin, isoniazid, rifampicin and pyrazinamide followed by thiacetazone and isoniazid[30]. When the initial intensive phase lasted for two months and the total duration of treatment was six months the relapse rate was 12 per cent, but no relapses occurred when an additional two months of thiacetazone and isoniazid was given to make an eight-month period of treatment. Reduction of

Table 9. Low cost short course regimens compared in East Africa (58-82 patients in each treatment group).

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

the initial intensive phase from two months to one month or the omission of pyrazinamide during the initial phase resulted in unacceptably high relapse rates after a six-month treatment period and a fairly high rate of 6 to 7 per cent if treatment was prolonged to eight months.

Intermittent regimens

Intermittent regimens are of particular value in urban communities, and Table 10 records a regimen in which

Table 10. An intermittent short course regimen explored in Hong Kong (74-90 patients in each treatment group).

Regimen	Relapse (%)	
	6-month	8-month
2SHRZ/S ₂ H ₂ Z ₂	7	3
4S ₃ H ₃ R ₃ Z ₃ /S ₂ H ₂ Z ₂	6	1

the four potent drugs were given three times weekly for four months and were then followed by twice-weekly streptomycin, isoniazid and pyrazinamide[23]. This intermittent regimen was as satisfactory as a regimen which started with two months of daily treatment. The intermittent regimen had considerable operational advantages for Hong Kong and, unlike regimens in which rifampicin was given twice- or once-weekly, there was no evidence of immunological toxicity. Routine treatment in Hong Kong is now based upon the use of regimens in which drugs are given three times weekly.

Regimens for high prevalence of initial resistance

Countries vary in the incidence of initial drug resistance in tubercle bacilli isolated from patients who supposedly have not had previous chemotherapy. One of the considerable advantages of short course chemotherapy is the success achieved with such patients, mainly because initial resistance to rifampicin is very rare. Table 11 summarises the response during treatment in three recent short course chemotherapy studies in which patients received at least four months of treatment with rifampicin[23, 29, 30]. There were no failures among the 51 patients who had initial resistance to isoniazid alone and only two failures among 18 patients who had initial resistance to streptomycin and isoniazid. Preliminary evidence from the Hong Kong study suggests that inclusion of ethambutol (in place of pyrazinamide) as well

Table 11. Failures during treatment in patients with initial resistance to regimens containing rifampicin for at least four months (Hong Kong, E. Africa, Singapore).

Regimen*	Initial resistance to:			
	H alone		SH	
	No. of patients	No. of failures	No. of patients	No. of failures
4S ₃ H ₃ R ₃ Z ₃ /S ₂ H ₂ Z ₂ 2SHRZ/HRZ SHRZ/HR	51	0	18	2

*Total duration of regimens was 4-8 months.

as rifampicin may have improved the response in patients with initial two-drug resistance. Thus, although ethambutol appears inferior to pyrazinamide as a sterilising drug, it is probably superior in preventing the emergence of acquired resistance. In those patients who had a satisfactory response to treatment, the subsequent relapse rate in patients with initially resistant strains was very similar to that encountered in those with initially sensitive strains. This finding indicates that isoniazid is not an essential component of short course regimens.

Table 12. Bacteriological relapse during 12 months in patients with initially negative cultures.

Regimen	No. of patients	Relapses (%)
Selective	181	34
2SHRZ	175	1
3SHRZ	168	1

Regimens for less severe disease

So far, the patients in the various chemotherapy studies considered have all had serious pulmonary tuberculosis, always with positive cultures at the start of treatment and usually with positive smears as well. It is of interest to know whether less severe disease requires even shorter periods of treatment. Table 12 presents some of the results of a recent study in Hong Kong[31] on patients with small but radiographically active lesions. Among the patients with initially negative cultures, a group was given selective chemotherapy, in the sense that patients were watched and treated only when there was bacteriological, radiographic or clinical evidence of relapse. Other groups were treated with two or three months of streptomycin, isoniazid, rifampicin and pyrazinamide. This reduced the relapse rate from 34 per cent over a year of observation to 1 per cent. The optimal period of treatment for patients who are smear-negative, but culture-positive, has not been defined but appears to be longer than three months.

Regimens for technically advanced countries

Finally, we come to the short course regimens recommended for technically advanced countries such as

Table 13. Studies of short course chemotherapy in France and Britain.

Study	Regimen	Duration (months)	No. of patients	No. of relapses
France [32]	SHR → HR EHR → HR	6	76	3
		9	86	0
		12	78	0
Britain [21, 22]	SHR → HR EHR → HR	6	160	8
		9	135	0
		12	155	2
		18	127	0

Britain. Table 13 summarises the results of two studies in which treatment was given with isoniazid and rifampicin with the addition of streptomycin or ethambutol for the initial two months. The relapse rate after a six-month period of treatment was about 5 per cent, but after treatment for nine months or longer it was negligible. A nine-month period of treatment, particularly with ethambutol in the initial phase is now standard practice among many chest physicians in Britain. It is possible that the treatment period might be reduced by the addition of pyrazinamide at the start of treatment. How much pyrazinamide is necessary is not known so that the additional toxicity introduced by the use of this drug is uncertain. The use of fully supervised treatment given three times weekly might also improve patient compliance and it might have prevented the two patients in a limited disease group in the British study from relapsing even after treatment for 12 months.

The Future

Most physicians throughout the world are now moving towards the use of short course chemotherapy in one form or another. This move appears likely to establish higher standards of treatment. However, there is still much to be done. For instance, the amount of pyrazinamide that should be given and the rhythm with which it should be administered urgently need exploration. We also need further information on the balance between the amount of rifampicin, whether given daily or intermittently, and the duration of treatment. Of even greater importance, we need to know whether the encouraging result obtained in carefully supervised controlled clinical studies can be reproduced under routine conditions, particularly in developing countries. Tuberculosis is increasingly a disease of the Third World and the progress we appear to make in its treatment in controlled clinical studies must be reflected by an equivalent improvement under programme conditions in the countries where it is most prevalent.

References

1. Styblo, K. and Meijer, J. (1978) *Bulletin of the International Union against Tuberculosis*, 53, 283.
2. Grzybowski, S., Styblo, K. and Dorken, E. (1976) *Tubercle*, 57, (Suppl.), S1.
3. East African/British Medical Research Council (1966) *Tubercle*, 47, 1.

4. East African/British Medical Research Council (1966) *Tubercle*, 47, 315.
5. East African/British Medical Research Council (1970) *Tubercle*, 51, 123.
6. East African/British Medical Research Council (1972) *Lancet*, 1, 1079.
7. East African/British Medical Research Council (1974) *Lancet*, 2, 1100.
8. Tuberculosis Chemotherapy Centre, Madras (1959) *Bulletin of the World Health Organisation*, 21, 51.
9. Tuberculosis Chemotherapy Centre, Madras (1960) *Bulletin of the World Health Organisation*, 23, 535.
10. Tuberculosis Chemotherapy Centre, Madras (1966) *Bulletin of the World Health Organisation*, 34, 483.
11. Tripathy, S. P. (1974) Symposium on Rifampicin in Tuberculosis Treatment, Helsinki, *Undermaan Kirjapaino Oy*, p. 91.
12. Singapore Tuberculosis Service/British Medical Research Council (1975) *Lancet*, 2, 1105.
13. Singapore Tuberculosis Service/British Medical Research Council (1978) *American Review of Respiratory Disease*, 119, 579.
14. Tuberculosis Chemotherapy Centre, Madras (1970) *Bulletin of the World Health Organisation*, 43, 143.
15. WHO Collaborating Centre for Tuberculosis Chemotherapy, Prague (1976) *Tubercle*, 57, 235.
16. Poole, G., Stradling, P. and Worledge, S. (1971) *British Medical Journal*, 3, 343.
17. Aquinas, M., Allan, W. G. L., Horsfall, P. A. L., Jenkins, P. K., Wong Hung-Yan, Girling, D., Tall, R. and Fox, W. (1972) *British Medical Journal*, 1, 765.
18. WHO Expert Committee on Tuberculosis (1974) *Technical Report Series*, 552. Geneva.
19. East African/British Medical Research Council (1969) *Tubercle*, 50, 233.
20. Grosset, J. (1978) *Tubercle*, 59, 287.
21. British Thoracic and Tuberculosis Association (1975) *Lancet*, 1, 119.
22. British Thoracic and Tuberculosis Association (1976) *Lancet*, 2, 1102.
23. Hong Kong Chest Service/British Medical Research Council (1978) *American Review of Respiratory Disease*, 118, 219.
24. Dickinson, J. M., Aber, V. R. and Mitchison, D. A. (1977) *American Review of Respiratory Disease*, 116, 627.
25. Dickinson, J. M. and Mitchison, D. A. (1976) *Tubercle*, 57, 251.
26. Jindani, A., Aber, V. R., Edwards, E. A. and Mitchison, D. A. (1980) In preparation.
27. Long, M. W., Snider, D. E. and Farer, L. S. (1979) *American Review of Respiratory Disease*, 119, 879.
28. Grumbach, F., Canetti, G. and Le Lirzin, M. (1969) *Revue de Tuberculose et de Pneumologie*, 31, 749.
29. East African/British Medical Research Council (1978) *Lancet*, 2, 334.
30. East African/British Medical Research Council (1978) *American Review of Respiratory Disease*, 118, 39.
31. Hong Kong Chest Service/Tuberculosis Research Centre, Madras, India/British Medical Research Council (1979) *Lancet*, 1, 1361.
32. Brouet, G. and Roussel, G. (1977) *Revue française des Maladies Respiratoires*, 5, (Suppl. 1), 5.

Entrance to the College

Comitia is known for its gravitas, if not somnolence. The extraordinary happenings of 24th September 1767 are unique. For many years the Licentiates had grumbled that they could not become Fellows without an Oxbridge degree and at the beginning of 1767 a group of 31 Licentiates formed the Society of Collegiate Physicians. With Sir William Duncan in the chair they met at the Crown and Anchor in the Strand and agreed to dine there four times a year. This convivial start was followed by determined action at Comitia in June when nine of this group sat down with the Fellows to put forward their grievance. Naturally this intrusion was not welcome and as Comitia was 'growing very tumultuous, the President declared to them, that unless they would quietly withdraw, he should be under necessity of sending for constables. Hereupon Dr Hunter declared that if any man or constable offered to lay hands upon him . . . he would run him through the body'. 'The tumult increasing and the President finding it impracticable to transact any business', he dissolved Comitia.

It was reasonable for the President to take precautions before the September Comitia, so he had the outer gate locked and the key handed to the College solicitor, Mr Lawrence. About five o'clock several Licentiates who had dined with others at the Queen's Arms tavern came to the

outer gate in Warwick Lane accompanied by various hangers-on. Mr Lawrence would not admit them and what follows is recorded in his own words. 'Soon after by swinging the gate . . . forward and backward, they burst it open, and rushed violently into the courtyard. Soon after Mr Lawrence observing a blacksmith, in company with Sir William Duncan, advancing toward the hall door which was locked, with large hammers, and other iron instruments in his hands, charged him at his peril, not to break upon the door . . . some of the Licentiates said to Mr Lawrence that he was a prisoner; and together with some of the ragamuffins which they brought with them pushed and pulled or dragged him, as he conceives, with a view of removing him out of the hearing of the blacksmith, but pushing and pulling in different directions they hurt him very much; and he was sore for two or three days afterwards, as if he had been beaten. In the meantime one of them busied himself in breaking the College windows . . . he persisted until he had broken about forty squares and beat off the head of his cane; he then said God Damn it I have broke my cane and desisted.' The blacksmith did break open the door and the Licentiates entered Comitia which was promptly dissolved. That was that, apart from the scandal created and the bruises of the affronted solicitor. No wonder he wrote a strong report.