State of the Art

Short-Course Chemotherapy for Pulmonary Tuberculosis[1, 2]

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Introduction

There have been several major landmarks in our understanding of the chemotherapy of tuberculosis. The first was the introduction of streptomycin. The second was the finding that combined chemotherapy with streptomycin plus para-aminosalicylic acid (PAS) prevented the emergence of strains resistant to either of the 2 drugs. The third was the introduction of isoniazid (INH), leading to the development of uniformly successful primary chemotherapy. The fourth was the demonstration that ambulatory, domiciliary treatment was highly effective and that it did not expose close family contacts to appreciable risk of infection. The fifth was the introduction of fully supervised, intermittent chemotherapy with its consequent control over drug ingestion. We consider that short-course chemotherapy is beyond question the latest landmark.

We wish to emphasize that we are presenting findings that resulted from the joint activities not only of our own groups, but of large numbers of colleagues who collaborated in the program of the East African Tuberculosis Investigation Centre (Director: Dr. P. W. Kent) and the research program of the Hong Kong Tuberculosis Services (Coordinator: Dr. W. G. L. Allan), and from one vital observation on intermittent chemotherapy made in a study, with which we were both also closely associated, in the Tuberculosis Chemotherapy Centre, Madras (Director at the time: Dr. N. K. Menon).

Standard Regimens and Their Limitations

Standard regimens of chemotherapy, as exemplified by streptomycin plus INH plus PAS (or ethambutol), followed by INH plus PAS (or ethambutol), are given for a minimum of 18 months to 2 years, and some physicians prescribe them for even longer. Adverse reactions are common, especially to streptomycin and PAS (1, 2), and even when the reactions are minor, patients are expected to tolerate a lack of well-being for many months. It is psychologically undesirable for even a symptom-free patient to feel that he is suffering from, and receiving therapy for, a disease for such a long period of time. In practice, many patients discontinue treatment prematurely, either ceasing to take drugs, although continuing to attend the treatment services, or else stopping attending altogether. This happens often enough in the technically advanced countries, where middle-aged, vagrant men are a particularly difficult patient group of increasing importance, and it becomes a problem of major dimensions in developing countries. Indeed, the very high failure rate (as

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high as 50 per cent) of standard chemotherapy in program conditions in the developing countries stems directly from the difficulty of persuading patients to remain under treatment for a long enough period of time (3, 4).

Committee Report (38) and which was, incidentally, reiterated recently in its Ninth Report (39). Finally, when rifampin was introduced, some workers questioned whether it was because of its obvious potency, a unique drug with special bactericidal activity that would permit effective, short-course chemotherapy (40, 41). To us, rifampin provided the final justification to reinvestigate 6-month regimens that previously had been studied so incompletely.

The First East African Study

It was clear that the first study would have to investigate the problems in depth, and with this in view, a large-scale, cooperative, controlled, clinical trial was established in East Africa and Zambia in association with the East African Tuberculosis Investigation Centre (42–44). More than 1,100 patients with newly diagnosed, extensive, smear-positive, cavitary disease were admitted. Four 6-month regimens were compared, by random allocation, with a standard 18-month regimen (table 1). The first was streptomycin plus INH plus rifampin daily for 6 months. We reasoned that, if this regimen were not effective, then a 3-drug, 6-month regimen did not exist among the currently available drugs; if, however, it proved to be effective, the extent to which the rifampin had contributed to its success would be uncertain. Hence, in the second regimen, pyrazinamide was chosen as the third drug for several reasons: INH plus pyrazinamide has been one of the most effective sterilizing combinations for mouse tuberculosis (45); there was clinical evidence that these drugs form an effective therapeutic combination (46–48); addition of pyrazinamide enhanced the effectiveness of a standard triple regimen (49); it has been argued that streptomycin plus pyrazinamide together form a single bactericidal drug, with streptomycin active in tissues with an alkaline pH and pyrazinamide, in those with an acid pH (50); pyrazinamide is much cheaper than rifampin. If both rifampin and pyrazinamide regimens were highly effective, it would be important to know whether thiacetazone (not available in the United States) would be a suitable third drug. Thiacetazone, a standard drug in East Africa, is widely used because it is effective with INH and is very cheap, costing approximately one-threehundredth of the price of rifampin. If all 3 3-drug combinations were effective, it would be uncertain whether a third drug was necessary at all. For this reason, the 2-drug combination of INH plus streptomycin was also studied as a control regimen. Finally, to relate the efficacies of the 6-month regimens to that of traditional chemotherapy, the standard 18-month regimen for treatment of tuberculosis in East Africa, consisting of streptomycin plus INH plus thiacetazone daily for 2 months, followed by INH plus thiacetazone for 16 months (51, 52), was included. In this study, all drugs were given daily and in standard dosage: 1 g of streptomycin; 300 mg of isoniazid; 450 or 600 mg of rifampin, depending on body weight; 2 g of pyrazinamide, 150 mg of thiacetazone.

TABLE 1

REGIMENS STUDIED IN THE FIRST EAST AFRICAN/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDY

Regimen	Drugs	Duration (months)
SHR	Streptomycin + INH + rifampin	6
SHZ	Streptomycin + INH + pyrazinamide	6
SHT	Streptomycin + INH + thiacetazone	6
SH	Streptomycin + INH	6
STH/TH	Streptomycin + INH + thiacetazone; then INH + thiacetazone	2 16

The 30-month results of this study have been published (42–44) and need only be summarized briefly. It is convenient, in the light of the findings, not to refer to the standard 18-month regimen, although its results are given in the relevant tables.

Patients with drug-susceptible pretreatment strains.

The results obtained during chemotherapy were the following. (*1*) There were early deaths from tuberculosis on all regimens. The fact that desperately ill patients may die before even the most potent antibacterial combinations can have an effect represents a limitation of all tuberculosis chemotherapy and underlines the importance of earlier case finding and diagnosis. (*2*) The rifampin and pyrazinamide regimens produced more rapid culture negativity in the first 3 months (figure 1), i.e., they killed susceptible *M. tuberculosis* more effectively than did thiacetazone or the 2-drug combination. (*3*) All four

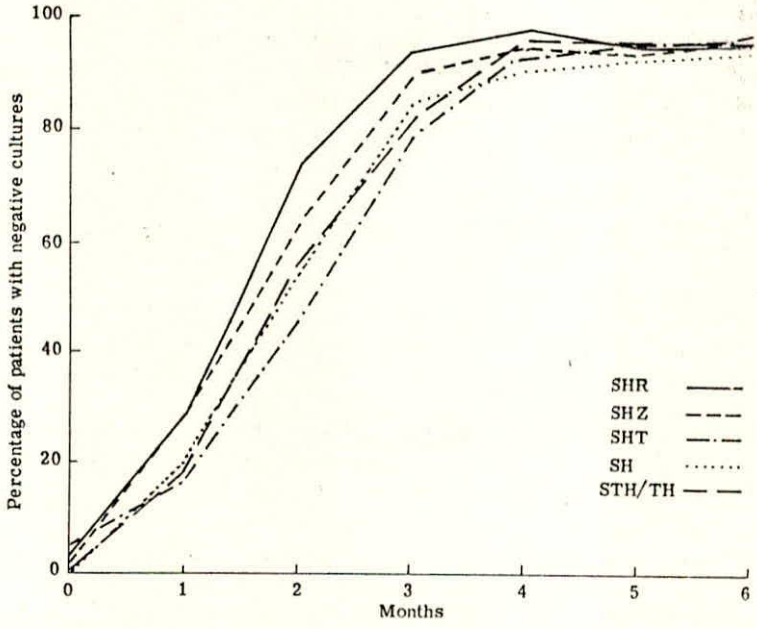

Fig. 1. Monthly culture results of single specimens of sputum for the 5 regimens in the first East African/British Medical Research Council short-course chemotherapy study. S = streptomycin; H = isoniazid; R = rifampin; Z = pyrazinamide; for drug schedules, see table 1.

6-month regimens were uniformly and very highly effective. In fact, among 690 patients assessed at 6 months, there was only 1 bacteriologic failure with a drug-resistant strain, striking confirmation of the efficacy of the combination of INH plus streptomycin, whether alone or supplemented by a third drug.

After stopping short-course chemotherapy, the bacteriologic relapse rates between 7 and 30 months showed important differences (table 2). The thiacetazone and the 2-drug regimens had high relapse rates (22 per cent and 29 per cent, respectively, with the difference not significant). Thus, it is uncertain whether the thiacetazone conferred any therapeutic benefit when added

We in the British Medical Research Council (BMRC) have been concerned with this problem for many years, because we have faced it in very sharp terms ever since we became involved, in the 1950s, in the organization of chemotherapy for patients in East Africa and in Madras in South India. Indeed, much of our program has been directed toward ensuring the cooperation of patients in treatment. Two approaches with which we have been deeply involved are of particular relevance: entirely supervised, intermittent chemotherapy, our research into which dates back to 1960; and the more recent approach of substantially shortened duration of chemotherapy.

At first, these approaches may appear to be alternative and mutually exclusive; however, we have had reason to believe that it should be possible to combine them (see later section). In fact, our target, formulated several years ago, has been to try to find a short-course regimen, given, perhaps, for as short as 6 months, but for not longer than 9 months, in which the chemotherapy is given intermittently for at least much of the time, possibly twice per week, but conceivably even once per week (5). In this article, we review the progress we have made.

Background of Short-Course Chemotherapy

First, we summarize the steps that led us to explore short-course chemotherapy in depth, after recalling important points in the history of the development of tuberculosis chemotherapy.

When chemotherapy was first introduced, patients were usually treated with single drugs for short periods, 6 weeks to 3 months, the latter being sufficiently long to produce a high rate of drug resistance in patients who remained bacteriologically positive (6). When it became possible to prevent the emergence of drug resistance by using combined chemotherapy (7–9),

and with the introduction of INH, courses soon became much longer, a year being the minimal duration; 2 years, usual; indeed, some physicians advocated indefinitely prolonged chemotherapy (10–13) and even chemotherapy for life (14)! There was a clear need to compare, in a controlled, clinical trial, courses of intermediate and longer durations. In the mid-1950s, the BMRC, aware of this need, undertook what we believe was the only controlled clinical trial in which 6-month chemotherapy was compared with therapy of longer durations, namely 12 and 24 months (1). This study showed that INH plus PAS for 6 months, even if supplemented by streptomycin for the first 6 weeks, was followed by an unacceptably high rate of relapse, often with fully drug-susceptible organisms. Furthermore, the rates of relapse after the end of courses of chemotherapy lasting 1 year were broadly similar, whether the regimen contained INH alone, or 2 drugs given daily (1, 15–22) or intermittently (18, 19). There appeared to be little prospect of substantially shortening the duration of chemotherapy.

The next step in our thinking was concerned with preventing the emergence of drug resistance during chemotherapy. In the mid-1960s, the efficacy of the combination of INH plus streptomycin, given daily, was reviewed (23). It was evident that the combination was much more effective than INH plus PAS and that it rendered practically all patients culture negative (24–30, and Russell, W. F., Jr.: Personal communication). In fact, it lived up to predictions based on studies of the large numbers of bacilli in tuberculous cavities in the lungs, and the small likelihood that doubly resistant mutants to INH and streptomycin would be present at the start of treatment in previously untreated patients (31–34).

We obtained further information on this combination in the course of a controlled clinical trial in Singapore (35), where the local physicians were particularly eager to study a regimen consisting of streptomycin plus INH daily for 6 months, followed by INH alone for a further 12 or 18 months. They hoped that this regimen, which was particularly suitable for local operational reasons, would be both effective and nontoxic. Among 114 patients so treated, only 1 case was a bacteriologic failure at 12 months; a recent report of these patients has shown no further bacteriologic failure in a 3-year follow-up period (36). The high efficacy of this regimen raised the possibility that its success might have been due solely to the combination of INH plus streptomycin in the first 6 months, i.e., that the INH in the continuation phase might have contributed nothing. At approximately this time, it had also become clear to us that the fully supervised, intermittent chemotherapy tried in program conditions was often organizationally disappointing in developing countries, and that alternative approaches were needed. This led us to consider the value of concentrating organizational resources and facilities on a period of chemotherapy shorter than the minimum of 1 year, which we had long advocated as the principal priority of chemotherapy (37), which had been recommended in the Eighth World Health Organization Expert to the 2-drug combination. In contrast, the rifampin and pyrazinamide regimens were strikingly and significantly superior (table 2). In a more precise comparison of these 2 regimens made on a larger population of patients, the rifampin regimen had a 3 per cent relapse rate in 152 patients, and the pyrazinamide regimen, an 8 per cent relapse rate in 153 patients; the difference was significant ($P = 0.05$). Thus, these latter 2 regimens, particularly the rifampin regimen, clearly were highly effective even in the severe disease studied.

Two important points concerning bacteriologic relapse emerged (table 2): (*1*) Most relapses in this study occurred between 6 and 12 months, i.e., in the first 6 months after stopping chemotherapy; of these, most occurred between 6 and 9 months. After 12 months, there were very few relapses on any regimen, and it was particularly noteworthy that between 18 and 30 months, there was not a single relapse on either the rifampin or the pyrazinamide regimen. (2) In nearly all patients whose disease relapsed, the organisms were fully susceptible to both streptomycin and INH (table 2), so that bacteriologic relapse was due to the reappearance of susceptible bacilli in the sputum, not to the emergence of drug-resistant strains during chemotherapy and their subsequent appearance in the sputum.

These findings suggest that the rifampin and pyrazinamide regimens were more effective because of their ability to eliminate susceptible bacilli, which they did sooner (figure 1) and more permanently than the other regimens (table 2). In terms of the Jawetz concept of synergistic bactericidal activity of drug combinations

TABLE 2

BACTERIOLOGIC RELAPSES FROM 6 TO 30 MONTHS, THEIR TIMING, AND DRUG SUSCEPTIBILITY OF THE ORGANISMS IN THE FIRST EAST AFRICAN/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDY, BASED ON PATIENTS WITH A FAVORABLE OR DOUBTFUL STATUS AT 6 MONTHS

Regimen	No. of Patients Assessed	Bacteriologic Relapses		Bacteriologic Relapse in Month				Relapse with Organisms Susceptible to INH and Streptomycin	Bactericidal Drugs	
		(no.)	(%)	7–12	13–18	19–24	25–29		No.	Drugs
SHR	112	2	2	1	1	0	0	2*	2.5	H + R + (S)†
SHZ	112	12	11	9	3	0	0	9	2	H + SZ
SHT	104	23	22	20	2	1	0	22	1.5	H + (S)
SH	112	33	29	28	3	2	0	32	1.5	H + (S)
STH/TH	102	4	4	3	0	1	0	3		

*These strains were susceptible to rifampin also.
†Parentheses indicate that it is "one-half" a complete bactericidal drug.

(53, 54), INH and rifampin can be considered "complete" bactericidal drugs that are active against the entire bacterial population, but streptomycin, effective only at an alkaline pH, can be considered as "one-half" a drug. Thus, the rifampin regimen contained 2.5 bactericidal drugs, INH and rifampin, and, in addition, streptomycin; the pyrazinamide regimen contained 2 bactericidal drugs, INH as one, and streptomycin and pyrazinamide acting together as the other. In contrast, the 2 unsatisfactory regimens contained only 1.5 bactericidal drugs, INH and streptomycin. We planned the subsequent program of research reported in this paper bearing in mind the importance of testing the working hypothesis that the effectiveness of short-course regimens is related to the number of bactericidal drugs, at least 2 being necessary.

The reason for the undoubted superiority of the rifampin regimen over the pyrazinamide regimen when given for 6 months to patients with fully susceptible organisms is worthy of comment, and we have suggested 3 explanations for this finding (43). (*1*) Streptomycin did, in fact, contribute to the effectiveness of the rifampin regimen (i.e., it was a necessary third drug). It has already been suggested that the pyrazinamide regimen contained, in bactericidal terms, no third drug, because at no point in the pH scale would both streptomycin and pyrazinamide be acting together on the same organisms. (*2*) There might, in fact, be a pH gap between approximately pH 6 and pH 7, with the alkaline range covered by the streptomycin, the acid range covered by pyrazinamide, but neither drug effective at intermediate pH values. (*3*) It is possible that rifampin might be especially bactericidal either on normal metabolizing organisms or on dormant organisms, or on both.

These explanations based on the Jawetz concept are probably oversimplifications. Rifampin is not appreciably more bactericidal than is INH against rapidly growing or dormant organisms (55, 56, and Awaness, A. M., Dickinson, J. M., and Mitchison, D. A.: Unpublished data). Furthermore, there is early bactericidal antagonism between INH and pyrazinamide in the mouse (57), and no synergism between INH and rifampin *in vitro* (55, and Awaness, A.M., Dickinson, J. M., and Mitchison, D. A.: Unpublished data). On the other hand, bactericidal synergism between streptomycin and INH does occur (58, 59). These issues are considered more fully later.

Patients with drug-resistant M. tuberculosis *pretreatment*

Most patients with initial drug resistance to INH alone, to streptomycin alone, and to both INH and streptomycin responded to both rifampin and pyrazinamide regimens; relapse rates were low, although with neither regimen was the response as satisfactory as in patients with fully susceptible organisms.

Drug toxicity

Drug toxicity was uncommon in this relatively young African patient population, and although 5 per cent of 225 patients who started treatment with rifampin had toxic reactions, as did 7 per cent of 232 patients receiving pyrazinamide, 9 per cent of 227 receiving thiacetazone, and 3 per cent of 227 receiving 2 drugs, only 2 patients receiving rifampin, 4 receiving pyrazinamide, and 7 receiving thiacetazone had 1 or more drugs stopped.

When this first study was designed, we were fully aware that none of the regimens was of immediate practical importance, because all involved a daily injection of streptomycin for 6 months. It was, however, essential to begin by studying the principles and establishing decisively whether or not 6-month regimens were feasible. Our further aims in developing the program have been to move toward widely applicable, practical regimens suitable for program conditions. The selection of the regimens for study, however, has been based on our views of the underlying mechanisms.

The Second East African Study

In the second study in East Africa (60), 4 regimens were investigated (table 3). Using the triple, rifampin (SHR) regimen of the first study as a control, several important questions were posed. The second (HR) regimen, INH plus rifampin, was introduced to investigate whether or not the streptomycin had contributed to the therapeutic success of the triple-drug regimen. The other 2 regimens explored whether the duration of daily rifampin could be reduced to 2 months without loss of therapeutic effectiveness, if followed in the continuation phase by a standard regimen of thiacetazone plus INH daily for 4 months (SHRZ/TH), or by a twice-weekly, intermittent, 3-drug regimen ($SHRZ/S_2H_2Z_2$).

Background of the Use of Intermittent Short-Course Chemotherapy

The background of the use of intermittent, short-course chemotherapy dates back to a study in the Chemotherapy Centre, Madras (61), with which the BMRC was closely associated. In this study, 4 regimens were compared: streptomycin plus high-dosage INH twice per week (S_2H_2); the same combination given only once per week (S_1H_1); a second, once-weekly regimen ($S_1H_1Z_1$), in which an attempt was made to strengthen the streptomycin and INH combination by adding a third drug, pyrazinamide; a regimen of streptomycin plus INH in standard dosage daily for 4 weeks, followed by once weekly combination of streptomycin plus high-dosage INH (S_7H_7/S_1H_1). The 12-month results of single-culture examinations of sputum are shown for the 4 regimens in figure 2. Despite the widely varying dosage schedules of streptomycin plus INH (once per week, twice per week, or daily for 4 weeks and then once per week), the 4 regimens produced culture negativity at an identical rate in the early months, i.e., they eliminated susceptible *M. tubercu-*

TABLE 3

REGIMENS STUDIED IN THE SECOND EAST AFRICAN/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDY

Regimen	Drugs	Bactericidal Drugs	
		No.	Drugs
SHR	Streptomycin + INH + rifampin daily for 6 months	2.5	H + R + (S)*
HR	INH + rifampin daily for 6 months	2	H + R
SHRZ/TH	Streptomycin + INH + rifampin + pyrazinamide daily for 2 months, then thiacetazone + INH daily for 4 months	3, then 1	H + R + SZ, then H
$SHRZ/S_2H_2Z_2$	Streptomycin + INH + rifampin + pyrazinamide daily for 2 months, then streptomycin + INH + pyrazinamide twice per week for 4 months	3, then 2 intermittently	H + R + SZ, then H + SZ

*Parentheses indicate that it is "one-half" a complete bactericidal drug.

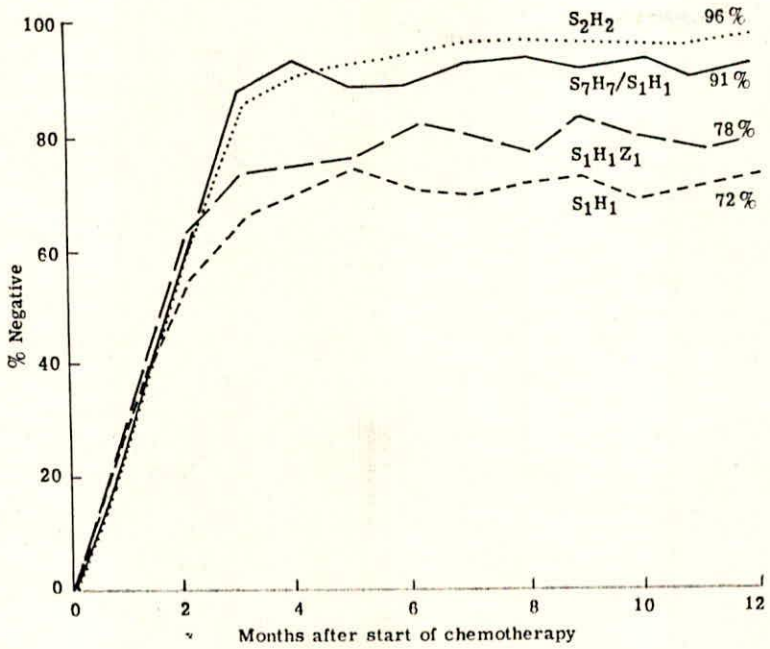

Fig. 2. Culture negativity of single collection specimens of sputum for the 4 regimens investigated in the Madras study of once-weekly regimens of chemotherapy. S = streptomycin; H = isoniazid; Z = pyrazinamide; the regimens are defined on page 330.

losis equally effectively. Only when drug resistance began to emerge did differences in the therapeutic efficacy of the 4 regimens become manifest. Because the effectiveness of short-course chemotherapy in patients with fully susceptible organisms depends on the effective elimination of susceptible bacilli, these observations raised the possibility that intermittent regimens could also be effective in short-course chemotherapy. This is why the regimen with intermittent chemotherapy after 2 months of daily chemotherapy was introduced into the second East African study.

The 1-year results suggested several main conclusions.

Patients with drug-susceptible strains pretreatment

Bacteriologic responses during chemotherapy were as follows. (*1*) In the first 2 months, the SHRZ regimens eliminated susceptible *M. tuberculosis* more rapidly; the proportion of patients

TABLE 4

BACTERIOLOGIC RELAPSES FROM 6 TO 12 MONTHS, THEIR TIMING, AND DRUG SUSCEPTIBILITY OF THE ORGANISMS IN THE SECOND EAST AFRICAN/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDY*

Regimen	No. of Patients Assessed	Bacteriologic Relapses		Bacteriologic Relapse in Month		Relapse with Organisms Susceptible to INH Streptomycin, and Rifampin	No. of Bactericidal Drugs†
		(no.)	*(%)*	7–9	10–11		
SHR	166	4	2	3	1	4	2.5
HR	170	9	5	5	4	8	2
SHRZ/TH	180	11	6	8	3	11	3, then 1 daily
SHRZ/$S_2H_2Z_2$	161	7	4	6	1	7	3, then 2 intermittently

*Excluding 1 HR and 2 SHRZ/$S_2H_2Z_2$ patients classified as treatment failures at 6 months.
†The bactericidal drugs are tabulated in the last column of table 3.

with negative cultures in these 2 regimens was 82 per cent, compared with 70 per cent for the triple (SHR) regimen ($P = 0.006$), and 64 per cent for the 2-drug (HR) regimen. By 3 months, however, all regimens had similar rates of culture negativity. (2) Of more than 700 patients assessed at 6 months, only 3 had an unfavorable bacteriologic response, 1 in the HR series and 2 in the intermittent ($SHRZ/S_2H_2Z_2$) series. Drug-resistant bacilli (resistant to INH) were obtained only for the HR patient, and the other 2 were probably late converters.

(3) The bacteriologic relapse rate after stopping chemotherapy was low on all 4 regimens (table 4). The triple SHR regimen had a very low relapse rate, 4 of 166 patients (2 per cent), just as in the first study. There was a suggestion that this regimen was marginally superior to the HR regimen, in which the relapse rate was 5 per cent of 170 patients; if this is confirmed in longer follow-up, streptomycin may, in fact, have contributed to the therapeutic success in a small number of patients.

(4) After an initial 4-drug (SHRZ) phase of 2 months, effective regimens resulted, whether the continuation chemotherapy was with the standard daily (TH) regimen (relapse rate: 6 per cent of 180 patients), or with the twice-weekly, fully intermittent ($S_2H_2Z_2$) regimen (relapse rate: 4 per cent of 161 patients).

Despite the short follow-up, it is evident that the pattern of bacteriologic relapse observed in the first study was again repeated (table 4): most relapses occurred in the first 3 months after stopping chemotherapy; relapse occurred with drug-susceptible strains. Thus, 22 of 31 relapses had occurred by 9 months, and only 9 occurred in the next 2 months. In all but 1 patient, relapse occurred with strains susceptible to streptomycin, INH, and rifampin, confirming that relapse was due to the failure of the regimens to eliminate susceptible *M. tuberculosis*, and was not a consequence of emergence of drug-resistant bacilli during chemotherapy.

In bactericidal terms (table 4), the findings for the patients with susceptible organisms can be interpreted as follows. (1) Streptomycin might have contributed to the bactericidal action of the SHR regimen. We would expect this contribution, if it exists, to be small, because streptomycin contributes only "one-half" a drug to the 2 complete drugs, INH and rifampin. In practical terms, addition of streptomycin appears unnecessary in most patients. (2) The findings with the 2 SHRZ regimens suggest that an initial intensive phase with 3 complete bactericidal drugs for 2 months, whether followed by a single bactericidal drug (H) daily or by 2 complete bactericidal drugs (SHZ) twice per week, are effective regimens. It is uncertain whether 2.5 bactericidal drugs (SHR) in the first 2 months, or 2 (HR) would have been equally effective. It seems unlikely that the 2 complete bactericidal drugs (SHZ) would have been equally effective in the first 2 months, because in the first East African study they were not, even when given daily for 6 months in the SHZ regimen (42–44). It is not clear whether thiacetazone contributed at all to the efficacy of the SHRZ/TH regimen, or whether INH alone in the continuation phase might have been equally effective in patients with fully susceptible organisms. Further, it is uncertain from this study whether, for an intermittent regimen to be successful in short-course chemotherapy, it is necessary that it be preceded by an initial intensive phase; this question is being investigated in a study in Hong Kong (Hong Kong Tuberculosis Treatment Services/BMRC: Unpublished data).

Patients with drug-resistant strains pretreatment

Responses during treatment were as follows. Nearly all patients with initial drug resistance to INH alone had a favorable response to their regimen at 6 months, as did all 20 patients with streptomycin resistance. Although the number of patients with doubly resistant strains was small, their response was less satisfactory.

Although the relapse rate in patients with initial resistance to INH alone was clearly higher than that in patients with fully susceptible organisms, it was still relatively low; so far, none of the patients with initial resistance to streptomycin alone has relapsed.

The likely level of therapeutic success obtained by the effective regimens in the presence of initial drug resistance was best assessed by amalgamating the findings of the rifampin and pyrazinamide regimens in the first East African study with those of all 4 regimens in the second investigation (table 5). The estimated failure rates in the last column of the table were derived by adding the number of failures in the 6 months while the patients were on chemotherapy and the number of relapses in the 6 months after stopping chemotherapy, adjusted on the assumption that all patients with ini-

TABLE 5

ONE-YEAR RESULTS IN PATIENTS WITH PRETREATMENT DRUG RESISTANCE IN THE 2 EAST AFRICAN/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDIES

Drug Resistance	Assessment	Regimen					All Regimens	Estimated Failure Rate (%)
		SHR	HR	SHRZ/TH	SHRZ/$S_2H_2Z_2$	SHZ		
INH alone	No. of patients	24	9	10	10	12	65	22
	Unfavorable status at 6 months	0	1	0	1	0	2	
	No. assessed for relapse	23	8	8	5	8	52	
	Relapses 7–12 months	4	1	3	0	2	10	
Streptomycin alone	No. of patients	6	—*	6	5	2	19	5†
	Unfavorable status, at 6 months	0	—	0	0	1	1	
	No. assessed for relapse	6	—	5	2	1	14	
	Relapses 7–12 months	0	—	0	0	0	0	
INH and streptomycin	No. of patients	5	8	2	0	4	19	52†
	Unfavorable status, at 6 months	2	3	2	0	1	8	
	No. assessed for relapse	3	5	1	0	3	12	
	Relapses 7–12 months	0	1	1	0	0	2	

*On this regimen, streptomycin resistance was not resistance to a relevant drug.
†This percentage is based on fewer than 25 observations.

tial drug resistance had been followed for 1 year. The rates were 22 per cent of 65 patients with resistance to INH alone, 5 per cent of 19 patients with resistance to streptomycin alone, and 52 per cent of 19 patients with resistance to the 2 drugs. Furthermore, the 30-month evidence from the first East African study (42–44) suggests that these estimated failure rates were unlikely to become much higher when all patients had completed longer follow-up. It seems safe to conclude that streptomycin resistance alone had very little over-all influence on the results of therapy with the regimens containing rifampin (the number of observations on the SHZ regimen was too small to draw conclusions about this regimen). In contrast, resistance to INH alone had a definite effect observable in all the regimens, and resistance to both drugs carried a bad prognosis. These findings suggest that streptomycin contributes less than INH to the bactericidal action of the regimens under consideration. That it has some activity is probable from the higher failure rate in patients with double-drug resistance, confirming the conclusions on drug activity drawn from the patients with initially susceptible organisms; however, the difference might also have been due to a greater frequency of true primary resistance in patients with resistance to INH alone (62, 63), because some response to treatment with INH alone is common (64), although it is very unlikely to occur in those with undisclosed acquired resistance (65, 66).

It should be noted that in the patients with initial resistance to INH alone, the response at 6 months was almost uniformly favorable, but the relapse rate was substantial. It is probable, however, that had chemotherapy been prolonged for a relatively short period, e.g., to a total of 9 months or less, the relapse rate might well have been appreciably less, as was the case in the Hong Kong short-course study (Hong Kong Tuberculosis Treatment Services/BMRC Investigation: Unpublished data).

Drug toxicity

Adverse reactions to the drugs were uncommon. Of 943 patients (237, SHR; 237, HR; 239, SHRZ/TH; 230, SHRZ/S_2H_2) who started treatment, only 3 had 1 or more drugs terminated; all 3 drugs in an SHR patient, and thiacetazone plus INH in 2 SHRZ/TH patients.

The Hong Kong Study

A study in Hong Kong was undertaken as part of a cooperative research program by the Hong Kong Tuberculosis Treatment Services and the BMRC (Unpublished data). In this study, the potential of the pyrazinamide (SHZ) regimen, which was effective in the first East African study, was explored in depth. Background factors in this study were that (*1*) Hong Kong could not afford a daily rifampin regimen for 6 months as standard primary chemotherapy; (2) treatment services in Hong Kong are geared to provide entirely supervised regimens of chemotherapy on a large scale, even when chemotherapy is given daily to outpatients, although streptomycin plus high-dosage INH twice per week is now the standard outpatient continuation regimen used for most Hong Kong patients (67). The Hong Kong Tuberculosis Services were, therefore, eager to search for a short-course, intermittent regimen that could readily be given under supervision to outpatients. Rifampin is an exceptional drug (68) in that it produces adverse reactions more frequently when given intermittently than when given daily (69, 70); most of these reactions are immunologic. There is good evidence, however, that large, intermittent doses of pyrazinamide not only have low toxicity (61, 71), but are also somewhat more effective, weight for weight, when so given than when given daily (72, 73). For these reasons, 3 schedules of administration of streptomycin plus INH plus pyrazinamide were studied by random allocation (table 6): daily (SHZ), 3 times per week ($S_3H_3Z_3$), and twice per week ($S_2H_2Z_2$). It was also decided to study by random allocation both the 6-month duration and a longer course, 9 months, because of the possibility that chemotherapy prolonged beyond 6 months might substantially reduce the relapse rate or eliminate all relapses. In terms of bactericidal drugs, the study was a comparison of 2 complete bactericidal drugs given daily, 3 times per week, or twice a week.

The main analysis concerned 137 SHZ patients; 141, $S_3H_3Z_3$, and 126, $S_2H_2Z_2$.

Patients with drug-susceptible strains pretreatment

Responses during chemotherapy were as follows. Although there was evidence that the proportion of patients with negative cultures was lower in the $S_2H_2Z_2$ regimen than in the other 2 regimens, the difference was accounted for by patients whose treatment failed because of emergence of drug-resistant organisms. There was, however, no evidence of any difference between the regimens in the rate at which they eliminated susceptible organisms. At 6 months (table 7), it was noteworthy that the $S_2H_2Z_2$ regimen had 5 failures among 126 patients (4 per cent), compared with 2 of 141 (1 per cent) $S_3H_3Z_3$ patients and 0 of 137 patients on the daily regimen. Although the inferiority of the twice-weekly regimen was only marginal, we nevertheless consider it axiomatic that (*1*) at the end of a short-course treatment, the regimen should be practically uniformly successful in patients with pretreatment drug-susceptible strains and (2) this failure rate, although low is unacceptable for countries that achieve very high levels of success under program conditions with primary regimens of standard durations.

All failures in patients receiving chemotherapy, even in the 9-month series, occurred in the first 6 months (table 7), with the exception of 1 $S_2H_2Z_2$ patient.

The relapse rates in the first 6 months after stopping chemotherapy in patients on all 3 regimens in the 6-month series were relatively high:

TABLE 6

THREE REGIMENS OF STREPTOMYCIN PLUS ISONIAZID (INH) PLUS PYRAZINAMIDE STUDIED IN THE HONG KONG/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDY

Regimen	No. of Bactericidal Drugs	Schedule	Duration Comparison	Dosage		
				Streptomycin	INH	Pyrazinamide
SHZ	2	Daily*	6 months	0.75 – 1.0 g	300 mg	1.5 – 2.0 g
$S_3H_3Z_3$	2	Three times per week	and	0.75 – 1.0 g	15 mg/kg	2.0 – 2.5 g
$S_2H_2Z_2$	2	Twice per week	9 months	0.75 – 1.0 g	15 mg/kg	3.0 – 3.5 g

*Between 6 and 9 months, the 9-month series received the 3 times per week ($S_3H_3Z_3$) schedule.

TABLE 7

BACTERIOLOGIC RESPONSE DURING CHEMOTHERAPY IN THE HONG KONG/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDY

Duration of Chemotherapy (months)	Patients	SHZ		$S_3H_3Z_3$		$S_2H_2Z_2$	
		(no.)	(%)	(no.)	(%)	(no.)	(%)
6*	No. assessed at 6 months	137		141		126	
	Unfavorable response	0	0	2	1	5	4
9	Favorable response at 6 months	70		67		74	
	Relapsed between 6 and 9 months	0	0	0	0	1	1

*Including patients treated for 9 months.

13 per cent of 63, 16 per cent of 69, and 18 per cent of 38, respectively (table 8), between 6 and 12 months. In contrast, when given for 9 months, all 3 regimens clearly had lower relapse rates in the 6 months after stopping chemotherapy (9 to 15 months): 3, 4, and 4 per cent, respectively, of groups of over 50 patients.

All strains from patients in both the 6- and 9-month series whose disease relapsed had organisms fully susceptible to streptomycin and INH.

Thus, although the 6-month regimens had unsatisfactorily high relapse rates, the 9-month SHZ and $S_3H_3Z_3$ regimens were not only effective while patients were on them, but, so far, have low relapse rates. Apart from the failure of a small proportion of patients during chemotherapy with the $S_2H_2Z_2$ regimen, the 9-month regimen with this combination was also highly effective. Thus, the hypothesis deduced from the Madras study data (61), that intermittent doses and short-course chemotherapy could be effectively combined, was confirmed in the Hong Kong study; unlike the intermittency in the continuation phase in the second study in East Africa, it was intermittency from the very start of treatment. Clearly, the East African and Hong Kong studies suggest that further exploration of intermittent, short-course regimens should become a major objective of further research.

The Hong Kong study demonstrated that 2 complete bactericidal drugs, given daily or intermittently, can be highly effective; but when the intermittent schedule is altered from 3 to 2 times per week, the effectiveness during the actual period of chemotherapy becomes marginally less, owing to emergence of drug resistance. Further, the superiority of the 9-month regimens over the 6-month regimens demonstrated that chemotherapeutic activity on the bacterial population continued beyond 6 months with all 3 regimens.

In comparing this study with the first African study, the relapse rate after 6 months of chemotherapy with the regimen containing daily streptomycin, INH, and pyrazinamide was higher in the Hong Kong patients. The disease in Hong Kong was less acute, as assessed radiographically, and it was our impression that it was also less extensive and had less cavitation.

TABLE 8

BACTERIOLOGIC RELAPSE IN FIRST 6 MONTHS AFTER STOPPING CHEMOTHERAPY IN HONG KONG/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDY

Duration of Chemotherapy (months)	Regimen	Patients with Favorable Status at End of Chemotherapy	Relapses			
			Total*		First 3 Months	Second 3 Months
			(no.)	(%)		
6	SHZ	63	8	13	5	3
	$S_3H_3Z_3$	69	11	16	9	2
	$S_2H_2Z_2$	38	7	18	6	1
9	SHZ	62	2	3	2	0
	$S_3H_3Z_3$	67	3	4	2	1
	$S_2H_2Z_2$	52	2	4	1	1

*All strains were susceptible to streptomycin and INH.

TABLE 9

BACTERIOLOGIC RESPONSE DURING CHEMOTHERAPY OF PATIENTS WITH RESISTANT STRAINS PRETREATMENT IN THE HONG KONG/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDY

Duration of Chemotherapy (months)	Patients	SHZ (no.)	SHZ (%)†	$S_3H_3Z_3$ (no.)	$S_3H_3Z_3$ (%)†	$S_2H_2Z_2$ (no.)	$S_2H_2Z_2$ (%)†
6*	Assessed at 6 months	33		41		36	
	Unfavorable response	10	30	15	37	14	39
9	Favorable response at 6 months	14		11		11	
	Relapse between 6 and 9 months	0	(0)	1	(9)	2	(18)

*Including patients treated for 9 months.
†Percentages in parentheses are based on fewer than 25 observations.

These observations, which suggest differences in the host/parasite relationship between African and Hong Kong patients, will be the subject of a further communication. Attention has already been drawn to this possibility in another context (74).

Patients with drug-resistant strains pretreatment

The numbers of patients with drug-resistant strains were relatively small, but the findings (table 9) suggested that approximately one third of the patients with strains resistant to INH, to streptomycin, or to both drugs had an unfavorable response by 6 months. The only further failures encountered between 6 and 9 months in the 9-month series occurred in patients on the intermittent regimens. There was also an important difference between the SHZ and the 2 intermittent regimens. Streptomycin resistance alone (data not tabulated) had little influence on the response to treatment with the SHZ regimen; only 1 of 15 patients had an unfavorable response by 6 months, compared with 8 of 18 such patients on the $S_3H_3Z_3$ and 7 of 16 on the $S_2H_2Z_2$ regimen. Finally, although the numbers are small, the findings so far available suggest that the 9-month regimens may well have lower relapse rates after stopping chemotherapy than the 6-month regimens (table 10).

Drug toxicity

Although possible adverse reactions were recorded in a substantial proportion of patients, the proportions in whom either one of the drugs or the whole regimen were actually terminated were low in all 3 regimens (table 11). Pyrazinamide was not particularly troublesome, as might have been feared.

It merits comment that the earlier literature on pyrazinamide toxicity in primary chemotherapy concerned daily regimens and, usually, higher dosages of the drug than were used in the Hong Kong study. In failure regimen chemotherapy, in which most clinicians have obtained

TABLE 10

BACTERIOLOGIC RELAPSES IN THE FIRST 6 MONTHS AFTER STOPPING CHEMOTHERAPY IN PATIENTS WITH RESISTANT STRAINS PRETREATMENT IN THE HONG KONG/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDY

Duration of Chemotherapy (months)	Regimen	Favorable Response at End of Chemotherapy	Relapses (no.)	Relapses (%)*
6	SHZ	7	2	(29)
	$S_3H_3Z_3$	14	1	(7)
	$S_2H_2Z_2$	10	2	(20)
9	SHZ	11	0	(0)
	$S_3H_3Z_3$	9	0	(0)
	$S_2H_2Z_2$	7	1	(14)

*Parentheses indicate percentages based on fewer than 25 observations.

TABLE 11

CHANGES OF CHEMOTHERAPY FOR ADVERSE REACTIONS IN THE FIRST 6 MONTHS IN THE HONG KONG/BRITISH MEDICAL RESEARCH COUNCIL SHORT-COURSE CHEMOTHERAPY STUDY

Regimen	No. of Patients	One Drug Terminated						Regimen Terminated	
		Streptomycin		INH		Pyrazinamide			
		(no.)	(%)	(no.)	(%)	(no.)	(%)	(no.)	(%)
SHZ	194	3	2	0	0	6	3	4	2
$S_3H_3Z_3$	207	0	0	0	0	4	2	3	1
$S_2H_2Z_2$	182	1	1	1	1	3	2	5	3

their experience of pyrazinamide, it was combined with the toxic drugs ethionamide and/or cycloserine. Further, it was usually given to vulnerable groups, middle-aged and elderly patients, in whom primary chemotherapy had already failed because of drug toxicity or noncooperation. In these circumstances, it is difficult to identify, even in a general way, the level of adverse reactions to or toxicity of pyrazinamide. Moreover, interpretations of abnormal hepatic function tests have added to the confusion, and many of the reports of hepatic toxicity in the literature rested solely on such tests.

We have been involved in a number of studies in developing countries in which pyrazinamide in moderate dosage (20 to 30 mg per kg of body weight) was used daily and in combination with streptomycin (72, 75) or streptomycin plus PAS (76) and in intermittent chemotherapy in combination with streptomycin (72) and with streptomycin plus INH (61) in dosages that were increased with the interval between doses, reaching 90 mg per kg of body weight in a once-weekly regimen (71 and Hong Kong/BMRC study, unpublished data). We have been impressed by the convenience and low toxicity of pyrazinamide; the main complaint was arthralgia, and this was less common on intermittent regimens. We believe that it is now necessary for physicians in the technically advanced countries to obtain practical experience with the use of regimens containing pyrazinamide, especially regimens that are intermittent from the start or after a short daily phase, in newly diagnosed, previously untreated patients. Such an appraisal, if carefully conducted with suitable control regimens, would establish the real levels of toxicity of regimens containing pyrazinamide. One such investigation is currently in progress in Hong Kong.

An Alternative Approach to Bactericidal Mechanisms

The concept of bactericidal synergism, which we have used as a working hypothesis in planning clinical studies and in explaining their results, has, as mentioned previously, certain defects. In particular, despite the high efficacy of INH and rifampin in short-course chemotherapy, no bactericidal synergism has been demonstrated between these drugs *in vitro*. Bactericidal activity may, perhaps, be more usefully considered under 2 headings: (*1*) the initial kill of actively growing bacilli; (2) the "sterilizing" activity on persisting bacilli. That bacterial persistence is of particular importance is indicated by the much longer time taken for reduction of viable counts in the sputum of patients than in *in vitro* experiments, in which bacilli in the logarithmic phase of growth are exposed to realistic drug concentrations.

It is well established that drugs do not kill bacilli when their growth (metabolic activity) has been completely prevented by low temperature, anaerobic conditions, certain types of nutritional deficiency, or when they are in the stationary phase of growth (56, 77–80). The simplest explanation of bacterial persistence during chemotherapy is, therefore, that a proportion of the bacterial population is in a nonmultiplying (dormant) state. An alternative explanation is that bacilli are in sites to which drugs do not penetrate in adequate concentration. This probably does not apply to INH, rifampin, or pyrazinamide, because they all readily cross biologic membranes, including the normal blood-brain barrier; their intralesional concentrations approximate those in blood, and they appear to be active against intracellular bacilli (81–88). On the other hand, streptomycin fails to penetrate many cell membranes and is much less ac-

tive against intracellular than extracellular bacilli (82, 89, 90).

Mouse and man. In examining the bactericidal activity of the drugs in detail, evidence obtained from tuberculosis experimentally induced in mice has been of greatest value. We have drawn especially on the pioneering work done at Cornell University and on the extensive studies at the Pasteur Institute.

Certain features of the murine model are particularly important. (*1*) Histologic examination of the organs suggests that most bacilli are intracellular, except in advanced pulmonary lesions. (*2*) Although direct measurements of the pH of the environment of bacilli have not been made, the bactericidal activity of pyrazinamide in the mouse shows that it must be less than approximately pH 5.6 for most bacilli, because the drug is inactive at a more alkaline pH *in vitro* (91). (*3*) In chronic murine tuberculosis, viable counts in the lungs remain constant, not because there is a balance between growth and death of bacilli, but because the immune mechanism is essentially bacteriostatic (92, 93). Although the mice used in experimental chemotherapy have either had acute disease or were changing from acute to chronic disease, it is reasonable to suppose that at least a proportion of the bacilli are held static by the immune process.

These conclusions suggest that bacilli usually grow within the macrophage in an environment where acidity and perhaps low Po_2 limit their multiplication, as originally suggested by Dubos (94). Streptomycin would be of low efficacy, partly because of the intracellular site, and partly because of the acid reaction. Isoniazid and rifampin, whose activities are unaffected by pH, would kill growing organisms. In advanced pulmonary lesions, the accumulation of bacilli (and therefore their antigens) within an individual macrophage would destroy the cell (95), and the bacilli would be liberated to the extracellular environment, where streptomycin would be more effective (96). Finally, after a period of chemotherapy, the bacterial load would be reduced, so that the bacilli would no longer destroy their macrophages, but would remain more or less dormant within them. Under these circumstances, the bactericidal activity of the drugs, and particularly that of streptomycin, would be greatly reduced. This model can explain many of the findings in experimental chemotherapy of murine tuberculosis, although it does not, as yet, account for the remarkable sterilizing action of INH plus pyrazinamide or of INH plus rifampin.

Man develops a much higher degree of hypersensitivity to antigens of *M. tuberculosis* than does the mouse. In consequence, few bacilli are found intracellularly; most occur in well-aerated cavity walls, at least in the patients usually studied in controlled clinical trials. The pH of resected tissue and caseous material has been found to be 6.94, on average (range for 95 per cent of observations: 6.8 to 7.2), using glass electrodes (97). Thus, most bacilli, lying extracellularly and at a neutral pH, should be susceptible to streptomycin in relatively low concentrations. Little is known concerning the factors causing dormancy of bacilli in human lesions. That there are dormant organisms is shown by the long periods of conventional chemotherapy necessary to achieve low ultimate relapse rates and, indeed, by the early observations on endogenous reactivation of tuberculosis. We may surmise that dormant bacilli survive either within the macrophage (endotheliod cell) or within areas of caseation that do not communicate with a bronchus and therefore have a decreased Po_2. That Po_2 is an important factor limiting growth is shown by the small numbers of bacilli found in the closed lesions of spinal tuberculosis (98, 99).

Initial bactericidal activity of drugs. In table 12 are summarized the early bactericidal activity *in vitro* (58, 59, 100, 101, and Dickinson, J. M., and Mitchison, D. A.: Personal communication), in the mouse (102–104), and in the guinea pig (105, 106, and Dickinson, J. M., and Mitchison, D. A.: Personal communication) of the 4 most important drugs used in short-course chemotherapy. The comparisons

TABLE 12

SHORT-TERM BACTERICIDAL ACTIVITY OF MAIN CHEMOTHERAPEUTIC DRUGS USED IN SHORT-COURSE CHEMOTHERAPY

Drug	Bactericidal Activity		
	In vitro	In mouse	In guinea pig
INH	2+	2+	2+
Rifampin	2+	2+	2+
Streptomycin	3+	1+*	2+
Pyrazinamide	2+†	2+*	0*

*Drug given in a dosage considerably higher than that used in man.

†pH: 5.2 to 5.6 units.

can only be approximate, because the effective *in vivo* concentration of each drug is not certain; but except for streptomycin and pyrazinamide in the mouse, the estimates of activity are based on experiments using concentrations or dosages likely to approximate those obtained or used in man.

The bactericidal activity of INH *in vitro* is changed only to a small extent by large alterations in drug concentration (59). Likewise, the size or rhythm of INH dosage in man was not found to influence speed of sputum conversion (107–109). The bactericidal activity of rifampin alone is, however, affected to a considerable extent by changes of concentration or dosage, so that the drug is only slowly bactericidal at low dosage. The concentration of streptomycin profoundly influences bactericidal activity *in vitro*. Here we can be guided by well-established observations on drug resistance, which indicate that the effective *in vivo* concentration in man is only 4 to 8 times the minimal inhibitory concentration (110, 111). Finally, pyrazinamide is bactericidal *in vitro* at an acid pH; the relationship between concentration and activity will be discussed subsequently.

The broad conclusion emerges from table 12 that, although INH, rifampin, and pyrazinamide have fairly similar, moderate bactericidal activities *in vitro*, streptomycin has the highest activity. In contrast, streptomycin at the dosage given in man is virtually inactive in the mouse, and, even when the dosage is increased 10-fold, it is less active than INH or rifampin. In the guinea pig, streptomycin is moderately bactericidal at the same dosage and serum concentration used in man. Pyrazinamide in high dosage is bactericidal in the mouse, but appears to be inactive in the guinea pig. These apparently contradictory findings in mouse and guinea pig can be explained on 2 grounds: (*1*) that the environmental pH of actively growing bacilli is more acid in the mouse than in the guinea pig; (*2*) that the immune system in the mouse depends on low Po_2 and acidity, whereas other mechanisms, less dependent on pH (such as peroxide production), are of greater importance in the guinea pig.

When we attempt to apply these findings in tuberculosis experimentally induced in mice and guinea pigs to man, we can only be guided by broad generalizations. With regard to environmental pH, streptomycin is known to be effective in preventing the emergence of INH-resistant organisms when patients are treated with INH and streptomycin. On the other hand, pyrazinamide is of only moderate efficacy in preventing resistance to another drug. These findings are compatible with the view that the range of environmental pH is greater in man than in either the mouse or the guinea pig, but that most bacilli are in a more alkaline (extracellular) environment than that in the mouse. Evidence that cannot be reviewed here in detail on the virulence in man of various types of attenuated bacilli, including INH-resistant and South Indian strains, also suggests that the immune process in man is intermediate between that of the mouse and the guinea pig, but is closer to that of the mouse.

We can, therefore, expect that streptomycin would be a more important bactericidal drug in human disease than in the disease of mice. In the early stage of killing of actively growing bacilli, pyrazinamide would be considerably less effective than it is in the mouse. These expectations are illustrated diagrammatically in figure 3.

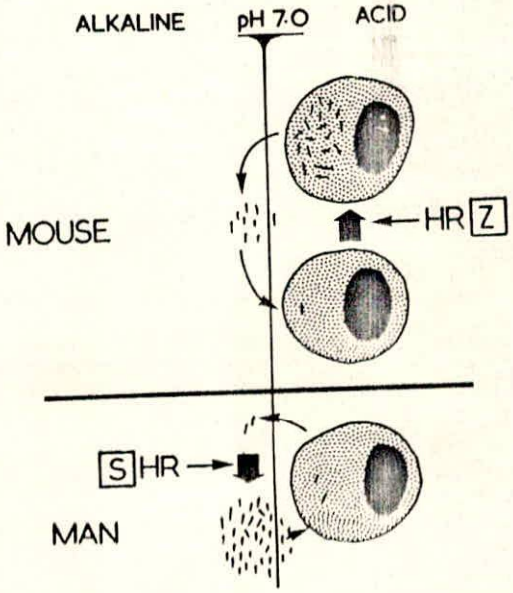

Fig. 3. Activity of drugs in the early stages of chemotherapy in mouse and in man. The figure illustrates diagrammatically that pyrazinamide acts largely on intracellular organisms in an acid medium; streptomycin, on extracellular organisms in an alkaline medium. The broad arrows indicate the principal sites of bacillary multiplication, intracellular in the mouse and extracellular in man. H = isoniazid; R = rifampicin; Z = pyrazinamide; S = streptomycin.

TABLE 13

STERILIZING ACTIVITY OF DRUG COMBINATIONS IN MURINE TUBERCULOSIS

Drugs	Duration of Treatment (months)	Lung/Spleen Culture	Relapse After Chemotherapy	Study
INH + ethambutol	4–6	3+	–	Grumbach (112) Grumbach *et al.* (113)
INH + streptomycin	4–6	2+	–	Le Lirzin (114)
Streptomycin + rifampin	4	1+*	–	Le Lirzin (114)
INH + rifampin †	4–6	0	1+	Grumbach (101) Grumbach *et al.* (113) (116) Le Lirzin (114) Batten (115) Kradolfer and Schnell (117)
INH + rifampin + streptomycin	4–6	0	1+	Grumbach *et al.* (114)
INH + streptomycin	16–18	1+	2+	Grumbach *et al.* (114)
INH + pyrazinamide	3	0†	2+	McCune *et al.* (45) Grumbach (103)
INH + pyrazinamide	6	0	0	McCune *et al.* (118)
Streptomycin + pyrazinamide	3	0†	–	McCune *et al.* (45)

*Two of 8 lungs each yielded 1 colony.

†Positive cultures of spleen from 0 of 77 mice after INH plus pyrazinamide, and from 1 of 8 mice after streptomycin plus pyrazinamide.

Thus, the main agents responsible for the early kill would be INH, rifampin, and streptomycin, with streptomycin affecting only part of the population. As noted earlier, there is no demonstrable early bactericidal synergism between INH and rifampin, but some synergism exists between INH and streptomycin. Furthermore, INH and pyrazinamide were found to be antagonistic in the early stages of treatment in the mouse. It can be concluded that giving a multiplicity of drugs at the start of treatment should be of relatively little extra benefit in killing actively growing, drug-susceptible organisms, although the results are probably quite different for such combinations considered in their capacity as sterilizing drugs.

Sterilizing activity of drugs. Some of the findings in the chemotherapy of murine tuberculosis that are of particular relevance to the sterilizing activity of short-course regimens are summarized in table 13. In these experiments, mice were treated for long periods with drug combinations, and when culture of the lung yielded no apparently viable bacilli at the end of chemotherapy, survivors were observed for relapse for several months. Comparisons between the top one half of the table, derived mainly from work at the Pasteur Institute, and the bottom one half, derived mainly from the earlier studies at Cornell University, are somewhat uncertain, because the experimental conditions were different. Conclusions that can tentatively be drawn include the following. (*1*) Isoniazid in combination with ethambutol was the least bactericidal regimen, an expected finding in view of the essentially bacteriostatic action of ethambutol in the dosage used in mice and in man. (*2*) Isoniazid plus rifampin was the most effective sterilizing combination. Because streptomycin plus rifampin reduced lung counts to a substantially lower level than did INH plus streptomycin, rifampin appears to be the main agent responsible for the sterilizing activity. That rifampin has a special role in sterilizing was also shown by the experiment of Kradolfer and Schnell (117), who treated mice with INH plus rifampin for various periods, followed by rifampin, INH, or streptomycin alone; rifampin was the only drug capable of sterilizing the lungs and preventing ultimate relapse. Nevertheless, rifampin was only effective when given in a dosage that produced serum concentrations approximately 3 times higher than those usually achieved in man. Streptomycin plus rifampin (table 13) was a little less effective than INH plus rifampin, demonstrating that there is some synergism between INH and rifampin. The low efficacy of streptomycin in the murine model is shown by this comparison and also by the finding that the addition of streptomycin to the

combination of INH plus rifampin produced no additional benefit. (3) Pyrazinamide in very high dosage was of exceptional value as a sterilizing drug. The absence of any relapses after 6 months of INH plus pyrazinamide, compared with their occurrence after the same duration of INH plus rifampin, together with the slight superiority of streptomycin plus pyrazinamide over streptomycin plus rifampin, suggests that pyrazinamide may be superior to rifampin in the mouse.

It is of interest to note that the Cornell group found that 4 weeks of INH followed by 8 weeks of pyrazinamide were as effective as 12 weeks of both drugs together from the start of chemotherapy. This finding emphasizes the sharp distinction between the initial kill and the sterilizing period that was so beautifully demonstrated in their murine model. A clear temporal distinction between these 2 phases is much less likely to be true for the more heterogenous conditions in human lesions. Thus, the sterilizing activity of drugs may be more important in the early stages of chemotherapy in man than in the mouse. It should also be noted that obtaining a negative culture from patients, which often occurred at 1 or 2 months, may well involve sterilizing activity as well as early kill, again suggesting that absence of a well-demarcated biphasic response.

When the conclusions drawn from the murine model are applied to human short-course chemotherapy, it is clear that the 3 key drugs are INH, rifampin, and pyrazinamide. Pyrazinamide should be relatively less effective in man than in the mouse. On the other hand, streptomycin, of very limited value in the mouse, should provide slight additional benefit in man.

Special roles of rifampin and pyrazinamide. There are reasons, derived from experiments on pulsed exposures of *M. tuberculosis* to drugs, to suggest that rifampin and pyrazinamide have especially important, but different, bactericidal activities against bacilli that are nearly dormant. In these experiments, cultures in the logarithmic phase of growth were exposed to pulses lasting 6 hours, 24 hours, or longer (106, 119, 120). Bactericidal activity was accompanied by a period after the pulse during which growth did not occur (lag period). The results of experiments with bactericidal drugs are summarized in table 14. Isoniazid was only bactericidal after exposures of 24 hours or more, although the effects of several shorter exposures were cumulative (121). The duration of the lag period after an exposure was also long.

Streptomycin, rifampin, and pyrazinamide were the only drugs capable of inducing lag after an exposure of only 6 hours. In the case of streptomycin, induction of lag by a short exposure was subsequently found to be highly dependent on the ionic strength of the medium used to wash the bacilli after exposure to the drug; it is, therefore, uncertain whether the *in vitro* experimental conditions truly represent those in lesions. Rifampin appears to be unique among the remaining drugs in the speed with which its bactericidal activity starts. Thus, reduction in ribonucleic acid formation was evident within 20 minutes of exposure to a realistic concentration (56). Although rifampin is no more effective against slowly growing organisms than is INH (55, and Awaness, A. M., Dickinson, J. M., and Mitchison, D. A.: Unpublished data), we can imagine that it is particularly lethal to bacilli in human lesions that have resist-

TABLE 14

LAG PERIODS AFTER PULSED EXPOSURES TO BACTERICIDAL DRUGS (106, 119, 120)

Drug	Drug Concentration (μg/ml)	Lag period (days) after exposure for	
		6 hours	≥ 24 hours
INH	1	0	6–9
Streptomycin	5	8–10	8–10
Rifampin	0.2	2–3	2–3
Pyrazinamide	50	5–40*	> 40*
Ethionamide	5	0	10
Cycloserine	100	0	4–8
Ethambutol	10	0	4–5
Capreomycin	10	5	6

*Dependent on pH of medium.

ed drug action because they are dormant and then start to grow for a short period of, perhaps, a few hours, too short a time for them to be killed by INH. It should, however, be noted that rifampin is only bactericidal at high concentrations, and that recovery from an exposure is also very rapid (56, 106). Thus, rifampin may only be bactericidal in patients receiving therapy during certain periods of the day, when tissue concentrations are at their peak.

In the case of pyrazinamide, the bactericidal activity and the length of the subsequent lag period increase as the growth rate of bacilli is progressively slowed by increasing acidity of the culture medium (table 15) (122). It is remarkable how even a brief exposure inhibited for long periods the subsequent growth of bacilli that could only just multiply in drug-free acid medium. Hence, it might be a particularly effective drug against organisms that grow very slowly, and are therefore relatively immune to the bactericidal activity of other drugs.

TABLE 15

LAG PERIODS AFTER PULSED EXPOSURES TO 50 μg OF PYRAZINAMIDE PER ML (122)

pH of Medium *(units)*	Rate of Growth *(Log_{10} viable units/day)*	Lag Period *(days)* After Exposure for	
		6 hours	96 hours
6.2	0.36	0	9
5.8	0.27	0	72
5.6	0.14	40	> 76

In summary, rifampin and pyrazinamide may have special activity against nearly dormant organisms, rifampin against those going through a temporary period of active metabolism at the time that high intralesional drug concentrations are attained; pyrazinamide, against those with more persistent, but very slow, growth due to acid inhibition. Isoniazid would provide a "back-stop" for organisms that grow slowly but continuously, irrespective of the environmental pH. Because the bacilli concerned would be different, strong synergism would be expected between these 3 drugs to provide the most effective elements of a sterilizing regimen. Because conditions of pH, O_2 supply, and, indeed, the basic immune process are likely to be more heterogenous in man than in any conventional animal model, this synergism should be more apparent in clinical trials than in experimental murine tuberculosis. The relevant experiments have not been done in animals, but the results of the second East African study certainly suggest that the combination of INH, rifampin, pyrazinamide, and streptomycin is of remarkably high efficacy. We have yet to see whether streptomycin contributes an element of any real importance to this combination. It should also be noted that the suggested synergism is effective against physiologic heterogeneity in the bacillary population arising from their environment, whereas the type of synergy conventionally associated with combined chemotherapy is effective against genetic heterogeneity (presence of resistant mutants) in the population.

In this section we have presented a series of hypotheses in an attempt to unify the findings of many workers in the field of experimental chemotherapy. These hypotheses will stand or fall according to whether they are supported by additional experimental work and whether they lead to predictions validated by the results of further clinical trials. They emphasize the importance of studies on the immune process in experimental animals and in man, particularly on how the growth of bacilli is controlled. For instance, is the environmental pH really as decisive as it seems to be in murine tuberculosis, and what is the mechanism, probably different, that operates in the guinea pig and in man? Is the physiologic state of bacilli in man as heterogenous as has been suggested? Predictions that might be tested in clinical trials include the following. (*1*) The dose of rifampin may be of considerable importance, because a larger dose would lead to higher and more prolonged peak concentrations, which could kill a larger proportion of the organisms in a semidormant state. (*2*) Given quantities of rifampin and pyrazinamide may be at least as effective if given after the initial kill than if given from the start of chemotherapy. (*3*) It should be possible to develop short-course regimens that are effective in preventing relapse when given for periods even shorter than 6 months. The rational planning of further clinical trials must, in any case, be supported by theory, and it is this that we have attempted to provide.

Other Workers' Findings

In 1973, Poppe de Figueiredo and associates (123) studied the combination of INH plus rifampin plus ethambutol for 6 months, with one half of the patients in hospital for the full 6 months, one half, for 2 months, followed by 4

months of self-administered, ambulatory chemotherapy. After 24-month follow-up, there were 3 bacteriologic relapses among 89 patients with fully susceptible organisms and 1 among 13 patients with INH-resistant organisms pretreatment. Although the intensity of bacteriologic investigation was low, the findings nevertheless confirm those from East Africa, both for susceptible and resistant infections.

Brouet and Roussel (124), in a cooperative investigation involving 13 centers in France, studied rifampin plus INH for 6, 9, and 12 months, supplemented in the first 3 months, at the choice of the physician in charge, by either streptomycin daily or ethambutol daily. Two years after the start of chemotherapy, there was only one certain bacteriologic relapse in the 18-month follow-up among 59 patients in the 6-month series, none of 62 in the 15-month follow-up of the 9-month series, and none of 49 in the 12-month follow-up of the 12-month series. Thus, all the regimens were effective.

Although these reports confirm the effectiveness of short-course chemotherapy in 2 other areas of the world, they contribute relatively little to our understanding of the underlying mechanisms. The assumption has widely been made that because rifampin may be a uniquely bactericidal drug, it must therefore not only be included in all short-course regimens, but it must also be given for the full duration of chemotherapy. It is clear from the studies in East Africa and Hong Kong that adherence to this assumption is no longer tenable, and also that it narrows the exploration of possible approaches to short-course chemotherapy.

A British Thoracic and Tuberculosis Association study (125) is investigating rifampin plus INH for 6 or 12 months, supplemented by streptomycin or ethambutol for the first 8 weeks in patients with pretreatment cavitation less than 2 cm in diameter; 9-month and 18-month durations are being compared for patients with more extensive cavitation.

A study by Leston and co-workers (126) is of particular interest in relation to the bactericidal hypothesis we have put forward. They reported preliminary findings of a study in which all the patients are being treated for 2 months with daily INH plus rifampin plus ethambutol, then one-half, by random allocation, with 10 mg of rifampin per kg alone daily for 4 months and one-half, with 8 mg of INH per kg alone daily. Although it is too early to report relapse rates, the findings will be especially interesting, because they will provide a direct comparison of the relative effectiveness of INH alone and rifampin alone when used in the continuation phase of short-course chemotherapy of 6-month duration.

Other Possible Combinations for Short-Course Chemotherapy

The question arises, what drugs would it be fruitful to investigate in short-course regimens other than those based on INH plus streptomycin plus rifampin, or INH plus streptomycin plus pyrazinamide? There is, of course, particular interest in regimens that do not involve rifampin because of the yet unsolved problem of adverse reactions to this drug when given in intermittent regimens, and because of its cost. A study in Hong Kong is relevant (127, 128) because it is informative concerning PAS as the third drug when combined with streptomycin plus INH. Patients were allocated this triple regimen either for 3 or for 6 months daily; every dose of the oral medicament was given under supervision for the 6 months, followed by self-administered INH plus PAS for 18 or 24 months. Among 184 3-month, triple-regimen patients, there was a 5 per cent bacteriologic relapse rate during chemotherapy, and a 3 per cent relapse rate after stopping in patients who had fully susceptible strains on admission (unpublished data). The corresponding relapse rates in 186 patients on the 6-month triple regimen initially were 5 per cent and 2 per cent, respectively. Also, there was good evidence from monitoring the drug intake by urine testing that relapses while the patients were still on the regimen resulted from irregularity in self-administration of the 2-drug oral regimen in the continuation phase. Hence, it can safely be assumed that a 6-month, short-course regimen of streptomycin plus INH plus PAS would have had an even higher relapse rate. Thus, it seems wisest to regard this triple combination daily for 6 months as likely to have a relatively unsatisfactory relapse rate when compared with the triple-drug regimen containing rifampin (SHR) of the 2 East African studies.

A point of special interest arises in relation to the continuation phase of the SHRZ/TH regimen, in which phase only one bactericidal drug, INH, was used and which, nevertheless, appeared reasonably effective. It is likely that the combination of PAS plus INH daily (also

containing the same single bactericidal drug), or even INH alone would be as good in the continuation phase. There is, furthermore, evidence that when high-dosage INH plus PAS is given twice per week, the rate of sputum conversion is as rapid as when the combination is given daily in standard dosage, and it is less toxic (129). It is tempting to speculate whether the twice-weekly regimen of INH and PAS, containing, as it does, the single bactericidal drug, INH, in high dosage, but intermittently, would be as effective as the low daily dosage of the same bactericidal drug. It is already established that the $S_2H_2Z_2$ intermittent continuation regimen, the twice-weekly 2-bactericidal drug regimen, is effective. A further possible oral 2-drug regimen is INH plus pyrazinamide, which might well be better than INH plus thiacetazone or INH plus PAS.

Ethambutol has been used with INH and rifampin in short-course studies. There is some justification for its use to prevent the emergence of rifampin-resistant organisms in patients with strains initially resistant to INH; however, in the currently used dosage of 12 to 25 mg per kg, experimental studies in the mouse (112), and in the guinea pig (120) suggest that it is only bacteriostatic, and in combination with INH does not increase the speed with which viable bacilli are eliminated from the lungs. When larger doses of ethambutol (45 to 90 mg per kg) were given twice weekly or once weekly with INH for 1 year to patients at the Chemotherapy Centre, Madras, the subsequent relapse rates were much higher than those encountered after courses of standard chemotherapy of the same duration, showing that even if larger doses are used (albeit intermittently), ethambutol remains a bacteriostatic drug (130).

Experimental work in the mouse suggests that ethionamide plus rifampin is as effective a sterilizing combination as INH plus rifampin (101). Because of the high rate of adverse reactions to ethionamide, this finding has, in practice, no immediate application in primary chemotherapy. It might, however, be relevant in some circumstances in retreatment regimens for patients with organisms initially resistant to INH.

The importance of pyrazinamide as one of the 2 drugs with a special sterilizing activity suggests that further experimental work should be done to search for other drugs with similar properties (131) and to explore the mechanism of action of pyrazinamide itself.

The Influence of Initial Drug Resistance on Short-Course Chemotherapy

In conventional chemotherapy, there are 2 reasons for giving an initial intensive phase of treatment with 3 drugs. (*1*) In patients with initially susceptible organisms, the likelihood of the emergence of drug resistance is decreased (23), especially when it is proposed to give INH with a weak drug in the continuation phase. (*2*) It also improves the chances of eliminating resistant bacilli present at the start of treatment. A triple-drug regimen is usually effective against strains resistant to only one drug because the bacilli will still be acted on by 2 drugs, whose effects are unimpaired. It may also be effective because only a proportion of the bacilli in the strain are resistant to 2 or all 3 drugs. If the hypothesis that 2 bactericidal drugs are important to the effectiveness of short-course chemotherapy is correct, it is evident that in the presence of pretreatment drug resistance, the organisms would not usually be exposed to 2 bactericidal drugs, unless at least 3 bactericidal drugs are included in a short-course regimen. Rifampin or pyrazinamide or both drugs must clearly be included in view of their special sterilizing activity in animals and in man. Luckily, primary resistance to either of these drugs is still very rare. These considerations must be borne in mind when planning studies of regimens for use in areas with high prevalence of initial drug resistance, especially if intermittent regimens are under consideration.

In organizing chemotherapy programs with regimens of conventional duration, there are 2 main alternative approaches to initial drug resistance. One is to adjust the regimen of chemotherapy for the individual patient on the basis of pretreatment susceptibility tests. The other is to ignore the pretreatment susceptibility of the strains and give a regimen of chemotherapy known to be able to achieve quiescence of the disease in at least a proportion of patients with resistance to one or more relevant drugs; retreatment with a reserve regimen is started when patients remain consistently bacteriologically positive (127, 128). In technically advanced countries, it is common to find that undisclosed acquired resistance is virtually nonexistent and that the prevalence of primary resistance is low (often less than 5 per cent). It has been pointed out (23) that the benefit from routine pretreatment susceptibility testing under such circumstances is very limited.

At least 95 of each 100 patients will have fully susceptible organisms, and the tests will therefore in no way alter or improve their chemotherapy. More than three fifths of the remaining 5 per cent of patients will have resistance to a single drug, and it has long been recognized that this has very little influence on prognosis with standard triple regimens of long-term chemotherapy, for example, streptomycin plus INH plus PAS. Less than 2 per cent of all patients will have strains resistant to 2 or all 3 drugs. Thus, only in this latter, very small proportion of patients is there potential benefit from pretreatment susceptibility tests. It has been estimated on a sound basis (127, 128) that in Britain, only 1 of each 200 bacteriologically positive patients would benefit from the routine use of accurate pretreatment susceptibility tests if the regimen being prescribed is the standard regimen described. The benefit to this patient would be that a reserve regimen would be introduced sooner, leading to the more rapid achievement of quiescent disease. The same considerations apply to North America, where the prevalence of initial drug resistance is similar (132–141).

It has also been demonstrated (127, 128) that even in an area where there is a high level of initial resistance (i.e., both primary and concealed acquired), the contribution it makes to failure may still be relatively small in comparison with the proportion of failures that result from patients with fully susceptible organisms who attend regularly, but become irregular in self-administering their oral drugs. Moreover, stopping attending for treatment altogether can be an even greater threat (3, 142).

Consider now short-course chemotherapy against this background. If the traditional practice of the technically advanced countries of starting chemotherapy and adjusting the regimen in the light of susceptibility tests is followed, there is no reason why the results should be any worse in short-course chemotherapy than with regimens of standard duration; however, for patients on short-course regimens whose chemotherapy is changed, the retreatment regimen may have to be given for the usual longer period.

If, in fact, the rate of initial resistance is low, it would be rational and operationally much simpler to ignore such tests and to wait until patients fail to respond to their short-course regimen, then retreat them with a regimen of conventional duration. The evidence already available suggests that a substantial proportion of patients with resistant strains will respond satisfactorily to short-course regimens.

Given a standard level of efficiency of organization of programs, however, the over-all success achieved by the currently available short-course regimens, without pretreatment susceptibility testing, is potentially lower in areas where the prevalence of resistance to INH, whether alone or with other drugs, is high. The important need for areas with high rates of initial drug resistance is the development of regimens that will still prove effective without reference to the pretreatment susceptibility of the strain in the individual patient. This is especially so because it is in the developing countries that not only may high rates of initial resistance be present, including high rates to 2 (table 16) and even 3 standard drugs, but susceptibility testing may not be available at all or be unreliable, or, at best, reliable testing may be limited to 1 or 2 laboratories. Hence, finding suitable

TABLE 16

LEVELS OF INITIAL DRUG RESISTANCE IN HONG KONG, EAST AFRICA, AND BRITAIN IN RECENT STUDIES; TESTS WERE DONE IN BRITISH MEDICAL RESEARCH COUNCIL OR ASSOCIATED REFERENCE LABORATORIES

Drug	Hong Kong Short Course (1974) (%)	East African Short Course		Chemotherapy Study in Britain (1973) (%)
		First (1972) (%)	Second (1974) (%)	
Streptomycin alone	9	1	3	2.1
INH alone	5	7	5	1.5
Both drugs	8	1	1	0.4
Total resistance	21	9	9	4.1
No. of patients in study with susceptibility tests	586	1,073	883	467

regimens that can be effective without resort to routine susceptibility testing is of special importance. In all research into short-course chemotherapy, in developing countries and in technically advanced countries also, it is important to study the response of patients with pretreatment resistant strains, for without such knowledge, only a partial evaluation of a regimen will be obtained.

The Implications of Short-Course Chemotherapy

What are the implications of short-course chemotherapy under program conditions, assuming that we can expect to cure almost all patients within a period of 9 months or less? (*1*) The total delivery of health services in terms of patient attendance, supervision of the actual ingestion of drugs, routine investigation of the patients, are all curtailed. Less total quantity of drug is used, and so the cost is lowered. In technically advanced countries, the total demands made on the resources of the health service should be substantially reduced. In the developing countries, limited resources can be put to better use.

(*2*) It is self-evident that there will be less chronic drug toxicity. Although much of the drug toxicity to standard regimens occurs in the early months and even weeks of treatment, particularly the hypersensitivity reactions, adverse reactions continue to arise for the first time even in the later months of long-term chemotherapy (143). A shortening of the total duration would therefore reduce the incidence of drug toxicity.

(*3*) Early default from treatment is less hazardous to the patient. This is because the patients who discontinue their treatment in the early months are more likely to be culture negative and remain permanently so than similar patients on standard chemotherapy; however, to obtain more precise facts on this point, it is important when undertaking research into short-course chemotherapy to make every effort to obtain a bacteriologic follow-up for patients who discontinue their regimen prematurely.

(*4*) More effort can be concentrated on ensuring that the patients continue to attend and actually remain on their chemotherapy for the full period prescribed.

It is already being stated in some circles that short-course chemotherapy is of little importance in developing countries, because it cannot appreciably influence the common finding that within the first 2 or 3 months of chemotherapy, as many as 30 per cent of patients stop attending completely. It is argued that this is just as likely to happen with a 6-month regimen as with a 12- or 18-month regimen. This view, however, represents a failure to appreciate the full implications of short-course chemotherapy. Currently, a patient on standard chemotherapy in the technically advanced countries is expected to remain under treatment for at least 18 months and, in developing countries, for at least 12 months. When, as is almost always the case, a patient feels well and has, within a month or two of starting treatment, lost all symptoms of his disease, he faces the prospect of having to continue to cooperate in treatment, not only by attending the treatment services, but also by ingesting his medicament regularly for many months to come, medicament which he may find is unpleasant or produces minor side effects. The demands made on a symptom-free patient are much less if he knows that to be cured requires cooperation for only a few more months. There can be little doubt that adequate explanation of the new type of therapy, its short duration, and the certainty of success, combined with the improved organization that will result from concentrating the available resources on a short-course regimen, could well lead to a dramatic improvement in cooperation under program conditions. Adequate explanation would be necessary at the start of treatment and would need to be repeated if and when the patient showed signs of irregularity in attendance, or failure to ingest his medicament regularly, if it is to be self-administered.

(*5*) Routine follow-up after the end of chemotherapy can be drastically curtailed, or abandoned altogether. We have followed with great interest recent articles and correspondence (144–150) in the American Review of Respiratory Disease concerning the duration of follow-up of patients who have completed their treatment. Also, early in this year, the U. S. Public Health Service Center for Disease Control (151) recommended discharging patients with tuberculosis who complete adequate drug therapy from medical care, and Dr. Reichman moderated a panel discussion on the topic at the May 1974 meeting of the American Thoracic Society in Cincinnati (152). The same point has recently been made in a survey of patients treated in Scotland (153). Regular long-term follow-up, as undertaken in the prechemotherapy and early years of the chemotherapy era, was practiced

because it was undoubtedly necessary, for relapse was common. We have, however, pointed out for some years (19) that, because the relapse rate is very low when good regimens of chemotherapy are given for an adequate period of time and under good supervision, long-term follow-up is illogical.

The prospect now is that with short-course chemotherapy, it will be even easier to ensure that a patient really does complete a full course of excellent chemotherapy. Hence, the likelihood of relapse will be even less than in the past. Because a high proportion of relapses arise within 6 months of stopping chemotherapy, and most of them within 3 months, the maximal follow-up that even the greatest caution would indicate might be 6 months; however, with increasing experience and confidence in short-course chemotherapy, even such a short follow-up would be likely to be abandoned, always provided that the supervision of chemotherapy remains efficient. The prospect that we visualize is that at the end of short-course chemotherapy, it will be possible to discharge the patient with advice to present himself again for diagnosis if respiratory symptoms recur. If it is found that the cause is a relapse of tuberculosis (or a reinfection), he can be treated with an appropriate regimen.

Conclusion

From the evidence reviewed in this report, there can be no doubt that it is just a matter of time before the standard durations of chemotherapy in general use, both in the technically advanced and developing countries, will be short. Although in the light of current knowledge this is already practicable, there are many problems still to be solved, especially for the developing countries. These include the need to find regimens that can be applied with uniform success in areas with a high prevalence of initial drug resistance, without reference to susceptibility tests. There is much to discover concerning the role of an initial intensive phase and of regimens of chemotherapy both intermittent from the start and in the continuation phase. It is important to discover how little rifampin is needed in short-course chemotherapy and how best to use that little amount, and to explore alternative regimens that do not include rifampin at all for use in the many developing countries where the cost of drug is, and is likely to remain, an important consideration for many years to come. There remains much to learn concerning the role of pyrazinamide. The extension of the principle of short-course chemotherapy to failure regimen chemotherapy also merits consideration. The desirability of planning studies on a sound scientific basis, rather than selecting regimens empirically and without consideration of the possible underlying mechanisms, cannot be overstressed.

Finally, the practical problems involved in the application of short-course chemotherapy under program conditions, particularly in developing countries, is a subject of outstanding importance.

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