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RECENT CONTROLLED CLINICAL TRIALS IN PULMONARY TUBERCULOSIS

by

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During the past five years controlled clinical trials in pulmonary tuberculosis have been largely directed towards solving one major problem — making effective treatment easier for the patients.

Two factors limit the efficacy of treatment: the need to co-operate in drug administration and the need to continue co-operation for long periods. The effects of these limiting factors can be reduced in several ways.

First, the co-operation of patients can be improved by explanation and exhortation, by general health education, by better trained staff and by eliminating all unnecessary work in clinics so that the staff can give more time to each patient. The easier the treatment is for the patient the better he will co-operate. Long journeys to clinics, long waits in queues, inefficient and unsympathetic service and large numbers of tablets to be swallowed each day will not help patients to maintain regular treatment.

Secondly, co-operation can be monitored. By this is meant detecting irregularity of drug administration so that the necessary action can be taken to achieve regularity. This has been attempted in the case of self-administration of drugs by urine tests and surprise

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visits to the patients' homes to check that the correct numbers of tablets have been taken. It is, I think, of only small value. If the drugs are not administered by the patients but by some other person there is a complete check on regularity. Regularity will not necessarily be improved; but irregularities will be known and action can be taken.

Hence the concept of supervision of chemotherapy regimens.

If it is necessary to give drugs daily, a supervised regimen becomes difficult for the patient; this may lead to even more irregularity or complete cessation of treatment. A practical supervised regimen requires, in most instances, a non-daily regimen — an intermittent regimen. The two concepts — supervision and intermittency — are quite separate. A daily regimen can be supervised and an intermittent regimen can be self-administered. The regimens that have been explored by controlled clinical trials have been both supervised and intermittent.

Although intermittent regimens were first used in order to make supervision easier, there is, in fact, good experimental evidence to support them in the case of some of the antituberculosis drugs. Indeed, in the case of three of them — isoniazid, rifampicin and pyrazinamide — there is evidence that in certain doses they are more effective given at intervals longer than one day.[1]

The second limiting factor is the length of treatment. The minimum duration with the old regimens has been at least one year. This is far too long for many patients to continue co-operating either in taking drugs at home or in attending a clinic for supervised drug administration. The duration of treatment must be considerably reduced.

Successful treatment has two phases. In the first, the initial 'kill', the drugs kill tubercle bacilli that are dividing. But some are not; they are in a dormant state. The long period of treatment has in the past been necessary in order to suppress bacterial multiplication and to kill those bacilli that escape the suppression. To reduce the duration of the suppression phase it is necessary to kill as many as possible of the bacilli during the 'killing' phase. To do this requires highly bactericidal drugs. Those with the greatest killing power are rifampicin, isoniazid and the combination of streptomycin and pyrazinamide. Thus, these are the drugs most likely to be of value in reducing the period of treatment by increasing the efficacy of the 'killing' phase.

The objectives are reduction of the frequency of drug administration — to make supervision easier — and shortening of the total duration of treatment. Rifampicin, isoniazid and streptomycin with pyrazinamide are likely to succeed in both.

Controlled clinical trials have, therefore, been mainly concerned during the past five years with exploring the possibilities of regimens including some or all of these drugs.

Supervised intermittent regimens

The high efficacy of streptomycin and high-dose isoniazid was reported in 1964[2]. It is well-known. 91 per cent of patients with initially sensitive cultures had quiescent disease at one year. Trials reported during the past five years have confirmed its efficacy and explored the value of an initial intensive phase.

In 1970 the International Union against Tuberculosis reported a trial of this regimen with a four-week initial daily phase of streptomycin, isoniazid and thiacetazone[3]. After a year's treatment 93 per cent had quiescent disease. In Czechoslovakia a trial with a three-month's daily phase of streptomycin, isoniazid and PAS produced 100 per cent quiescent[4]; and the results were similar when the daily phase was reduced to six weeks[5]. With the same regimen in Singapore 98 per cent quiescence was reported[6]. In Great Britain a controlled trial was reported in 1973: the three-drug regimen for the first three months followed by twice-weekly streptomycin and isoniazid produced 95 per cent quiescence[7].

The figures of quiescence reported in these trials should not be compared with each other. There were differences, among other factors, in the definition of quiescence used. It is not known whether the initial phase with three drugs does, in fact, improve results in patients with sensitive cultures; for no direct comparison of regimens with and without a daily phase has been made.

The results in patients with initially resistant cultures have, as expected, been less good; and in these an initial three-drug phase is probably important. Adding a third drug — PAS or thiacetazone — in both the initial daily phase and the intermittent phase does not improve the results in patients with sensitive cultures; but there is a suggestion that it may do so in those with resistant cultures, but at the cost of increased toxicity and unacceptability of the regimen[8].

As the twice-weekly regimen has been so satisfactory it was reasonable to increase the interval further, to once a week. Using the same doses of streptomycin and isoniazid as in the twice-weekly regimen, the results were much worse[9]. Only 66 per cent had a favourable response. The response was greatly influenced by the rate of inactivation of isoniazid. With slow inactivators 76 per cent had a favourable response, but only 56 per cent of rapid inactivators. Adding pyrazinamide made no difference. When the streptomycin and isoniazid were given daily at the start the response was improved in both groups, to 95 per cent in slow inactivators but to only 76 per cent in rapid inactivators. Neither increasing the dose of isoniazid nor adding PAS improved the results[10].

A slow-release form of isoniazid may make the once-weekly regimen efficient in rapid inactivators. It can bring the serum concentrations and durations of coverage up to those

found with ordinary isoniazid in slow inactivators[11]. But trials of its therapeutic efficacy have not been completed.

Other drug regimens have been tried in supervised intermittent regimens. Ethambutol and isoniazid once or twice a week after an initial two weeks supplement of streptomycin is not highly effective - especially in rapid inactivators [12]. But a similar regimen with PAS instead of ethambutol twice weekly gave results similar, though probably slightly less good, to those obtained with isoniazid and PAD daily [13]. The twice weekly regimen was much more acceptable, only 6% complaining of side-effects compared with 21% on the daily regimen. Thiacetazone and isoniazid after eight weeks supplement with streptomycin have also given good results [14]. An orally administered twice-weekly regimen has some practical advantages in certain circumstances.

Rifampicin is another drug that experimentally appears suitable for intermittent regimen. In Hong Kong a trial was done in patients with cultures resistant to isoniazid[15]. They received either rifampicin and ethambutol daily, rifampicin and ethambutol twice or once weekly, and a fourth group had the weekly continuation phase supplemented by a daily phase for two months. The results were less good in the twice-weekly (80 per cent favourable) and once-weekly (82 per cent favourable) than in the daily group (89 per cent favourable). But the once-weekly regimen produced 91 per cent favourable results when the drugs were given daily for the first two months.

The disadvantage of intermittent rifampicin is the frequency of unpleasant side-effects. Febrile episodes ('flu-like) occurred in 54 per cent of those given weekly doses from the start[16]. These are mediated by an immune mechanism and rifampicin-dependent antibodies can be detected in the serum[17]. An attempt to overcome them by giving small doses of rifampicin daily in addition to the large weekly doses has not been entirely successful[18].

In Poland[19] good results were also reported with ethambutol and rifampicin either once or twice weekly after an initial period of three months daily treatment. Twice weekly gave no better results than once weekly. Toxicity was much less than in the Hong Kong trial — only 18 per cent of 'flu episodes compared with 35 per cent. A once-weekly regimen has also been reported on favourably from the German Democratic Republic[20] and from Singapore[21]. In Singapore a lower dose of rifampicin — 600mg — was found to be as effective as 900mg in the twice-weekly regimen.

It should be noted that none of the trials has shown that a supervised intermittent regimen gives <u>better</u> results than giving the same drugs in a daily unsupervised daily regimen in <u>co-operative</u> patients. There is nothing magical about supervision or intermittency. Both are merely ways of trying to obtain regular drug administration. A supervised inter-

mittent regimen is valuable in certain types of patients and in certain environments. With other patients and other environments supervision and intermittency are unnecessary or unobtainable. One regimen should not be used to the exclusion of all others.

Shortened regimens

The British and East African Medical Research Councils carried out a trial of a six-month regimen of rifampicin, isoniazid and streptomycin given daily.[22,23,24] The patients were followed up for two years after the end of treatment. The results were compared with those of the standard regimen of isoniazid and thiacetazone for eighteen months with daily streptomycin for the first eight weeks. Of those with a favourable status at the end of treatment in both regimens — almost all those who completed treatment — only 3 per cent had relapsed after thirty months of observation from the start of treatment. Thus the six-month rifampicin regimen had produced as good, and as lastingly good, results as the eighteen-month regimen. Moreover, almost all who relapsed did so within the first six months after stopping treatment and had sensitive cultures, so that they could be retreated with the same drugs.

This particular six-month regimen is, of course, not a practically useful one for many countries, requiring daily injections and costing much money, as rifampicin is a very expensive drug. The next step, therefore, was to investigate whether streptomycin was necessary, whether the duration of rifampicin treatment could be reduced, and whether the second phase of treatment could be given with cheaper drugs or with a twice-weekly regimen which could be adequately supervised.

In the first trial a third regimen had been used: isoniazid with streptomycin and pyrazinamide. These latter two drugs together form a bactericidal combination. The results were less good than the rifampicin regimen — 8 per cent relapses — but they were still quite encouraging. In the second trial, therefore, pyrazinamide was added to strengthen the bactericidal effect.

The regimens were: SHR daily, HR daily, SHRZ for eight weeks followed by TH or S2H2. The relapse rates six months after treatment stopped were: SHR - 2 per cent; HR - 5 per cent; SHRZ/TH - 6 per cent; SHRZ/S2H2 - 4 per cent. The differences were not significant. Further observation is, of course, necessary. But we can tentatively conclude that, in patients with initially sensitive cultures 1) streptomycin is unnecessary if rifampicin and isoniazid are given daily for six months; 2) rifampicin need be given for only eight weeks with streptomycin and pyrazinamide if 3) for the remaining four months isoniazid and thiacetazone are given daily or streptomycin and isoniazid are given twice a week[25].

Similar rifampicin regimens have been investigated in France, Great Britain and Brazil. In France only one certain bacteriological relapse was observed during the eighteen-month follow-up of 59 patients treated for six months with rifampizin and isoniazid with either streptomycin or ethambutol for the first three months. With the period of treatment extended to nine months no relapses were observed[26]. In Great Britain only three per cent relapses were reported at eighteen months after a similar regimen given for six months; and no relapses had been observed after nine months treatment[27]. In Brazil 3 per cent relapses were observed after two years follow-up after six months treatment with rifampicin, isoniazid and ethambutol[28].

As the degree of supervision of drug administration and the criteria for assessing relapses were different in these trials the results should not be uncritically compared.

All that can be stated at present is that rifampicin-containing regimens of six or nir months duration can be highly effective in producing lasting non-infectiousness of even far-advanced pulmonary tuberculosis.

But rifampicin is expensive. Need it be used at all? In Hong Kong a trial was carried out to explore the possibilities of streptomycin plus pyrazinamide as one bactericidal agent and isoniazid as the other[29].

Three regimens were given for either six or nine months. In one, all three drugs were given daily. In another, they were given three times a week, and in the third twice a week. Observation has so far extended to only six months after the end of treatment — the period during which most relapses are likely to occur. When given for only six months the relapse rates were high (13 - 18 per cent). But with nine months treatment the relapse rates were low (3 - 4 per cent). The three times weekly regimen for nine months was as good as the daily regimen. But the twice-weekly regimen appeared less good; for, although the relapse rate was low, the proportion with unsatisfactory results at the end of treatment w slightly, though not significantly, higher than the proportions in the daily and thrice-weekly regimens.

These results all refer to patients with initially sensitive cultures. But, because of bad treatment and inefficient medical organization many patients coming to health centres already have resistant cultures. From the Hong Kong results it was possible to estimate the total effect of applying the streptomycin, isoniazid, pyrazinamide regimen in all patients, both those with sensitive and those with resistant cultures. In Hong Kong 21 per cent of patients coming for treatment have resistant cultures. In such a population hily streptomycin, isoniazid and pyrazinamide for nine months would produce lasting non-infectiousness in about 90 per cent of <u>all</u> patients who co-operated for the whole period of

treatment. With a thrice-weekly regimen the proportion would be about 85 per cent. This is an impressive demonstration of the potency of short regimens of bactericidal drugs.

Prospects for more efficient treatment

It is highly likely that even shorter and less exacting regimens will be discovered within the next ten years. The duration of treatment may be reduced to less than six months, with part of it being given once weekly.

The drugs and the ways in which to use them are already available to control tuberculosis in the world. All that is lacking is the social organization to put into practice the discoveries of laboratory investigations and controlled clinical trials. The scientists have provided the tools: the politicians, the administrators and the people themselves must use them efficiently.

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APPENDIX I

Doses of drugs used in clinical trials of intermittent regimens

	Intermittent regimen	
	Twice weekly	Once weekly
Streptomycin	19	19
Isoniazid	15 mg/kg	15 mg/kg
Rifampicin	17-25 mg/kg	25 mg/kg
Ethambutol	45 mg/kg	90 mg/kg
Pyrazinamide	3-3.5 g. (2-2.5 g. three times weekly)	
Thiacetazone	300-450 mg.	
PAS	7.5-12 g.	

APPENDIX II

Regimens and doses of drugs used in clinical trials of short regimens

Ref.	REGIMEN	Doses of drugs					
		S	T	H	E	R	Z
24	SHR or SHZ 6/12	1g.		300 mg.		450-600 mg.	
25	SHR or HR 6/12 SHRZ 2/12 - S2H2Z2 or TH 4/12	1g. 1g.	150 mg.	300 mg. 300 mg. daily 600-900 mg.x2		450-600 mg. 450-600 mg.	 1.5-2g. daily 3 - 4g. x 2
26	S(E)HR 3/12 - HR 3 or 6/12	1g.		450 mg.	25 mg/kg	600 mg.	
27	S(E)HR 2/12 - HR 4 or 7/12	0.75 g.		300 mg.	25 mg/kg	600 mg.	
28	EHR 6/12			500 mg.	1.2 g.	600 mg.	
29	SHZ 6 or 9/12 S3H3Z3 S2H2Z2	0.75-1 g. 0.75-1 g. 0.75-1 g.		300 mg. 15 mg/kg 15 mg/kg			1.5-2 g. 2.0-2.5 g. 3.0-3.5 g.