A STUDY OF OPERATIONAL FACTORS INFLUENCING THE APPLICABILITY OF TWO REGIMENS OF SHORT COURSE CHEMOTHERAPY UNDER CONDITIONS OF AN URBAN TUBERCULOSIS PROGRAMME

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Introduction

An operational study of two regimens of Short Course Chemotherapy (SCC) to assess their efficacy under programme conditions, applicability in terms of initial acceptability, drug default and adverse reactions due to drugs and feasibility for District TB Programme (DTP) Organisation was undertaken in an urban TB Centre.

The operational efficacy of these two regimens, namely 1SHRZ/7TH and 2SHR/6TH was found to be 87% and 92% respectively. The findings in detail have already been reported in an earlier paper (Jagota *et al;* 1989). The various factors *i.e.,* initial willingness, drug default, treatment completion pattern, adverse drug reactions and initial drug resistance with their potential harmful effects on the outcome of the SCC regimens under study as well as work load and extra cost these regimens entail for DTP organisation are discussed in this paper.

Objectives

(*i*) Acceptability of two 8 month regimens in terms of

- (*a*) proportion of patients initially willing to attend the clinic daily for 2 months,
- (*b*) pattern of drug default among study patients in intensive as well as in continuation phase and defaulter retrieval,
- (*c*) treatment completion pattern.

(*ii*) The proportion of patients reporting adverse drug reactions during treatment.

(*iii*) Work load on the centre due to :

- (*a*) administration of supervised treatment,
- (*b*) taking of defaulter retrieval actions and
- (*c*) management of adverse drug reactions.

(*iv*) Cost

- (*a*) cost to the organisation,
- (*b*) cost to the patient.

Material and Methods

Patients residing in Bangalore City limits and attending Lady Willingdon State TB Centre (LWSTC); of 12 years of age or more; with pulmonary tuberculosis, whose sputum was positive for acid fast bacilli on smear examination and who had not received any previous anti-TB chemotherapy-"core group"- were allocated at random to two 8 month treatment regimens as follows :

Regimen A : Streptomycin, Isoniazid, Rifampicin and Pyrazinamide daily under supervision for 1 month followed by isoniazid and Thioacetazone daily self-administered for 7 months given as monthly collection (1SHRZ/7TH).

Regimen B : Streptomycin, Isoniazid, Rifampicin daily under supervision for 2 months followed by Isoniazid and Thioacetazone daily for self administration at home for 6 months given as monthly collection (2SHR/6TH).

The usually recommended dosages were prescribed. Patients with a history of previous chemotherapy were termed as "Non-core group" and allocated to these two regimens in a separate random allocation.

Compensatory period of upto 15 days in case of Regimen A and upto 30 days in case of Regimen B was offered to the patient to complete the missed doses of intensive phase, provided he had completed at least 50% of due doses within

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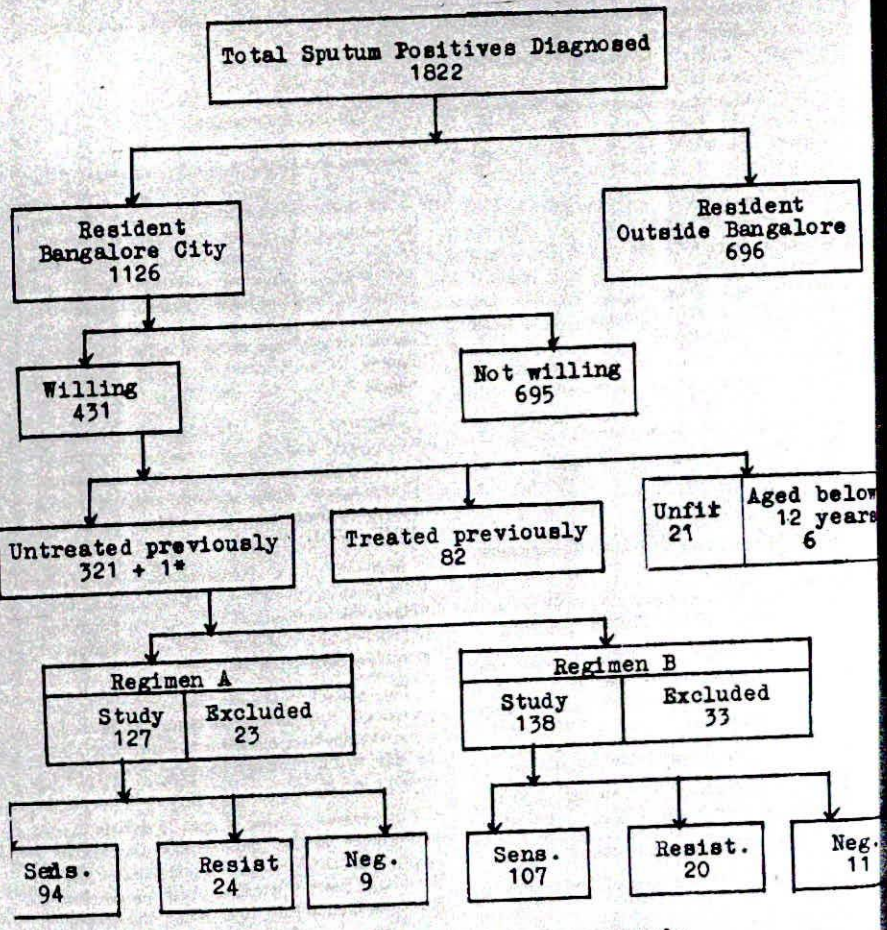
the originally stipulated period; otherwise he was excluded form the study.

Drug Default

The DTP criterion to label a patient "defaulter" was modified in this study with the twin objectives of reducing the duration of drug free period as well as studying the feasibility of implementing it in DTP. Drug default was defined as failure to report for drug

Table 1. *Classification of Sputum Positive TB Patients diagnosed at the Centre during the intake period (February 1984 to May 1985)*



* One patient was excluded by mistake on grounds of allergy to Streptomycin.

administration/collection on the day he was due. The first action was in the form of a letter posted on the evening of the due date. The IInd action consisted of a home visit on 4th day, if patient failed to return for drugs.

Adverse drug reaction

An adverse reaction was classified as minor if it subsided with or without symptomatic treatment, e.g. itching without rash, gastro-intestinal symptoms without evidence of clinical jaundice or ulcer or joint pain without swelling. An adverse reaction was classified as major toxicity warranting modification of chemotherapy in the event of development of clinical jaundice, intractable vomiting, rash, exfoliation, persistent giddiness, etc.

Adverse drug reactions were recorded as and when patient reported the same. At the time of initiation of treatment patient was informed to report any untoward symptom experienced during treatment.

Results

Classification of patients attending the Centre during intake period

Out of a total of 1,822 sputum positive TB patients diagnosed at the LWSTC during intake period (February 1984 to May 1985), 1,126 were residents of Bangalore City. Of these, 695 (61.7%) were unwilling to attend the clinic daily for 2 months. Of the remaining 431 who were willing, 21 were unfit for intake in the study on medical grounds; and 6 patients were below 12 years of age. Thus, 404 patients were classified as either "Core group" or "Non-core group" (321 and 82 respectively). One patient was excluded from the study by mistake, on grounds of allergy to Streptomycin.

Table 2. *Reasons for unwillingness*

Reason for unwillingness	No.	%
Total number of unwilling patients	695	100.0
Unable to attend daily	539	77.6
Not prepared for daily injection	89	12.8
Wants to take treatment elsewhere	67	9.6

Initial Willingness

The initial acceptability rate of 38.3% is applicable to Regimen B only, as all eligible patients were asked for their willingness to attend the Centre daily for 2 months, and allocation to Regimen A (1 month intensive phase) or Regimen B (2 month intensive phase) was made later on.

Reasons for unwillingness

Of the 695 unwilling persons, a majority (77.6%) were those who pleaded inability to attend daily for 2 months without specifying any particular reason. Refusal of SCC due to daily injections accounted for 12.8% and 9.5% wanted to take treatment elsewhere. (The acceptability of a fully oral self administered regimen is currently under study at N.T.I.).

Old age influenced willingness adversely; however, sex did not influence willingness (not shown).

Pattern of treatment completion

Table 3 shows the pattern of treatment completion of 321 patients with no history of previous anti-tubercular treatment. There was no significant difference in overall pattern of treatment completion in the two regimens. The

Table 3. *Pattern of treatment completion*

	Regimen A		Regimen B		Total	
	No.	%	No.	%	No.	%
No. allocated	150		171		321	
No. excluded	23	15.3	33	19.3	56	17.4
No. eligible for continuation phase	127		138		265	
No. made 80% of TTT in intensive phase	121	80.7	129	75.4	250	77.9
No. made 80% of TTT in continuation phase	100	66.7	103	60.2	203	63.2
No. made 80% of TTT in both phases	98	65.3	103	60.2	201	62.6

optimum treatment completion (≥ 80% treatment in both the intensive and continuation phases) rates were sixty five and sixty per cent respectively. Excluding 23 and 33 patients of the respective regimens, who took less than 50% of intensive phase doses in the originally stipulated period, among the remaining 265 patients 76% completed optimum treatment.

Drug default and patient behaviour

Onset of default

Default started as early as the start of treatment. A total of 56 patients (23 on Regimen A and 33 on Regimen B) were excluded due to early default resulting in patient missing a large number of doses of intensive phase. They consumed, on an average, 8 and 11 intensive phase doses respectively, after making a total of 118 defaults. Defaulting among the remaining patients continued at an almost constant rate throughout the treatment period.

Pattern of default

The distribution of patients according to number of defaults made, regimenwise, is presented in Table 4. In the intensive phase of Regimen A, 61 out of 127 (48%) did not make a single default, while in case of Regimen B, 48 out of 138 (34%) were completely regular. It may be noted that majority of defaulting patients made only one or two defaults, and thus a markedly irregular pattern of intensive phase treatment was not seen. Mean default was 1.1. per patient of Regimen A, and 2.2 per patient in case of Regimen B. Default in intensive phase thus appeared to be commensurate with its duration in each of the regimens.

In continuation phase, mean default per patient was 1.9 and 1.7 respectively.

Response to defaulter action

A total of 1,002 defaults were made during the entire period of chemotherapy. Of these 92 defaults were made in the compensatory phase for which no defaulter-retrieval action was taken. Response to defaulter action taken for the remaining 910 defaults is presented in Table 5. Of these 910 defaults, 434 (49%) were made during

Table 4. *Distribution of patients by number of defaults made in intensive and continuation phase (Regimen-wise)*

Phase of chemotherapy	Total patients	Number of defaults 0	1	2	3	4	5+	Mean default
Regimen A								
Intensive	127	61	30	20	5	7	4	1.1
Continuation	125	18	31	39	18	11	8	1.9
Regimen B								
Intensive	138	48	29	16	11	12	22	2.2
Continuation	133	14	52	33	26	7	1	1.7

Table 5. *Retrieval of defaulting patients after I and II defaulter actions*

Defaulter retrieval	Total	Chemotherapy phase INT.	CONT.
No. of I actions (letters) taken	910	434	476
No. returned for drugs within 3 days of letter posting	617	385	232
No. of II actions (home visits) taken	293	49	244
No. returned for drugs due to letter, after home visit	23	5	18
No. returned for drugs due to home visit	212	37	175
No. not returned for drugs	58	7	51

intensive phase, and the defaulter was retrieved on 85% (390) occasions. In continuation phase defaulter retrieval rate after letter posting was of the order of only 52%. 293 defaults required a home visit, as per protocol. However, 23 patients reported for drugs when the team had just left for home visiting and hence they were considered as retrieved by letter posting and not due to home visit. Of the remaining 270 defaults, on 69% of occasions, patient responded to home visit (*i.e.* they collected drugs within 10 days of home visit). Home visiting became necessary mostly for continuation phase defaults rather then intensive phase (244 in continuation phase and 49 in intensive phase).

Reasons for default

Reasons for default were not elicited from patients who reported for drugs within 4 days of due date, as these reasons are often casual and of little importance.

Reasons for the rest were elicited and recorded during home visit. The most frequent reason turned out to be : patient going out of station (52.9%) followed by patient being busy with work (19.1%). Default due to relief from symptoms accounted for 1.4% of defaults only.

Duration of default

On an average, a default during intensive phase lasted for 2.2 days (*i.e.* a defaulting patient attended for drugs approximately 2.2 days after the due date) and 5.8 days in continuation phase.

Compensatory Phase

156 (59%) of 265 patients missed one or more doses due to default and were eligible for compensatory phase. However, a very small number of patients required compensatory period to complete optimum intensive phase treatment (≥ 80% of doses), as shown in the Bar Diagram.

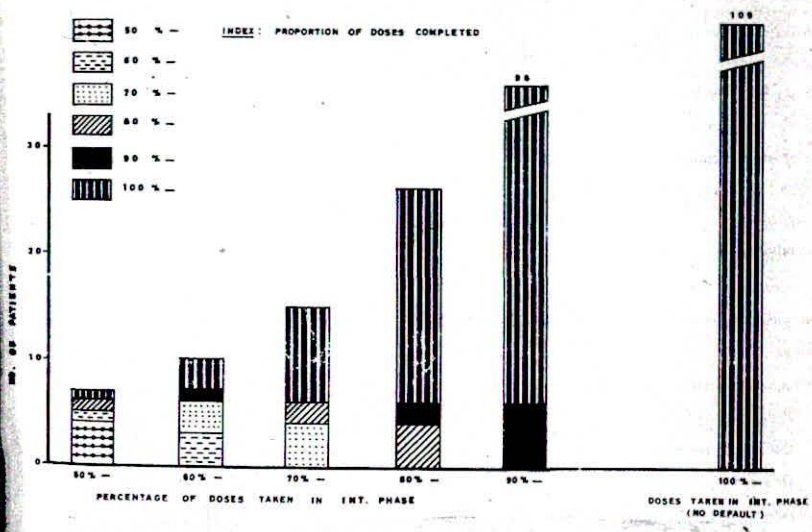


Fig. 1. Pattern of utilisation of compensatory phase to complete doses of INT phase, missed by default

Drop-out from treatment

58 patients out of 265 dropped out of treatment altogether : 32 were lost to treatment (7 in intensive phase and 25 in continuation phase) while 26 could not be classified as lost as they discharged themselves from treatment during the last two months of chemotherapy.

Incidence of adverse reactions

Minor adverse symptoms were reported by 73 (28%) patients - 38 Regimen A and 35 on Regimen B. Majority (almost two-thirds) of these symptoms were reported in intensive phase.

24 patients (10 or 7. 9% of patients on Regimen A and 14 or 10.7% of patients on Regimen B) experienced major toxicity which warranted modification of chemotherapy.

The incidence of major toxicity, according to type is shown in Table 6.

Table 6. *Major toxic reactions*

	Intensive phase		Continuation phase	
Toxic reactions	Regimen A	Regimen B	Regimen A	Regimen B
Gastro-intestinal	2	5	2	-
Jaundice	2	-	1	-
Joints	-	1	-	-
Vestibular	1	1	-	-
Cutaneous	-	2	3	5
Hyper sensitivity	-	1	-	1
Total	5	10	6	6

Table 7. *Work-load on centre*

Category of work	Total	Regimen A	Regimen B
Total patients	321	150	171
No. of patients excluded	56	23	33
Average per patient :	9	8	11
Doses per patient	2.1		
Default per patient	2.1		
Defaulter action-I	1.2		
Defaulter action-II	265	127	138
No. of patients under analysis	44.1	29.4	57.6
Average doses per patient (supervised drugs administration)	910	383	527
Defaults			
Average per patient :	3.4		
Defaults per patient	3.4		
Defaulter action-letter	1.1		
Home visit			
Adverse drug reaction	387	192	195
No. of times reported	1.5		
Average per patient			

It may be noted that clinical jaundice in intensive phase developed in 2 patients only (both on regimen A with the 4 drug intensive phase). Arthralgia, a common feature of Pyrazinamide toxicity was not encountered in this Study.

Twelve patients experienced major toxic reactions, *i.e.* intractable itching, itching with rash, giddiness or jaundice all attributed to Thioacetazone, in continuation phase. Most of them, certainly those with cutaneous symptoms, were changed over to Ethambutol. There was no exfoliative dermatitis.

Work load on the centre

(Table 7)

Due to excluded patients

The 56 excluded patients (of both regimens) made on an average 2.1 defaults per patient in intensive phase, and had 8 and 11 supervised doses per patient on the respective regimens. On an average 1.2 home visits/patient (II defaulter actions) were done for these excluded patients.

Due to administration of drugs to patients under analysis

In intensive phase of Regimen A, taking actual treatment completion rates into account, on an average, 29.4 doses of supervised treatment were administered, and in case of Regimen B, 57.6 doses were administered to each patient.

Due to defaulter retrieval actions

For 265 patients, 910 defaulter actions in the form of letter posting had to be taken or on an average 3.4 letters to be posted per patient on treatment.

Home visits became necessary on 293 occasions or 1.1 home visit per patient on treatment.

Due to adverse drug reactions

Both major and minor adverse reactions were reported on 387 occasions, 61% of them occurring in intensive phase. Adverse symptoms thus required the attention of a doctor on about 2 occasions for every patient on SCC regimen. There was no difference in the incidence of adverse symptoms reported by patients on either of the regimens.

All patients with adverse reactions including jaundice were managed as outpatients, without hospitalization.*

Cost

Cost of drugs to the organisation

The cost of these SCC regimens to DTP organisation works out to Rs. 220/- per patient in case of Regimen A and Rs. 268/- per patient in case of Regimen B.** The exact organisational cost of these regimens in terms of personnel, time, etc. cannot be calculated from this study. The relative costs of these regimens and conventional DTP regimens are presented in Table 8.

Table 8. *Cost of different regimens per patient to the organisation*

Regimen	Duration (in months)	Cost Rs.
1. *Study Regimens*		
1SHRZ/7TH (Regimen A)	8	220.00
2SHR/6TH (Regimen B)	8	268.00
2. *DTP Regimens*		
TH (R_1)	18	92.00
EH (R_4)	18	346.00

Estimated cost to the patient for fully regular treatment

Regimen	Cost Rs.	No. of visits
1SHRZ/7TH (Regimen A)	70.00	33
2SHR/6TH (Regimen B)	113.00	58
18TH/18EH	35.00	18

Cost to patient due to transportation

The average cost of transportation by bus, to the patient, works out to Rs. 70/- for Regimen A and Rs. 113/- for Regimen B.

*One excluded patient on account of persistent vomiting and dehydration–hospitalised.
**Cost is calculated according to prices at which the drugs were procured by DGHS in 1987-1988.

Table 9. *Distribution of patients with history of previous treatment according to allocation of drug regimen and initial culture status*

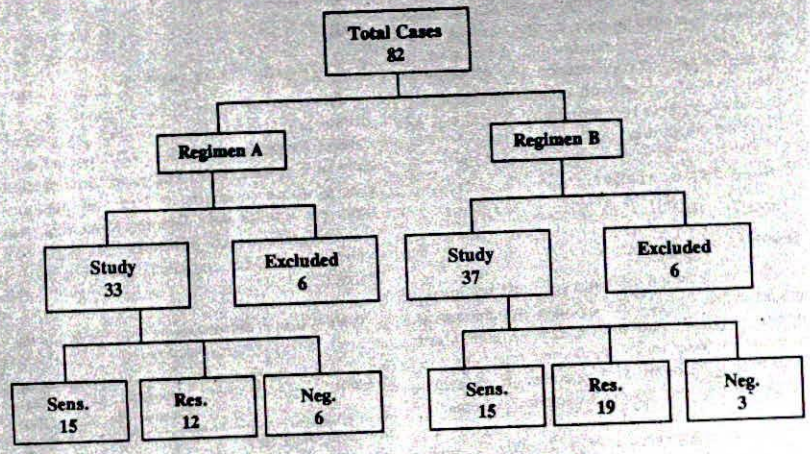


Table 10. *Bacteriological response to treatment (initial culture sensitive and resistant patients) as related to level of drug collection in patients with history of previous treatment*

Final culture and sensitivity status	Level of treatment 1	2	3	4	Total
Negative No.	1	1	1	30	33
%					(57%)
Positive	1	2	6	16	25
Not examined	-	-	2	1	3
Total	2	3	9	47	61

Sputum conversion and relapses in previously treated cases

Eighty two patients gave a history of previous anti-TB treatment. Their classification according to allocated drug regimen and initial culture status is given in Table 9.

Considering both drug sensitive and resistant patients together, 33 (57%) of 58 patients had a favourable response to chemotherapy. By the 24th month, 9 (27%) of these had relapsed.

Discussion

The success or failure of SCC on a large scale will depend largely upon initial acceptability and patient compliance. Factors such as distance, frequency of visits required, motivation, doctor-patient contact, defaulter-retrieval actions, etc would obviously influence patient compliance. In addition, adverse reactions, both minor and major, would influence acceptability of a regimen to both doctor and patient.

Selection of drug regimen

An informed decision to implement a new treatment regimen in a programme will, thus, require information on its overall applicability measured in terms of outcome for the patient, and organisational effort involved.

The regimens selected for the study had had a record of almost 100% sputum conversion, relatively low relapse rates of 7% and 6% respectively and a low incidence of adverse reactions under controlled clinical trial conditions. On the other hand, their low cost and short durations of 1 or 2 month supervised intensive phase respectively, made them an attractive proposition for large scale implementation in a programme. The cost of both regimens was approximately the same. However, acceptability and operational efficacies of these two regimens would determine which is more robust and suitable for widespread use in a programme.

Initial willingness

Initial low acceptability of about 40% is quite disturbing and needs further exploration (It may be noted that it applies to Regimen B only). This order of refusal of these regimens could be due to the abnormally rapid expansion of Bangalore city requiring the patients to travel long distances to reach the treatment centre. In this study the mean distance a patient covered was 7 kms as compared to 4 kms in a previous study of DTP regimens conducted in 1973.[3] Majority (84%) of the refusals were due to inability to attend the Centre daily for 2 months, or due to daily injections. Thus, it would be reasonable to expect that when largely unsupervised oral short course regimens are offered to patients, requiring less frequent visits to the centre, a majority of patients would be willing for SCC. Significantly, only 6% (66 of 1126) of urban patients, diagnosed at this Centre in a metropolitan city, wanted to take treatment from other sources, which included Sanatoria, ESI, CGHS and other organised health schemes. Further, only 6% (27 of 431) of patients were judged unfit for these domiciliary SCC regimens due to various reasons emphasising the fact that about 95% patients can be treated on an ambulatory basis.

Role of compensatory phase

The reason for offering a compensatory treatment period was to help patients compensate the missed doses of the crucial intensive phase which is the period of maximum sterilization of tubercular lesions. At the same time, compensatory period could not be allowed to patients whose compliance in the intensive phase was very poor and, therefore, carried the risk of multiple drug resistance due to wide spacing of doses. Such an outcome would be disastrous for the programme. Hence, it was offered only to patients who had already completed at least 50% of due doses within the originally stipulated period. Majority of patients (88%) had already completed 80% or more doses within the originally stipulated period. Nevertheless, the fact remains that the vast majority of patients could complete nearly 100% of doses, owing to provision of compensatory phase, and this could have gone a long way in both sputum conversion and prevention of relapse in these marginal regimens, where the continuation phase of Isoniazid and Thioacetazone for 6 to 7 months was too weak to sustain an incomplete intensive phase.

Drug default

Defaulting appears to be an inbuilt part of human behaviour. In fact, it is naive to expect 100% compliance for entire duration of treatment by merely giving instructions at the time of initiating treatment.

In this study, while drug default was of quite a high order, defaulter retrieval was also very high. Letter posting, when a patient defaulted, was of negligible cost considering that two thirds of patients returned to treatment. Similarly, a home visit on 4th day of default, mostly succeeded in retrieving the remaining defaulters. At the same time, it should be remembered that defaulter actions become meaningless if accurate postal address is not elicited at the time of opening a treatment card. The work load due to defaulter actions is within manageable limits of existing DTP organisation. Provision of staff and means of transportation for prompt home visit yielded good results in terms of treatment completion.

These facts are again borne out by a comparison between various settings of chemotherapy.

Table 11 shows a variety of situations, from a clinical trial situation of highly selected "compliant" patients with many a staff to

Table 11. *Default pattern in different chemotherapy situation at a DTC*

Chemotherapy situation	No. of patients	Proportion of patients making various number of defaults					
		0	1	2	3	4*	Range
Short course Chemotherapy							
Current operational study							
Int. phase 1/2 months	321	34.3	26.5	14.0	8.7	16.5	0-13
Cont. phase 7/6 months	258	12.4	32.2	27.9	17.0	10.5	0-5
Clinical trial[1]							
Daily phase 3 months	287	49.1	24.0	9.8	5.9	11.1	0-13
Bi-weekly phase 2 months	183	34.4	28.4	16.4	7.7	13.1	0-8
Conventional DTP Regimens							
Operational Study[2]							
Self-administered daily Regimen (R_1)	189	11.1	45.0	14.3	12.2	16.4	0-8
Bi-weekly supervised Regimen (R_2)	134	9.7	29.1	16.4	6.7	38.1	0-17
Under Service Programme[3]							
12 Collections within 15months Self-administered daily	522	20.1	19.3	16.5	12.1	32.0	0-10

1. KS. Aneja *et al*- Ind J Tub, 1982, 29, 19
2. GVJ. Baily *et al* - Ind J Tub, 1974 21, 52
3. MA. Seetha *et al* - Ind J Tub, 1976, 23 90.

motivate patients and retrieve the defaulters, the operational study conditions with well defined effort for case-holding, to a service programme obliged to treat every patient diagnosed with variable availability of personnel and resources for case-holding. In these three varied situations, a majority of patients have defaulted. Majority of patients in the clinical trial complete treatment owing to intensive defaulter actions.

Adverse reactions

It has often been feared that adverse reactions in SCC, where 3-4 drugs are used in intensive phase, would seriously limit its application under routine programme conditions. Both frequency and severity of adverse symptoms encountered seem quite manageable within the existing frame work of DTP. There were 387 occasions when the patient required doctor's attention to manage adverse symptoms -- on an average less than 2 per patient on SCC. The occurrence of jaundice in these regimens was a little over 1% (3 out of 265). There was no case of exfoliative dermatitis. Hospitalisation was not required for management of any patient with adverse symptoms -- major or minor.

Drug resistance at the start of treatment

As was emphasised in the previous paper (Jagata *et al;* 1989), many patients with history of varying periods of anti-TB treatment will be diagnosed as sputum positive new patients in DTPs. Their drug sensitivity status will not be known owing to lack of culture facility in DTP. The outlook for such patients put on SCC would be of interest; such patients constituted about 20% of this cohort put on SCC. Among them, 44% turned out to be excreting organisms resistant to Isoniazid. Fifty seven per cent of the group with history of various periods of anti-TB treatment had a favourable response to chemotherapy. Thus, considering previously treated and untreated patients together, the overall sputum conversion was 81% (compared to 90% conversion in the culture sensitive group). Thus, in this cohort, the proportion of previously treated patients was too small to substantially influence the outcome of SCC in the entire cohort. It should be remembered that a larger proportion of previously treated cases could substantially dilute the outcome.

In conclusion, domiciliary short course chemotherapy proved feasible and advantageous in an urban tuberculosis programme. Between these two regimens, while Regimen A equalled Regimen B in efficacy, it has operational advantages over Regimen B. In fact, a regimen with a 2 month intensive phase of four drugs, largely self-administered would possibly improve upon the initial acceptability and results observed with these regimens.

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ANTI-TUBERCULOSIS REGIMENS OF CHEMOTHERAPY

Recommendations from the Committee on Treatment of the International Union Against Tuberculosis and Lung Disease

1.0 Introduction

Short-course chemotherapy is now widely accepted as the treatment of choice for pulmonary tuberculosis. A number of regimens of chemotherapy have been shown in controlled clinical trials and in clinical practice to be highly effective in many countries and in a wide variety of patient populations and health service conditions. From the results of clinical trials and of complementary laboratory studies, the mechanisms of action of the main antituberculosis drugs and their contribution to regimens are also becoming increasingly well understood. At its meeting in Singapore in November 1986, the Committee on Treatment of the International Union Against Tuberculosis and Lung Disease, following a survey among its members, therefore, decided to make specific recommendations on antituberculosis regimens and drug dosages to be used in the treatment of adults and children with active pulmonary or extra–pulmonary tuberculosis requiring chemotherapy.

2.0 Drug Action

The antituberculosis drugs vary in (1) their bactericidal action, defined as their ability to kill large numbers of actively metabolising bacilli rapidly, (2) their sterilising action, defined as their capacity to kill special populations of slowly or intermittently metabolising semi-dormant bacilli : the so-called "persisters", (3) their ability to prevent the emergence of acquired resistance by suppressing drug-resistant mutants present in all large bacterial populations, and (4) their suitability for intermittent use.

2.1 Bactericidal Action

Most of the antituberculosis drugs, with the exception of the bacteriostatic drugs thiacetazone and PAS (para-aminosalicylic acid), have some bactericidal action but isoniazid is the most potent bactericidal drug. It has been estimated that isoniazid alone may kill some 90 per cent of the bacillary population in a patient's lesions during the first few days of chemotherapy. Rifampicin is also an important bactericidal drug. Streptomycin and pyrazinamide are less potently bactericidal, and although large doses of ethambutol are bactericidal, the difference between a therapeutically inadequate dose and a toxic dose is small.

2.2 Sterilising Action

Rifampicin and pyrazinamide are the most important sterilising drugs because of their ability to kill semi-dormant bacilli capable of surviving the bactericidal action of isoniazid and so of giving rise to relapse after treatment. The bacilli specifically killed by rifampicin are probably bacilli which are dormant but subject to transient favourable changes in their environment and so to short periods of active metabolism. The bacilli specifically killed by pyrazinamide are probably those with their metabolism inhibited by an acid environment, those, for example, within macrophages and in areas of acute inflammation. To achieve maximum sterilising effect in 6-month regimens in the treatment of human pulmonary tuberculosis, pyrazinamide need be given for only the first 2 months but rifampicin throughout the 6 months, further evidence that these two drugs are uniquely active against special components of the bacillary population.

2.3 Preventing the Emergence of Acquired Resistance

Even populations of tubercle bacilli which have not been exposed to antituberculosis drugs contain small proportions of drug-resistant mutants If inadequate drug combinations are used, these mutants are likely to replace killed susceptible bacilli and give rise to drug-resistant disease. The effectiveness of drugs in preventing the emergence of acquired resistance depends upon the extent to which they can inhibit bacilli continuously, whatever their rate of metabolism, even when there is some irregularity in drug taking. Isoniazid and rifampicin are the most effective at preventing the emergence of resistance to other drugs, and streptomycin and ethambutol are only slightly less so Pyrazinamide is less effective, and PAS and thiacetazone are the least effective.

2.4 Suitability for Intermittent Use

Isoniazid, rifampicin. pyrazinamide, streptomycin and ethambutol are all effective when given 3 times or twice a week. Thiacetazone is less effective when given intermittently than when given daily.

*Reproduced from Bulletin of the I.U.A.T.L.D., June 1988 issue.

3.0 Regimens of Chemotherapy

3.1 Recommended Regimen for Newly-Diagnosed Patients

In the treatment of newly-diagnosed patients, the regimen should include, whenever possible, the main sterilising drugs and those most effective at preventing the emergence of resistance, namely isoniazid (H), rifampicin (R), and pyrazinamide (Z) (Table-1). Isoniazid also reduces patients' infectivity rapidly because of its highly effective bactericidal action. Isoniazid and rifampicin should be given daily for 6 months and pyrazinamide in addition for the first 2 months or 8 weeks : 2HRZ/4HR.

Fixed-dose combination preparations of isoniazid, rifampicin and pyrazinamide, and of isoniazid and rifampicin should be used when available to aid compliance and to reduce the risk of incorrect dosage, but it is essential that only those preparations are used for which bio-availability studies have been carried out and have shown that serum drug concentrations are not altered by the combination.

The above 6-month daily regimen is now standard and should be used in the treatment of pulmonary and extra–pulmonary disease in both adults and children. Because of its ability (1) to cure patients rapidly (even the majority of those who default after only 2 to 3 months of treatment), (2) to cure the great majority of patients with strains of bacilli initially resistant to isoniazid, streptomycin, or both drugs, and (3) to prevent failure due to the emergence of acquired resistance, it is more cost-effective than cheaper and less potent regimens (such as those which do not include rifampicin or pyrazinamide), even in developing countries.

There are variants of this regimen which are equally effective and which, in some circumstances, have advantages :

3.1.1 *Intermittent administration.* In the continuation phase, isoniazid and rifampicin may be given 3 times or twice a week : 2HRZ/$4H_3R_3$, 2HRZ/$4H_2R_2$. This has the advantage that the continuation phase can be administered on an outpatient basis under full supervision, every dose being given under the direct observation of outpatient health service

Table 1

Regimens of Chemotherapy

Recommended standard 6-month regimen
2HRZ/4HR

Variants of standard 6-month regimen

1. When fully supervised intermittent chemotherapy can be organised
   2HRZ/$4H_3R_3$
   2HRZ/$4H_2R_2$
   $2E_3H_3R_3Z_3$/$4H_3R_3$
   $2S_3R_3Z_3$/$4H_3R_3$
2. When there is a high level of initial resistance
   2EHRZ/4HR
   2SHRZ/4HR
   Or add E(or S), where appropriate, to the initial phase of one of the variants

Alternative less potent regimens of longer duration

1. With a potent initial 4-drug phase
   2SHRZ/6HT
   $2SHRZ/6S_2H_2Z_2$
2. With a less potent or no initial phase
   2SHR/7HR
   2EHR/7HR
   9HR
   2SHT/10HT
   2SHE/10HE
   2SHP/10HP
   2SAT/$10S_2H_2$
   2SHP/$10S_2H_2$

S=streptomycin; H=isoniazid; R=rifampicin; Z=pyrazinamide; E=ethambutol; T=thiacetazone; P=PAS.

staff or of a paramedical worker or lay person who has been taught to supervise chemotherapy. In this way the level of compliance is known and a high level can be encouraged. Intermittency should not be used purely as a cost-saving measure.

In programmes where chemotherapy is administered throughout under full supervision on an outpatient basis, the regimen may be given 3 times a week from the start. When this is done, either ethambutol or streptomycin should be added to the initial phase: $2E_3H_3R_3Z_3/4H_3R_3$, $2S_3H_3R_3Z_3/4H_3R_3$, but see paragraph 8.4.

3.1.2 *Populations with a high rate of initial drug resistance.* When there is a high rate of initial drug resistance, or if it is suspected that the patient's strain is resistant to isoniazid, it is desirable to add a fourth drug to the initial phase of the regimen. Ethambutol is a good fourth drug because initial resistance to it is rare, but streptomycin may be preferred in some populations in the hope that it will encourage compliance as it has to be given intramuscularly (see paragraph 8.4). Also, the orally administered drugs can be given fully supervised at the time the streptomycin injections are given.

3.2 Alternative Less Potent Regimens

When optimum chemotherapy cannot be used in a population or in individual patients, one of the following alternative regimens may be used. It must be appreciated, however, that these regimens involve less potent drug combinations than the recommended 2HRZ/4HR regimen and its variants and, therefore, have to be given for longer than 6 months. They are inferior regimens which, although in some cases cheaper purely in terms of drug costs, are unlikely to reduce the total cost per patient cured. If it is decided to use one of the alternative regimens, priority should be given to the first two, both of which have a highly potent initial 4-drug phase (SHRZ) daily for the first 2 months.

2SHRZ/6HT—streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 2 months, followed by isoniazid and thiacetazone daily for 6 months (total duration 8 months). Isoniazid alone may be given in the continuation phase if there are problems with thiacetazone toxicity, but only if the level of initial resistance to isoniazid in the population is known to be low.

2SHRZ/$6S_2H_2Z_2$—streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 2 months, followed by streptomycin, isoniazid, and pyrazinamide fully-supervised twice a week for 6 months.

2SHR/7HR, 2EHR/7HR or 9HR—isoniazid and rifampicin daily for 9 months, with or without streptomycin or ethambutol in addition daily for the first 2 months. 9HR should only be used if the level of initial resistance to isoniazid in the population is known to be very low.

2SHT/10HT, 2SHE/10HE or 2SHP/10HP—streptomycin, isoniazid, and thiacetazone (or ethambutol, or PAS) daily for 2 months followed by isoniazid and thiacetazone (or ethambutol, or PAS) daily for 10 months.

2SHT/$10S_2H_2$ or 2SHP/$10S_2H_2$—streptomycin, isoniazid, and thiacetazone (or PAS) daily for 2 months, followed by streptomycin and isoniazid fully-supervised twice a week for 10 months.

3.3 For Patients in whom Relapse has Occurred after Chemotherapy

Relapse after chemotherapy is rare if the recommended 2HRZ/4HR regimen or one of its variants is administered regularly by an efficient treatment service and the patient complies and responds well during chemotherapy. If relapse occurs in these circumstances, or in a patient who defaulted after only a short period of regular chemotherapy, acquired resistance (or additional resistance if the initial strain was already resistant) is unlikely to have emerged, and the patient should be retreated with the same drug combination, although for 9 rather than 6 months and under stricter supervision.

If one of the less potent alternative regimens has been used, or if relapse has occurred in a patient whose chemotherapy (whatever the regimen) has been poorly supervised and who has taken drugs irregularly for much of the time, acquired resistance is more likely to have emerged and a careful assessment must be made before a retreatment regimen is chosen (see paragraph 3.4).

3.4 For Patients whose Primary Chemotherapy has Failed

When there is no response to chemotherapy in a patient who is known to have taken it regularly this is probably because of multiple resistance in the initial strain; and when there is a bacteriological response at first, followed by bacteriological failure whilst chemotherapy is still being given (fall and rise phenomenon), this is probably because acquired resistance or additional resistance has emerged. In either case the regimen must be changed. But first it is necessary to try to establish whether 'failure' was in fact due simply to the patient's having failed to take any chemotherapy or having stopped it prematurely (see paragraph 3.3). Once it is clear that the patient is no longer responding to the prescribed regimen a careful assessment is necessary. A detailed drug history should be drawn up, including the drugs used, their dosage and duration of administration, and the compliance of the patient in treatment. Sensitivity tests on the failure cultures may be helpful, but only if they have been done in a reliable laboratory undertaking good quality control.

Whenever possible, the patient should be retreated for at least 12 months from the time the sputum smears become negative, using a daily regimen containing, for the first 3 to 4 months, at least 3 drugs to which his organisms are likely to be sensitive: preferably 3 that he has never received before and which do not share cross-resistance with any that he has, chemotherapy with at least 2 drugs then being continued thereafter. Unless it is unavoidable, a single new drug should not be added to a previously failing or suspect regimen, because this will probably lead to the emergence of further resistance. It may, however, be done as a last resort when resistance to all other available drugs is likely to have emerged.

Rifampicin, ethambutol, and pyrazinamide (REZ) or streptomycin, PAS, and pyrazinamide (SPZ) are appropriate combinations if the drugs have not already been used. Other drugs which may be tried are prothionamide (or ethionamide), cycloserine, thiacetazone, and the aminoglycosides other than streptomycin, namely kanamycin or capreomycin. Previously used drugs may be used in addition, if it is doubtful whether the strain has become resistant to them. All the drugs should be given as a single dose daily except for cycloserine and PAS which are given in 2 divided doses.

Retreatment should be fully supervised, in hospital if necessary, especially in patients suspected or known to have been uncooperative in the past. Careful bacteriological monitoring is essential.

4.0 Cross-Resistance

There is no cross-resistance between isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol or PAS and other antituberculosis drugs. Cross-resistance exists between kanamycin and capreomycin and between thiacetazone and prothionamide (or ethionamide).

5.0 Drug Dosages

The recommended dosages for all the drugs are shown in Table 2. These dosages are appropriate for all forms of tuberculosis (including meningitis and miliary disease) and for children as well as adults. There has been a tendency in the past to prescribe high dosages for children, especially of isoniazid, leading to needless adverse effects such as hepatitis.

6.0 Supervision of Chemotherapy

Poor compliance by patients is by far the most important cause of poor results from potent regimens under programme conditions. The importance of complying in treatment throughout the whole duration of chemotherapy must be repeatedly emphasised to the patient and his family, and whenever possible every dose of the regimen should be administered under full supervision. In some countries this can be achieved by medical service staff on an entirely outpatient basis. In others, service staff can provide full outpatient supervision in the urban but not in the rural areas, while in others treatment is rarely, if ever, fully supervised by service staff. If the service staff cannot provide supervision, paramedical or lay persons, including a member of the patient's family, can be taught to do so.

It is wrong to assume that standards of supervision are necessarily better in hospital than in outpatients. In general, patients should not be admitted to hospital, even for a short initial period, unless there is a specific indication. Nevertheless, there is sometimes a case for admitting patients to hospital for the initial period of chemotherapy if this is necessary to achieve full supervision and if hospital beds are available. In most circumstances it is preferable to accustom the patient to receiving chemotherapy regularly and correctly on an outpatient basis from the start, organising supervision as efficiently as circumstances allow.

Whatever the level of supervision, compliances should be monitored by such measures as periodic pill counts and surprise urine tests for isoniazid or inspection of the urine for the red coloration of rifampicin.

7.0 Adverse Reactions

The important adverse reactions to the main antituberculosis drugs are listed in Table 3.

If clinically evident hepatitis occurs, treatment should be stopped until liver function tests have reverted to normal. It is then often possible to resume chemotherapy (even with the same drugs) without recurrence of the hepatitis.

Table 2

Drug Dosages

Drug	Daily dosage: Adults and children mg/kg	Daily dosage: Adults weight	Daily dosage: Adults dose	Intermittent dosage: Adults and children mg/kg	Intermittent dosage: Adults weight	Intermittent dosage: Adults dose
Isoniazid	5	—	300 mg	15	—	—
Rifampicin	10	<50 kg	450 mg	15	—	600-900 mg
		≥50 kg	600 mg			
Streptomycin	15-20	<50 kg	750 mg	15-20	<50 kg	750 mg
		≥50 kg	1 g		≥50 kg	1 g
Pyrazinamide	35	<50 kg	1.5 g	50	<50 kg	2.0 g
		≥50 kg	2.0 g	3 times a week	≥50 kg	2.5 g
				75	<50 kg	3.0 g
				twice a week	≥50 kg	3.5 g
Ethambutol[1]	25 for 2 months, then 15	—	—	30	—	—
				3 times a week		
				45 twice a week	—	—
Thiacetazone	4(for children)	—	150 mg	—	—	—
PAS (sodium)	300	—	10-15 g	—	—	—
Ethionamide and Prothionamide	15-20	<50 kg	750 mg	—	—	—
		≥50 kg	1 g			
Kanamycin[2]	10-15	—	500 mg-1 g	—	—	—
Capreomycin[2]	15	—	1 g	—	—	—
Cycloserine[2]	15	<50 kg	750 mg	—	—	—
		≥50 kg	1 g			

1. It is important to calculate the dose accurately to ensure efficacy and avoid toxicity.
2. Adults only.

Table 3

Adverse Reactions to the Main Anti-tuberculosis Drugs

Isoniazid

Uncommon : hepatitis, cutaneous hypersensitivity, peripheral neuropathy (preventable and treatable with pyridoxine).

Rare : Giddiness, convulsions, optic neuritis, mental symptoms, heamolytic anaemia, aplastic anaemia, agranulocytosis, lupoid reactions, arthralgia, gynaecomastia.

Rifampicin

Uncommon : hepatitis, cutaneous reaction, gastrointestinal reactions, thrombocytopenic purpura; febrile reactions ("flu" syndrome) during intermittent or irregular administration.

Rare (during intermittent or irregular administration) : shortness of breath, shock, haemolytic anaemia, acute renal failure.

Streptomycin

Common : cutaneous hypersensitivity, giddiness, numbness, tinnitus.
Uncommon : vertigo, ataxia, deafness.
Rare : renal damage, aplastic anaemia, agranulocytosis.

Pyrazinamide

Common : anorexia, nausea, flushing.
Uncommon : hepatitis (dose-related), vomiting, arthralgia, cutaneus hypersensitivity.
Rare : sideroblastic anaemia, photosensitisation.

Ethambutol

Uncommon : retrobulbar neuritis (dose-related), arthralgia.
Rare : hepatitis, cutaneous hypersensitivity, peripheral neuropathy.

Thiacetazone

Common : gastrointestinal reactions, cutaneous hypersensitivity, vertigo, conjunctivitis.
Uncommon : hepatitis, erythema multiforme, exfoliative dermatitis (more common in some populations than in others), haemolytic anaemia.
Rare : agranulocytosis.

PAS

Common : gastrointestinal reactions.
Uncommon : cutaneous hypersensitivity, hepatitis, hypokalaemia.
Rare : acute renal failure, haemolytic anaemia, thrombocytopenia, cypothyroidism.

Arthralgia can occur during pyrazinamide administration. It is less likely to occur during intermittent than during daily administration and is usually mild and self-limited, responding well to symptomatic treatment; for example, with aspirin.

It is not often necessary to desensitize patients to antituberculosis drugs for hypersensitivity reactions, because alternative drugs are available. If it should prove necessary, challenge doses of drugs should be given such that drugs which are *least* likely to have caused the reaction are used first.

If a serious reaction to rifampicin occurs, such as thrombocytopenic purpura, shock, haemolytic anaemia, or acute renal failure, the drug should be withdrawn immediately and never given again. Similarly, if ethambutol causes retrobulbar neuritis it must be withdrawn immediately and never given again. Patients on ethambutol should always be told to stop all their drugs and report straightaway to their clinician if they experience visual symptoms.

8.0 Interactions, Contra-indications and Special Problems

8.1 Isoniazid

Isoniazid interacts with phenytoin, carbamazepine, and ethosuximide, so that the dosages of these drugs may have to be reduced during its administration, particularly in slow acetylators.

8.2 Rifampicin

Rifampicin induces hepatic microsomal enzymes and hence reduces the serum half-lives and clinical efficacy of a number of drugs, including corticosteroids (the dosages of which should be doubled during rifampicin administration), digitoxin, coumarin anticoagulants, oral contraceptives, the orally administered antidiabetic sulphonylureas and biguanides, and dapsone, if given concurrently.

8.3. Pyrazinamide

Pyrazinamide is contraindicated in patients with gout, because pyrazinoic acid, its main metabolite, inhibits the renal tubular secretion of uric acid leading to a rise in the serum uric acid concentration and the risk of precipitating an acute attack of gout.

8.4 Streptomycin

Young babies and the elderly are at increased risk of streptomycin toxicity. If possible the drug should be avoided in such patients, but if it has to be given, lower dosages than those shown in Table 2 should be used. The drug is contraindicated in patients with conditions affecting the eighth cranial nerve because of its ototoxicity, in pregnant women because it crosses the placenta and can damage the fetal eighth nerve, in patients with myasthenia because it is a weak neuromuscular blocker, and in patients known to be hypersensitive to the drug because of the risk of a severe reaction. It should be avoided in patients with impaired renal function because it is excreted unchanged by the kidneys and can also be nephrotoxic. Whenever streptomycin is used it is essential either to use disposable needles (used only once) or to ensure sterilisation of needles. When proper facilities for the sterilisation of needles are not available and especially because of the risks of transmission of AIDS or hepatitis virus by inadequately sterilised needles, streptomycin should be replaced by ethambutol.

8.5 Ethambutol

Ethambutol is contraindicated in young children and in any patient unable, for whatever reason, to report early symptoms of ocular toxicity. It should be avoided in patients with impaired renal function because it can accumulate and cause serious ocular toxicity.

8.6 Patients with Impaired Renal Function

Patients with impaired renal function can safely be treated with isoniazid, rifampicin, and pyrazinamide all of which should be given in normal dosage whatever the degree of renal failure.

8.7 Patients with Impaired Liver Function

Since the main antituberculosis drugs can be hepatotoxic, it is important that in patients whose liver function is known or likely to be impaired, liver function should be closely monitored.

8.8 Pregnant Women

Streptomycin is the only one of the main drugs which should not be given to pregnant women (see paragraph 8.4).

8.9 Patients with Diabetes Mellitus

No modification to the chemotherapy regimen is necessary because of diabetes. However, diabetes must be brought under control expeditiously and rigid control maintained. Since rifampicin is known to interact with oral antidiabetic drugs, the dose of the latter will have to be carefully re-adjusted if chemotherapy includes rifampicin. The diabetic status of the patient should be closely monitored by periodic blood sugar estimation; monitoring by urine examination is inadequate.

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SHORT-COURSE CHEMOTHERAPY—REWARDS & CHALLENGES**

M.A. SEETHA*

Summary : Different regimens under Short Course Chemotherapy are being prescribed to-day with high hopes based on the results of clinical trials. But under field conditions many factors come in the way of success while using the Short Course Chemotherapy. Some of these issues are highlighted.

Introduction

During the last four decades, remarkable progress has been achieved in the chemotherapy of tuberculosis. The biggest breakthrough has been the discovery of potent bactericidal drugs like Rifampicin, Pyrazinamide, INH, Streptomycin and the development of drug regimens to prevent drug resistance.

Various clinical trials in different parts of the world using Rifampicin and Pyrazinamide have given very good results and many regimens have been developed, which have reduced the period of treatment to 6 to 9 months.

Today, most doctors treat tuberculosis patients with Rifampicin and Pyrazinamide usually.

Rewards with Short-Course Chemotherapy (SCC)

(i) Reduction in the duration of treatment from 12-18 months to 6-9 months.

(ii) Early sputum conversion.

(iii) No relapse, or even if it is there, it is minimal.

These spectacular rewards are the results of clinical trials which are similar to laboratory conditions where most of the variables are controlled. As a result of these rewards, the medical profession claims great advantages like:

(a) Early sputum conversion will have a great impact on the epidemiological situation and would help in reducing the problem in the near future

(b) Reduction in the duration of treatment will infuse greater confidence in the patient to complete the treatment in the prescribed period.

(c) Because of the short duration of treatment, the organisational efforts required in terms of repeat motivations, defaulter action etc., are comparatively reduced.

(d) The cost of treatment with SCC is less than that of treatment with standard regimens where Streptomycin and PAS are included.

Even though the rewards appear to be promising, it is not easy to reach them because the challenges are gigantic.

Challenges in the Success of SCC

The spectacular results in terms of early sputum conversion and no relapse were obtained in clinical trials where patients are highly selected and every dose of medicine is almost pushed into their mouth.

But, in the field conditions where a doctor has to treat patients irrespective of their previous treatment, place of residence, etc., the same results are difficult to obtain.

Some of the major reasons are:

(i) Lack of knowledge of proper regimen. The practising doctors—whether in government service or doing private practice, are generally not aware of the clinically proven regimens and write prescriptions with combination of drugs of their own choice. It is obvious that such combinations of drugs without proper dosage, rhythm of intake and duration will not give the expected results. They may even harm the patients by creating drug resistance.

(ii) Today, it is common knowledge that the patient is the deciding factor in com-

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pletion of treatment. The patient, the family, and even friends, influence the decision-making process of treatment completion.

The results of SCC regimens in the 18 districts where Tuberculosis Research Centre (TRC), Madras, made field trials, have not been encouraging as shown in Table 1. (Tuberasculosis Research Centre, Madras, Personal Communication). The treatment completion has been of the order of 49% to 55%.

Similar results have been seen in North Arcot district of Tamil Nadu where TRC carried out its first field study (Table 2) (Sudarsanam 1985) Patients who made >40 collections were 43.7%, among those treated at DTC and of those who were treated at Peripheral Health Institutions (PHIs), only 32.8% made more than 40 collections. In this district, inputs by TRC in terms of frequent visits to PHI, maintaining constant supply of drugs, etc., were more than what can be undertaken by any District Tuberculosis Officer (DTO). Then, in a district where DTO is left to manage the programme, completion of treatment may be the same whether it be for SCC or standard regimen.

These findings show that the challenges in the field conditions are gigantic.

(iii) Organisational efforts needed for the success of SSC. The belief that because of

Table 1

Cohort Analysis—SCC (7 Districts)

Regimens	No. of Districts	Cases Admitted	Treatment Completed (Mean) %	Lost %	Other %
2 $H_3R_3Z_3$/4 H_3R_3 or 2 HRZ/6 TH	3	3238	49.0	38.0	13.0
2 HRZ/6 TH	3	695	55.0	41.0	4.0
2 HRZ/4 H_3R_3 or 2 HRZ/6 TH	1	112	79.6	13.0	8.0

Table 2

SCC Field Conditions North Arcot District Drug Collection

Type of Centre Treating Patient	Distribution of Patients	
	Upto 40	More than 40
DTC	49 (56.3)	38 (43.7)
PHI	311 (67.2)	152 (32.8)
DTP	360 (65.4)	190 (34.6)

shorter duration of treatment, default actions, etc., are minimised may not be true.

Table 3, gives the defaulter pattern under different conditions. (Aneja 1982).

Table 3

Defaulter Pattern Under Different Situations

Situation	No. of Patients	Proporation of Patients Making	
		No Default	1 or More Default
Clinical Trial			
Daily Phase	287	49.4	50.9
Biweekly Phase	182	31.9	65.6
Operational Study			
Biweekly Supervised Regimen	282	9.7	90 3
Daily Self-Administered	242	11.1	88.9
Programme			
Self-Administered	522	20.1	79.5

Under the clinical trial with SCC which most often is biphasic, about 49.0% in the daily phase and 31.9% in the biweekly phase did not default even once. That is, almost half of the patients defaulted even though they were motivated repeatedly by doctors and other staff members.

In an operational study of National Tuberculosis Institute (NTI), 90.3% defaulted when they were on biweekly supervised regimen when patient himself had to come and 88.9% patients put on unsupervised daily regimen defaulted.

In the programme conditions when doctors and staff of PHIs are least bothered, 79.5% of the patients defaulted.

In an operational study conducted by NTI to study the feasibility of SCC under District Tuberculosis Centre (DTC) conditions, it was found that only 7.8% did not default. Table 4 gives the details (Jagota, (1987). It is seen in the Table that 170 (69.4%) patients have made 1 to 5 defaults.

With this defaulter pattern, the defaulter actions are not reduced, irrespective of the drug regimens. Table 5 shows the efforts made by doctors and the staff involved in a clinical trial to retrieve defaulters. (Aneja 1982).

Table 4

Distribution of Cases by Number of Defaults

No. of Defaults	Patients	
	No.	%
0	19	7.8
1	42	17.1
2	43	17.6
3	39	15.9
4	24	9.8
5	22	9.0
6	11	4.5
7	18	7.3
8	8	3.3
9+	19	7.7
Total	245	100.0

The number of motivations at the clinic in a month and the number of home visits are

Table 5

Clinical Trial : Number of Defaulters and Total Number of Actions Taken in Each Month

Month	No. of Patients	No. of Patients Making Default	Total No. of Home Visits	Total No. of Clinic Motivations
Daily Phase				
I	292	60 (20.5)	73	118
II	288	90 (31.2)	104	214
III	287	95 (33.1)	145	213
Biweekly Phase				
IV	185	88 (47.6)	139	157
V	183	87 (47·5)	134	167

so many that PHIs do not have the means nor the inclination to undertake the responsibilities to see that the patients complete the treatment.

(iv) **Adverse symptoms**

It is claimed that toxicity for Rifampicin and Pyrazinamide are not high enongh to cause worry. But adverse symptoms which may or may not be due to the drugs can cause concern to the patients and if treating physicians are not careful to attend to the patients they are bound to default. Table 6 gives the adverse symptoms observed in an operational study with SCC conducted by NTI. (Jagota, 1987). While 20 (10.3%) had adverse symptoms due to the drugs, 70 (34.4%) had adverse symptoms due to other reasons.

Table 6

Distribution of Cases by Adverse Symptoms

	No. of Patients	%
Adverse Symptoms Present		
(i) Due to Drugs	21	10.3
(Ii) Due to Other Reasons	70	34.4
No Adverse Symptoms	112	55.1
Total Patients	203	99.8

Table 7 shows the adverse symptoms observed in a clinical trial with SCC (Aneja, 1982.) The patients with adverse symptom were as high as 58% to 68% in daily phase of the treatment. If these are not attended to pr perly, the results from SCC would be no goo

Table 7

Clinical Trial SCC : Adverse Symptoms

Month	No. of Patients	No. with Adverse Symptoms	
		No.	%
Daily Phase			
I	292	169	57.9
II	288	195	67.7
III	287	166	57.8
Biweekly Phase			
IV	185	68	36.8
V	183	35	19.1

(v) The defaults due to adverse symptom or other reasons need defaulter action. Wh the adverse symptoms are more, it would b advisable to distribute drugs fortnightly, a least in the initial stages, so that the patient may be observed. The number of defaulte actions to be taken is calculated below. Whil calculating the actions to be taken, the assum ption is made that every drug collection has potential of a default requiring two action (assuming that patient does not respond t first action) so that maximum number o defaulter actions required is calculated.

Example 1: SCC 2SHR (Daily) + 6TH (drugs issue once a month

During first two months the patient has t come daily. There would be 60 occasion for default requiring a minimum defaulte action of one daily (??)

During the 6 months when monthly collections are to be made, 6 defaults ca occur requiring 12 actions.

Example 2 : INH + Ethambutol for 1 months (Patient collecting drugs once a month)

The maximum number of defaults could b 18 requiring 36 defaulter actions at the most.

The need for taking defaulter actions will be more if supervised regimens are offered.

Thus, the claim that fewer defaulter actions would be needed with SCC is not true.

(vi) **Relapse rates**

It is proved that the relapse rate with SCC under clinical trials is almost nil provid ed the patients complete the treatment in the stipulated period. Table 8 gives the relapse rate for standard drug regimen as provided in DTP to-day (Baily 1985). The relapse rate in R_2, R_3, R_5 is significantly low. Thus relapse rate can be reduced only when the patients complete the treatment as desired.

(vii) **Cost of treatment**

Cost of chemotherapy should be considered as (1) direct cost of the drug (2) indirect cost in terms of organisational efforts. Cost benefit analysis and cost effectiveness are also to be

Table 8

Relapse Rate for Standard Drug Regimens Provided Under DTP

Regimens	Efficacy (Clinical Trials)	Relapse Rate
R_1—INH + TZN	82%	5%
R_2—INH + SM (Bi-weekly Supervised)	94%	9%
R_3—INH + PAS	86%	15%
R_4—INH + ETMB	84%	?
R_5—Biphasic INH + SM + ETMB or TH	96%	6%

considered in policy decisions. DTP is part of social planning. Control of tuberculosis cannot be achieved at the cost of other developmental programmes. Excess expenditure on short course Chemotherapy should not be at the cost of improving basic health services at the periphery. If other drugs available in the country can give almost similar results, deep thought should be given to the chemotherapy policy. This argument is not to decry SCC but only to give a proper perspective in calculation.

Thus, the challenges are more in SCC. The success of SCC depends on the proper knowledge of doctors about the drug regimens. They should realise the importance of gaining the confidence of patients by prescribing acceptable drug regimens, repeated motivation, timely defaulter actions, taking care of adverse symptoms etc. High optimism about the SCC is already giving way to mild discordant notes as mentioned in the TRC Report of their experiences in 18 districts. The report has highlighted the factors that would give good results and these are strengthening of PHIs, more facilities to DTO and his team, constant supply of drugs etc., which are very crucial and improvement of these would also improve patient compliance with standard drug regimens. Community involvement in addition to strengthening of PHIs, qualitatively and quantitatively, is the key to the success of any chemotherapy regimen.

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FIELD TRIAL OF SHORT TERM INTERMITTENT CHEMOTHERAPY OF PATIENTS WITH PULMONARY TUBERCULOSIS IN WARDHA DISTRICT

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Summary : Short course intermittent chemotherapy regimens for pulmonary tuberculosis were given a field trial from February 1982 to June 1986 in district Wardha, Maharashtra The symptomatics were picked up by door to door survey and newly detected cases who were culture positive were put on treatment. The regimens for the urban patients were $2S_2H_2R_2Z_2/4S_2H_2$ (NU1) and in half of the randomly selected patients the regimen was extended by $2S_2H_2$ (NU2). For the rural population, the regimen was $2H_2R_2Z_2/4H_2R_2$ (NR1) followed by further $2H_2R_2$ (NR2) in the half of the patients selected randomly.

Under this field trial a total of 112 patients received the regimen NU1. The percentage of patients who become sputum negative at 15 days was 44.6%, at 60 days 54.5% and at the end of treatment i.e. 180 days, 69.6%. The extension of treatment by two months (NU2) in 61 subjects did not improve the efficacy but one bacteriological failure became negative.

In the regimen NR1, 217 patients were given treatment and at 15 days the sputum negativity was 57.9%, at 60 days, 63.5% and at the end of treatment, i.e. 180 days, 76.0%. In 140 patients the regimen NR1 was extended by two months (NR2) but there was no improvement in the negativity rate.

The efficacy of the regimens, when calculated in patients who had consumed 80% or more than 80% doses by the end of the treatment was 94.8% in NU1 and 97.5% in NR1. The defaulter rate in regimen NU1 was 26.8% and in NR1 22.1%. In both the regimens it was maximum in the first two months.

The relapse rates were 0%, 0.27%, 0.97% and 3.19% in regimens NU1, NU2, NR1 and NR2 respectively.

Introduction

Chemotherapy has revolutionised the treatment of tuberculosis. Short term chemotherapy has given new hope of tuberculosis control. A number of controlled clinical trials all-over the world have proved beyond doubt that the bactericidal drugs in various combinations offer effective treatment of tuberculosis in a much shorter time. Further, in the mid-sixties, the Chemotherapy Centre at Madras showed that it was the peak and not the sustained level of drugs in the patients' blood which was more important. This led to the concept of intermittent therapy with higher doses of drugs. The results were satisfactory. Both *in vitro* and *in vivo* experimental evidence provided by Grumbach, et al 1964, Dickson and Mitchison 1966a, 1966b, Grumbach, et al 1967, Mitchison 1970, has encouraged the use of intermittent therapy in the treatment of this disease.

As shown by some studies (Fox 1979, Sivaraman 1983), intermittent chemotherapy has the advantage of not only lowering the cost of drugs but also decreasing the toxicity and side-effects of the drugs, besides encouraging the patients to complete the treatment. While most of the short course regimens in the past have been used in controlled clinical trials with a daily intensive phase followed by an intermittent continuation phase, (Hongkong Chest Services/BMRC 1978, 1979; East African/BMRC 1972, 1974, 1978, 1981, Tripathi 1979, 1981, Zierski, et al 1980, 1981); some of these studies have also been operational, (Anastasatu 1977, 1982: Hongkong Chest Service/BMRC 1978, 1979, 1981; Eule, et al 1982, Krishnaswami, et al 1982). Controlled clinical trials with intermittent regimens throughout have also proved effective (Gonsalves, et al 1982, Pacheo, et al 1982, Iturbe, et al 1982, Farga, et al 1982) but their applicability in field conditions remain to be tested. It has been observed that the success rate of any chemotherapy under field conditions falls much below that observed under controlled clinical trials. Therefore, field trials of intermittent chemotherapy in rural and urban population were considered necessary.

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The present study was taken up in February, 1982 at the Mahatma Gandhi Institute of Medical Sciences, Sewagram, Wardha to assess the efficacy of two short term fully intermittent regimens under field conditions. The efficacy of two biweekly regimens, one suitable for urban and the other for rural conditions, in previously untreated pulmonary tuberculosis patients is reported, based on interim results upto 30th June, 1986.

Material and Methods

The symptomatics identified during door to door survey were asked to provide samples of sputum, one spot and other overnight collection. Whenever spot sample was not available, two overnight samples were collected.

Sputum specimens were collected in wide mouth sterile containers and brought to the Microbiology Laboratory of Mahatma Gandhi Institute of Medical Sciences within 5-8 hours. The samples were subjected to direct microscopy by Ziehl Neelson's method and cultured on Lowenstein Jenson medium. For analysis, symptomatics positive by culture only were considered as bacillary positive cases. And those culture negative at one examination but positive subsequently were categorised as positive.

It was decided to give 6 months of biweekly therapy. In the urban cases, for the first two months, four drugs i.e., Streptomycin, Isoniazid, Rifampicin and Pyrazinamide were given and for the next four months i.e. maintenance phase, only two drugs namely Streptomycin and Isoniazid were given (NU1). At the time of case detection, half of the patients were randomly allocated for extension of the two-drug maintenance phase by anothher two months; this group was labelled NU2. However, till the end of 6 months patients on both the regimens have been analysed together.

Similarly, all rural cases were given three drugs i.e., Isoniazid, Rifampicin and Pyrazinamide for two months and then only Rifampicin and Isoniazid for another four months (NR1). In the case of rural patients also, half were randomly allocated, at the time of case detection, to extended therapy for another two months with two drugs (NR2). Till 6 months, patients in regimens NR1 and NR2 also have been analysed together. All the patients were newly detected cases who gave no history of having taken antitubercular drugs in the past. All the patients were then subjected to a thorough clinical examination including chest skiagram.

The therapy given is summarised below :

Regimen	*Rhythm*	*Duration No. of doses*
1. New Urban (NU)		
NU1 : $2S_2H_2R_2Z_2/4S_2H_2$	Biweekly	6 months 57 (19+38)
NU2 : $2S_2H_2R_2Z_2/4S_2H_2/2S_2H_2$,	,,	8 months 76 (19+57)
2. New Rural (NR)		
NR1 : $2H_2R_2Z_2/4H_2R_2$	,,	6 months 57 (19+38)
NR2 : $2H_2R_2Z_2/4H_2R_2/2H_2R_2$	,,	8 months 76 (19+57)

Dosage

As assessment of weight under field conditions was difficult, the same doses were maintained for all the patients in all the regimens.

Streptomycin	(S)	0.75 gm
Rifampicin	(R)	600 mg
Isoniazid	(H)	600 mg
Pyrazinamide	(Z)	3.0 gm

In the urban areas patients were called to specified centres and the drugs were administered to them under direct supervision of the medical officer.

In rural areas the patients were supplied their quota of drugs every month at their door step and how to take the doses was fully explained. Their therapy was, thus, domiciliary and self administered. In these cases, surveillance of drug compliance was done by :

(1) counting the left over pills;

(2) checking the colour of the patient's urine for Rifampicin intake; and

(3) checking the excretion of INH metabolites in the patient's urine.

Checking under 2) and 3) was done by surprise on some of the patients.

During treatment, sputum samples were collected at 1st and 2nd months in the intensive phase in which four drugs were administered to the urban and three drugs to the rural patients and after every month in the continuation phase, in which only two drugs were administered. Sputum collection after 15 days of therapy was also done but was begun a little later in the study.

A patient was considered cured if he/she

became culture negative at the end of the treatment.

After completion of the therapy, patients were kept under surveillance for one year, and sputum was collected at the end of 1st, 4th, 8th and 12th months to detect any relapses.

Similarly, patients were monitored radiologically every two months during the treatment and at 6 months and 12 months in the follow up phase.

Patients becoming culture positive one month after stopping the treatment were considered as relapsed cases. Those who never became negative or those who became positive within one month after treatment were considered bacteriological failures.

Results

A total of 112 newly detected patients were put on regimen NU1, i.e., $2S_2H_2R_2Z_2/4S_2H_2$. However, at the end of 180 days only 82 patients could be analysed as three patients died and 27 were lost to treatment (Table 1)

The culture negativity of sputum at different check points in patients put on regimen NU1 is shown in Table 2. At 15 days, i.e., after 4 doses, 50 (44.6%) cases were found to be culture negative, 25 were still positive but in 29 the sample could not be examined and 8 patients had dropped out of the regimen. At the end of the intensive phase, i.e , at 60 days, 61 (54.5%) cases were found to be culture negative, and 16 (14.3%) were still positive.

At the end of the treatment at 180 days i.e., after 4 months of maintenance phase (S_2H_2), sputum was cultured in only 82 patients, 30 having dropped out. Seventy eight patients (69.6%) were found to be culture negative and 4 (3.6%) were still positive. The overall efficacy of the NU1 regimen under field conditions was, therefore, 69.6% with 3.6% treatment failures and 26 8% cases lost.

Analysis of the prescribed doses taken showed that 77 (68.75%) cases took 80 per cent or more of the total doses (Table 3). At the end of the intensive phase, i.e., at 60 days, sputum negativity was 80.3% and at the end of treatment it was 94.81 per cent among them.

There were 9 cases who had taken 50-79 per cent of the total doses and only 4 were available for analysis at 180 days. All the 4 patients were culture negative. Of the 26 patients who took less than 50 per cent doses only one was analysed at 180 days and was found to be negative.

Two hundred and seventy one patients were put on regimen NR1 i.e , $2H_2R_2Z_2/4H_2R_2$ (Table 2a). At the end of the treatment a total of 211 patients could be analysed, 52 were lost to treatment and 8 died. By the end of 15 days 157 (57.9%) cases were found to have culture negative sputum. The figures at 60 days were 172 (63.5%) and at 180 days were 206 (76.0%). The overall efficacy of this regimen under field conditions was therefore, 76.0 per cent. Five cases (1.9%) were bacteriological failures and 60 cases (22.1% were lost to treatment.

Table 1

Distribution of cases according to drug regimen at the time of intake inot study

Regimen/ Group	No. eligible for intake	No. dropped out or died	No. assessed at six months
NU1 (%)	112 (100.0)	30 (26.8)	82 (73.2)
NR1 (%)	271 (100.0)	60 (22.1)	211 (77.2)
Regimen/ Group	**No. eligible at intake**	**No. eligible at six months**	**No. assessed at eight months**
NU2 * (%)	61 (100.0)	41 (67.2)	41 (67.2)
NR2 * (%)	140 (100 0)	108 (77.1)	108 (77.1)

* These cases were randomly allocated at the beginning of the treatment to receive the extended therapy of two months from NU1 and NR1. Those available at 180 days were continued on treatment.

Table 2

Culture status of NU1 and NR1 cases at different check points during six months period of treatment

Category/ Check point	Not examined: dropped out	Not examined: missed out	Not examined: Total	Examined: Cul. + ve	Examined: Cul. − ve	Examined: Total
NU1 : 112 Cases in all						
—at end of 15 days (%)	8 (7.1)	29 (25.9)	37 (33.0)	25 (22.3)	50 (44.6)	75 (67.0)
—at end of 60 days (%)	8+15 (20.5)	12 (10.7)	35 (31.2)	16 (14.3)	61 (54.5)	77 (68.8)
– at end of 180 days (%)	8+15+7 (26.8)	—	30 (26.8)	4 (3.6)	78 (69.6)	82 (73.2)
NR1 : 271 Cases in all						
—at end of 15 days (%)	6 (2.2)	72 (26.6)	78 (28.8)	36 (13.3)	157 (57.9)	193 (71.2)
—at end of 60 days (%)	6+27 (12.2)	41 (15.1)	74 (27.3)	25 (9.2)	172 (63.5)	197 (72.7)
—at end of 180 days (%)	6+27+27 (22.1)	—	60 (22.1)	5 (1.9)	206 (76.0)	211 (77.9)

Table 3

Results of treatment according to regimen and regularity of taking prescribed doses at two completion points

Regimen/ Point	Total No. assessed	>80% doses: Number assessed	>80% doses: Cul. −ve.	>80% doses: Cul. + ve	<80% doses: Number assessed	<80% doses: Cul. −ve.	<80% doses: Cul. + ve
NU1 (N=112) —at 60 days (%)	77	66	53 (80.30)	13 (19.70)	11	8 (72.73)	3 (27.27)
—at 180 days (%)	82	77	73 (94.81)	4 (5.19)	5	5 (100.0)	—
NR1 (N=271) —at 60 days (%)	197	169	147 (86.98)	22 (13.02)	28	25 (89.29)	3 (10.71)
—at 180 days (%)	211	197	192 (97.46)	5 (2.54)	14	14 (100.0)	—

Dosewise analysis revealed that 197 (72.69%)patients had taken 80 per cent or more drugs (Table 2b). The bacteriological negativity of these patients at the end of 15 days was 82.32 per cent, at 60 days it was 86.98 per cent and at 180 days it was 97.46 per cent. The bacteriological failures were 2.54 per cent.

There were 30 patients who had taken 50—79 per cent of the treatment and only 12 were available for analysis at 180 days. All the 12 were found to be culture negative. In 44 patients who had taken less than 50 per cent doses assessment at 180 days was done in only 2 patients and they were both negative.

In 61 urban cases, maintenance phase was to be extended by another 2 months by random allocation (NU2: Table 1). At 180 days 37 (60.7%) sputum negative, 2 (3.3%) sputum positive, and 2 (3.3%) sputum not examined

i.e. 41 (67.2%) cases only were available for NU2 treatment. At the end of 8 months i.e., at 240 days 40 (65.6%) patients were sputum negative and one was still positive (1.6%).

In 140 patients out of 271 placed on rural regimen, the maintenance phase was to be extended by another 2 months (NR2). Out of these, 108 (77.1%) cases were available for NR2 at 180 days. The culture status of these patients at 180 days was 100 (71.4%) negative, 2 (1.4%) positive and 6 (4.3%) sputum not examined. At 240 days, it was 106 (75.7%) negative, and 2 (1.4%) bacteriological failures.

All the patients who were negative at the end of their treatment were followed up for relapses for one year. Out of the 78 patients who were negative at the end of the regimen NU1 (Table 2), 41 were given extended treatment for 2 months (NU2 Table 1), and the remaining 37 were left for follow up (Table 4). Similarly, out of the 206 patient on NR1, 108 were allocated to NR2 and 98 were followed up (Table 4).

Out of the 37 patients for follow up at the end of 6 months treatment in NU1, only 36 could be followed up and there was no relapse amongst them (Table 4). Out of the 41 subjects for follow up in NU2, 36 were contacted and one had relapsed. In NR1, 97 cases out of 98 were followed up and there was one relapse amongst them. In NR2, out of the 108 only 96 patients could be followed up and 3 cases of relapse were detected.

In the urban regimen NU1, out of the 112 patients assessed, 23 (20.5%) defaulted within 60 days of treatment (Table 2). Another 7(6.3%) defaulted during the period 60 to 180 days. The total defaulters in this regimen were 30 (26.8%) which is inclusive of three patients (2.7%) who died during the treatment. In the rural regimen NR1, 60 (22.1%) out of 271 patients put on treatment defaulted and these included 8 (3.0%) deaths. There were no defaulters amongst the patients whose treatment was extended beyond 180 days.

Out of a total of 112 patients put on urban regimen NUI, 46(41.1%) showed mild side effects. In rural regimen NRI, out of 271 patients. 94(34.6%) had side effects. The side effects in the urban regimens were apparently higher as compared to the rural regimens but the difference was not statistically significant.

The side effects observed in majority of the patients on urban regimen were pertaining to the gastro-intestinal tract (94% of the total side effects). Four per cent had central nervous system symptoms and 2 per cent had dermal problems. In the rural regimens, out of 94 patients who showed side effects, 81 (86.11%) had gastro-intestinal symptoms, 8(8.5%) had central nervous systems symptoms and 2 (2.17%) had symptoms concerning the skeletal system.

In two cases the regimens had to be discontinued because of toxicity, one was a case of 'flu' syndrome in regimen NU1 and the other of generalised skin eruptions developing two days after the consumption of drugs in regimen NRI.

Table 4

Regimenwise distribution of relapsed cases during a period of one year

Status of cases	Regimens			
	NU_1	NU_2	NR_1	NR_2
Patients eligible to be followed	37	41	98	108
Number followed-up (%)	36 (97.3)	36 (87.8)	97 (99.0)	96 (88.9)
Number relapsed (%)	0 (0.0)	1 (0.3)	1 (1.0)	3 (3.1)

Discussion

The present study was undertaken to determine the efficacy under field conditions of two totally intermittent regimens which would cost less and yet be efficacious. The urban regimens (NU1 and NU2) were supervised and included streptomycin injections in the intensive as well as in the maintenance phase. Rifampicin was not given to these patients in the maintenance phase. The rural regimens (NRI and NR2) were self-administered domiciliary regimens where the drugs were supplied to the patients at their door steps. The regimens were non-injectable and included rifampicin instead of streptomycin in the maintenance phase.

A good regimen is that which makes the sputum negative at an early stage so as to minimise the load of infectivity in the community. Mitchison (1979) stated that culture negativity at 2 months is an early index of sterilising activity of a regimen. In controlled clinical trials, many of the daily regimens have achieved more than 90 per cent culture negativity by the end of the second month (Hongkong Chest Service/BMRC 1978, Singapore Tuberculosis Service/BMRC 1979, 1981, Mehrotra 1981). Under field conditions also some of the studies have shown over 90 per cent sputum negativity at 2 months. Gonsalves et al 1982, Iturbe et al 1982, and Farga et al 1982, studied the regimen $2RHSZ/-4R_2H_2Z_2$ for 6 months and the sputum negativity at 2 months was 91.0, 94.5 and 97.0 per cent respectively. In these regimens, however, two months' daily intensive phase was followed by intermittent phase with three drugs biweekly. The present study is a field trial and differs from the above studies in drug combination and frequency of drug administration. Under field conditions, the efficacy of the regimen NUI at 60 days was 54.5 per cent and that of NRI was 63.5 per cent. This efficacy can be considered fairly good considering that the patients had taken only 19 doses in 2 months. The success rate at the end of 180 days was 69.6 per cent in NUI and 76.0 per cent in NRI. In the past, it has been experienced that in the developing countries, the conventional 12 months regimens achieved much less than 60 per cent cure rate under programme conditions. Regimens with cure rates of 69.6% and 76% can be considered as attractive and acceptable for our country.

The lower efficacy of the urban regimen was observed to be the result of more lost patients (26.8%) and the bacteriological failures (3.6%). The same figures for NRI were 22.1 and 1.9 per cent. The main reason for this was that besides being an injectable regimen, in the urban regimen the patients were asked to come and take the drugs at a specified place and many of them defaulted to avoid the stigma of going to the Centre. Use of paramedical personnel for supplying the drugs to the patients at their homes may yield better results than calling the patients for drugs to the tuberculosis centres.

In this study, an attempt was made to assess the bacteriological negativity of the patients at 15 days i.e., after giving 4 doses only. In patients who had taken 80% or more than 80 per cent doses, the bacteriological negativity at 15 days was 67.2 per cent in NUI and 82.3 per cent in NRI. This indicates a good sterilising activity of these regimens even though they are intermittent and biweekly. The importance of this in the reduction of infectivity in the community is obvious. As the idea of assessment of efficacy at 15 days was a later addition to the protocol of the study, in many cases the sputum was not collected at 15 days and hence the field efficacy at 15 days in both the regimens is low (44.6 and 57.9 per cent in NUI and NRI respectively).

In the same group of patients the culture negativity of the sputum at 60 days and 180 days in regimen NUI was 80.3 and 94.8 per cent respectively. The figures for NRI were better (86.98 and 97.46 per cent respectively). The bacteriological failure were 5.2 per cent in NUI and 2.5 per cent in NRI. These figures show that if the drugs are taken regularly then the regimens are highly effective. The regimen NRI which had rifampicin in the continuation phase was better though the difference is not statistically significant. Also, the addition of streptomycin to the regimen in the intensive phase has not yielded any additional benefit. However, the follow up study of these patients has shown that the relapse rate was much lower in patients on streptomycin regimen as compared to those on rifampicin (Table 4). The advantages of both inclusion and exclusion of streptomycin from the routine administration of antitubercular drug therapy therefore need to be studied further.

In both regimens the extension of the 6 months by additional 2 months in 61 patients in NU2 aud 140 patients in NR2 showed no improvement either in the bacteriological negativity or the relapse rate, though in the regimen NU1, 1 out of the 2 bacteriological failures did become sputum negative after 2 months of additional drug therapy. It seems that, even under field conditions, for biweekly regimens like NU1 and NR1, a duration of six months is quite sufficient and the therapy needs be extended only for treatment failures. This would reduce both the duration and expenditure on the drugs.

Defaulter in both regimens were maximum within the first two months. Those patients who were able to tolerate the drugs in the intensive phase had very little problem during the continuation phase and the drug that was not given in the continuation phase in any of the regimens was pyrazinamide. Probably, the high dose of 3 grams was difficult to tolerate and the patient suffered from gastritis, nausea and vomiting.

It is concluded that the present totally intermittent biweekly regimens with good

sterilising property, low cost and more than 60 per cent effectiveness could be used under field conditions to bring about a rapid reduction in the infectivity pool.

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LONG TERM FOLLOW UP AFTER STANDARD CHEMOTHERAPY OF PATIENTS WITH PULMONARY TUBERCULOSIS

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Summary : Two hundred ex-service personnel, presently in the age group 20-61 years, followed up for a total of 2470 person years, were analysed after they were given standard antituberculosis therapy 3 SHP/E and thereafter $S_2 H_2$ for periods varying from 6-24 months to ascertain the effect of the factors, viz. age, smear/culture acid fast bacilli positivity, initial radiological extent, radiological sequelae and duration of therapy in the reactivation of the disease.

The analysis revealed that eleven patients exhibited features of reactivation of the disease during the follow-up. Out of the factors considered in this study, reactivation was found more common in those who did not comply with regular and continued therapy for the recommended period

Introduction

Historically, tuberculosis has been a disease prone to relapse even after long periods of apparent inactivity (Edsall and Collins, 1973). Hence, long term follow-up of patients with inactive disease is recommended, particularly in developing countries where a fair number of patients do not comply with the antituberculosis regimen in the optimum dose and rhythm for the prescribed period (Philips, 1964; Grzybowski et al, 1966; Pamra et al, 1974; Nakielna et al, 1975). Recognition of reactivation of the disease in these cases is important as they contributed about one third of all active cases at a time and it forms a major part of the reservoir of infection (Grzybowski et al, 1966). While developing countries contribute to three fourths of these cases, reports of such long term follow-up are scanty in the literature, for various social and economic factors (Pamra et al, 1974; 1976; Chakravorty and Gothi, 1976; Tripathi, 1981; Crofton and Douglas, 1983). Hence, a retrospective analysis of these patients treated earlier with standard therapeutic regimen and reporting to a teaching service hospital (for assessment of disability for pensionary readjustment) was carried out to establish the relationship, if any, between their reactivation of the disease and associated factors.

Material and Methods

Ex-service personnel who suffered from pulmonary tuberculosis (PT) while in service and were treated as inpatients (initially in all cases) with standard antituberculosis regimen and later reported for assessment of medical disability formed the material for the present study.

Those reporting regularly for follow-up were subjected to clinical, radiological and bacteriological evaluation (at least three early morning sputum samples after saline mouth wash) for reactivation of the disease, if any. Patients with non-homogeneous, static fibrotic radiological lesions covering, in all, not more than one fifth of two lungs put together were declared to have insignificant radiological sequelae (Table 1).

Diagnosis was suggested in 'smear cum culture negative group' by features of tuberculous toxaemia duly supported by softer and increasing lung shadows (cavitary, non-cavitary, miliary or non-homogeneous) persisting even after exposure to non-antitubercular bactericidal antibiotics. Radiological extent was decided by the criteria devised by Tuberculosis Association of India. They were treated with Inj. Streptomycin (SM) 0.75—1.0g IM, INH 300 mg single dose and PAS 6-7.5g twice daily (or ethionamide 750 mg—1000 mg in two doses in patients not tolerating PAS) all daily for 3 months followed by twice weekly SM in the same dosage as above and INH 14 mg/kg body weight for periods ranging upto 15-21 months (total 18-24 months). Those given alternate regimes in different combinations and rhythms in 1950s or earlier (when drugs were not available) and those infected with AFB resistant to drugs as above were excluded from the present analysis.

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Table 1

Reactivation in relation to host factors

	Factor	No. of cases	Reactivation	%	Significance	RR*
1.	Age					
	(a) Above 45 yrs	59	5	8.47	P> 0.05	1.99
	(b) Below 45 yrs	141	6	4.26		
2.	Smear/Culture					
	AFB Positivity					
	(a) Positive	134	8	5.97	P> 0.05	1.31
	(b) Negative	66	3	4.54		
3.	Radiological Extent					
	(a) Moderate to Far Advanced	121	6	4.95	P> 0.05	0.78
	(b) Minimal	79	5	6.33		
4.	Radiological Sequelae					
	(a) Significant	159	11	6.92	—	—
	(b) Insignificant	41	—	—		
5.	Duration of Therapy					
	(a) <12 months	44	6	13.64	P< 0.05	4.20
	(b) >12 months	156	5	3.20		

Note :—Moderate to Far Advanced cases include cavitary lesions.

*RR=Relative Risk

Two hundred and seventy one patients, in the age group 20-61 years, who reported to a teaching service hospital in Pune for assessment of medical disability during the period from December 1983 to June 86 were analysed. Seventy one patients were excluded for want of proper medical data and or details of therapy administered at the time of the acute illness.

Results

Out of 200 patients thus evaluated, majority were in the younger age group. Eleven patients (5.5%) showed features of reactivation. The relative risk (RR) for reactivation, among those more than 45 years of age, is about twice as compared to the younger age group. When analysed in terms of sputum AFB positivity, RR for reactivation was found to be 1.31. There was no correlation between the initial radiological extent and the chances of reactivation (RR—0.78). It was interesting to note that none of the patients having insignificant radiological sequelae at the time of completion of therapy exhibited reactivation during the follow-up thereafter (Table 1).

Duration of therapy related to RR

Only 156 patients (78%) completed the recommended regime. The same could not be ensured in the remaining group who had to be released/invalided out of service for various service factors. The observed RR in those who did not complete therapy (minimum of 12 months' drug regimen) was statistically significant when compared to the remaining group ($P < 0.05$).

The reactivation rate dropped down as the duration of follow-up increased. There was only one case out of 39 patients when they were followed up for more than 15 years (Table 2).

Table 2

Reactivation in Relation to Follow up

	Years	No of cases	Reactivation	%
1.	1— 5	45	5	11.11
2.	6—10	64	2	3.12
3.	11—15	52	3	5.77
4.	16—20	21	—	—
5.	21—25	16	1	6.25
6.	26—30	1	—	—
7.	31—35	1	—	—

tom, though, in retrospect after replacement therapy, his gain in weight and vitality indicated that he may have been less fit than he realised before treatment.

A corticotrophin assay suggested increased activity. Release of corticotrophin and melanocyte-stimulating hormone appeared to occur separately. The usefulness of the water-load test in minor degrees of adrenocortical insufficiency is questioned.

I wish to thank Dr. T. M. Chalmers, under whose care the patient was studied, for assistance with the preparation of this report. I am indebted to Prof. A. Kekwick for criticism of the text, and to Miss Audrey Moxham for measuring the cortisol secretion-rate. Dr. Beryl Davies kindly estimated the plasma-corticotrophin.

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Preliminary Communications

INTERMITTENT TREATMENT OF PULMONARY TUBERCULOSIS

A Concurrent Comparison of Twice-weekly Isoniazid plus Streptomycin and Daily Isoniazid plus *p*-Aminosalicylic Acid in Domiciliary Treatment

From the Tuberculosis Chemotherapy Centre, Madras *

DOMICILIARY chemotherapy of tuberculosis has become accepted practice in developing countries, but the best method of administering the drugs is still in question. Self-medication for long periods may result in irregularities, and, although fully supervised daily chemotherapy has been used to avoid these, it imposes a considerable strain on clinic and patients, and is hardly practicable in developing countries (see review by Fox [1]). If, instead, supervised therapy could be given intermittently—e.g., twice a week—the method could become more generally applicable.

A rational basis for intermittent chemotherapy was suggested by previous studies at this centre. In a comparison of three regimens of isoniazid alone with a regimen of isoniazid plus *p*-aminosalicylic acid (P.A.S.) [2] it had been found that a daily dosage of isoniazid (7·8–9·6 mg. per kg. body-weight) was more effective when given in one dose than when given in two doses. There was evidence that this was because a high peak concentration of isoniazid in the serum played a more important role in the response to treatment than the maintenance of a continuous inhibitory level of the drug.[3] It was therefore reasonable to study regimens in which the interval between suitably high doses of isoniazid was extended. It seemed unlikely that efficacy would be seriously diminished by a limited degree of intermittency, in view of our observation that patients who showed irregularity (on the evidence of urine tests) in taking isoniazid in a large dosage every day responded to treatment as well as those who were completely regular.[4 5]

There is relevant experimental evidence that a high dosage of streptomycin or isoniazid given at intervals of five or seven days is effective in suppressing the development of tuberculosis in the guineapig.[6 7] There is similar evidence, in tuberculosis of the mouse, of the effectiveness of isoniazid every seven days,[8] and of isoniazid plus streptomycin every three days.[9]

In view of our finding and the experimental evidence we decided to test the effectiveness of a combination of the two most potent standard anti-tuberculosis drugs—namely, isoniazid and streptomycin—given twice-weekly under supervision, the minimum interval considered to offer substantial practical advantages over a daily regimen. Isoniazid was to be given in high dosage and streptomycin was to be administered in doses of 1 g., which, in view of the light weight of our patients, is a higher dosage than is usual.

THE INVESTIGATION

In June, 1961, we started a controlled comparison of this supervised intermittent regimen with our standard unsupervised daily regimen of isoniazid plus P.A.S. The findings are of sufficient importance to merit this preliminary communication, which gives bacteriological results at six and nine months. (Detailed findings at one year will be published later in the *Bulletin of the World Health Organisation*.)

Chemotherapeutic Regimens

The two chemotherapeutic regimens studied were:

SHTW.—Streptomycin sulphate by intramuscular injection in a dose of 1 g. irrespective of the patient's weight, plus isoniazid in a single oral dose of 650 mg. for a patient weighing 100 lb. (45·4 kg.); the two drugs were given together twice weekly (at intervals of three and four days). Each dose of streptomycin was, on average, 27·0 mg. per kg. initial body-weight (range is 18·2 to 53·7 mg.). The dosage of isoniazid was increased for heavier and reduced for lighter patients,[4] the average being 13·9 mg. per kg. body-weight initially (range 12·5 to 16·1 mg.).

PH.—Isoniazid 200 mg. daily plus P.A.S. (sodium salt) 10 g. daily in 8 cachets (4 in the morning, 4 in the evening) for a patient weighing 100 lb. or more. The dosage was reduced for lighter patients.[10] The average daily dosage of isoniazid was 4·4 mg. per kg. body-weight initially (range 3·7 to 6·3 mg.) and that of P.A.S. was 220 mg. per kg. (range 180 to 320 mg.).

Management of the Patients

The patients in the SHTW series attended the centre's clinic twice a week and received an injection of streptomycin; a dose of isoniazid was given at the same time under the direct supervision of the clinic staff. The PH patients attended the clinic once a week for a supply of cachets, which were to be taken at home. In other respects the management of the patients in both series followed the same lines as in a previous investigation at this centre.[2] All the patients were to be treated as outpatients for twelve months.

Among other procedures, specimens of sputum were

* The centre is under the joint auspices of the Indian Council of Medical Research, the Madras State Government, the World Health Organisation, and the Medical Research Council of Great Britain. The research of the centre is guided by a project committee consisting of representatives of the above agencies and the director of the centre. The British Medical Research Council (acting through their Tuberculosis Research Unit) are responsible for advising the World Health Organisation on the research. This preliminary communication has been prepared by the senior scientific staff of the centre.

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examined bacteriologically before treatment and monthly thereafter. These specimens were cultured on Löwenstein-Jensen medium according to the procedure described previously.[2] For the purpose of this communication, progress has been assessed only by the culture results of two "collection" (overnight) and one supervised "spot" specimen of sputum obtained at six and at nine months.

Definition of Suitable Cases

The patients were drawn from the same area in Madras City as before.[2 4 5] They all conformed to the same criteria as in the earlier studies. In particular, all had bacteriologically confirmed pulmonary tuberculosis on admission, were aged 12 years or more, and as far as was known had either received no previous anti-tuberculosis chemotherapy or had received it for not more than two weeks.

Patients Admitted to Study

In all, 165 patients were allocated by a random procedure either to the intermittent regimen (83 SHTW patients) or to the daily regimen (82 PH patients). 15 patients have been excluded from the analysis because they had been excreting resistant organisms on admission to the investigation; 7 (3 SHTW, 4 PH) had organisms resistant to isoniazid, 5 (1 SHTW, 4 PH) had organisms resistant to streptomycin, and 3 (all PH) organisms resistant to both drugs. There remain 150 patients (79 SHTW, 71 PH) for analysis.

Condition on Admission

The age, sex, and weight distributions of the patients (not tabulated here) were similar for the two series on admission. Table I shows their pre-treatment radiographic and bacteriological condition. The radiographic findings were reported from single full-plate radiographs by an independent assessor (Dr. J. Frimodt-Møller), who was unaware of the treatment series of any patient. He graded cavitation as extensive in 41% of the 79 patients in the SHTW series and in 15% of the 71 in the PH series; 5% and 6%, respectively, had no cavitation. With regard to total extent of disease, 28% of patients in the SHTW series and 31% in the PH series had extensive or gross disease; 48% and 52%, respectively, had four or more lung zones involved in disease. The distributions of the bacterial content of the first (or only) collection specimen of sputum were also similar. Thus, 10% of both series were negative on direct smear examination; the proportion with 2-plus or more positive smears were 67% for the SHTW and 72% for the PH series, respectively.

TABLE I—RADIOGRAPHIC AND BACTERIOLOGICAL CONDITION ON ADMISSION TO TREATMENT

Condition on admission to treatment	SHTW		PH	
	No.	%	No.	%
Extent of cavitation:				
Nil	4	5	4	6
Slight	26	33	26	37
Moderate	30	38	30	42
Extensive	19	24	11	15
Total extent of disease:				
Minimal or slight	6	8	1	1
Limited or moderate	51	65	48	68
Extensive or gross	22	28	22	31
Number of lung zones involved in disease:				
2 or 3	41	52	34	48
4 or 6	38	48	37	52
Bacterial content of sputum:				
(1st or only "collection" specimen):				
Direct smear negative	8	10	7	10
Direct smear positive:				
1-plus (scanty)	18	23	13	18
2-plus (moderate)	41	52	44	62
3-plus (heavy)	12	15	7	10
Total patients	79	100	71	100

TABLE II—PRESENCE OF TUBERCLE BACILLI IN MULTIPLE SPUTUM SPECIMENS AT SIX AND NINE MONTHS

Months after start of chemotherapy	Treatment series	Total patients (A)	Tuberculous death	Patients with at least one specimen positive on culture	Patients with all cultures negative	
					No.	% of A
6	SHTW	77	2	10	65	84
	PH	68	1	9	58	85
9	SHTW	72	2	3	67	93
	PH	65	1	6	58	89

RESULTS

Deaths

3 patients died of pulmonary tuberculosis, 2 (1 SHTW, 1 PH) in the first week, and the third (SHTW) in the sixth month. This patient's sputum was culture-negative at three and four months, but she had a serious radiographic deterioration in the fifth month (no culture results were available at five months). One other patient (PH) died suddenly from a non-tuberculous cause (believed to be pulmonary embolism) in the eighth month; the sputum had been culture-negative from one month. Permission for necropsy was refused for all 4 patients.

Premature Termination of Originally Prescribed Chemotherapy

3 patients (all PH) had their original regimen terminated for drug toxicity, 1 in the first, 1 in the fifth, and 1 in the ninth month. 6 patients (5 SHTW, 1 PH) became uncooperative and stopped the treatment, 2 (SHTW) in the third month, 1 (SHTW) in the seventh, and the other 3 in the eighth month; in 3 of the SHTW patients streptomycin toxicity may have been a contributory factor.

The patient who died from a non-tuberculous cause in the eighth month has been included in the analysis at six months, and the 9 whose originally prescribed chemotherapy was terminated prematurely have been included up to the time of the termination. The patients who died of tuberculosis have been retained in the analysis.

Bacteriological Findings

The results of culture examination of the sputum specimens at six and nine months are shown in table II. (Apart from the above exclusions, results are not available for 1 patient [PH] at six months and 3 [2 SHTW, 1 PH] at nine months.) The average number of culture results per patient was 2·7 in each series at six months and 2·8 in each series at nine months. At six months all the cultures were negative in 84% of 77 SHTW patients, compared with 85% of 68 PH patients; at nine months the corresponding figures were 93% of 72 and 89% of 65, respectively.

Drug Toxicity

2 patients in the SHTW series had toxic symptoms attributed to isoniazid. One patient had convulsions a few hours after the administration of chemotherapy on two occasions in the first two months of treatment; these did not recur after pyridoxine in a dosage of 6 mg. twice weekly was added to the chemotherapy. The other patient first complained of symptoms attributable to peripheral neuropathy in the second month; pyridoxine in a dosage of 6 mg. twice weekly was given with the chemotherapy with subsequent improvement in the clinical symptoms and signs. Complaints of giddiness were recorded in 24 of the 79 patients in this series (7 of 71 PH patients also complained of giddiness), once in 15 of them and on two or more occasions in 9. In 5 of the latter it was necessary to reduce the high dosage of streptomycin to approximately 15 mg. per kg. body-weight for each dose; 4 of the 5 remained under treatment to the end of the period.

3 patients in the PH series developed hypersensitivity reactions to P.A.S. in the early weeks of treatment; as noted above, it became necessary to change to a different chemotherapeutic combination. Desensitisation was attempted and was initially successful in 2 patients; however, both again developed reactions which could not be controlled. All 3 patients received prednisone.

DISCUSSION

In the treatment of pulmonary tuberculosis with combined chemotherapy, it is standard practice to give the two or more drugs in one or more doses daily; regimens consisting of one drug (isoniazid or P.A.S.) given daily and another (usually streptomycin) given on two or three days a week are no longer regarded as adequate by most authorities.

There have been a few reports of studies in which the entire medication, whether with a single drug or a combination, was less frequent than once a day.

Frimodt-Møller et al.[11] compared isoniazid alone every fourth day with the same dosage given daily, and found similar radiographic responses in the two series at twelve weeks.

Katz et al. [12] and Chambers et al.[13] treated a small group of patients with streptomycin 2 g. plus isoniazid 500 mg., both being given together by injection twice weekly. They considered that the radiographic and bacteriological improvement was inferior to results achieved previously with daily isoniazid plus twice-weekly streptomycin.

Tyrrell [14] gave newly diagnosed cases streptomycin 1 g. and isoniazid 400 mg. on the same day twice weekly, half being treated in hospital and half as ambulatory outpatients. At six months, sputum conversion had occurred in 78% of 45 inpatients and in 80% of 46 outpatients; there was no comparative group on daily drug administration.

Holmes et al.[15] reported on 29 patients given a large dose of isoniazid once a week for periods of up to three months, but only 2 became culture-negative.

Streptomycin plus isoniazid, the two drugs being given together every other day, has been used with success by Mackay-Dick and his colleagues,[16–19] and by Hutton et al.[20]; but in these series the intermittent regimen was used as continuation therapy after a period of one to three months of daily combined chemotherapy.

In our controlled study, streptomycin plus isoniazid, both drugs being given together twice a week in high dosage under supervision as a primary treatment (SHTW regimen) has proved to be therapeutically as effective as the standard oral two-drug regimen of P.A.S. plus isoniazid, prescribed for self-medication daily (PH regimen). Although results are at present complete only up to nine months, there is no reason to think that the position will be different when all the results at twelve months are available.

Evidence of toxicity was seen in some patients in both series.

In the SHTW series, it was necessary to reduce the dosage of streptomycin in 5 patients because of giddiness. In 15 other patients who reported giddiness, it was not considered necessary to reduce the dosage, and in most it is uncertain how far, if at all, their complaints were due to the streptomycin. Isoniazid caused convulsions in 1 patient and peripheral neuropathy in 1 other; both responded to 6 mg. of pyridoxine given twice weekly with their chemotherapy. Probably the isoniazid toxicity could have been prevented if this small dose of pyridoxine had been given from the start of treatment.[9]

In the PH series 3 patients developed hypersensitivity to P.A.S., and their original treatment had to be terminated.

5 of 79 patients on intermittent chemotherapy became uncooperative and stopped their treatment. The reasons are uncertain, though streptomycin toxicity may have been a factor in 3. A fuller assessment of the acceptability of the intermittent regimen should be possible when the findings for one year are available, but it will be difficult to make valid comparisons with the regimen for daily self-medication.

The encouraging therapeutic results of intermittent chemotherapy in this trial suggest that a change in orientation of drug administration for tuberculosis may become possible in the developing countries, from the present daily self-administration to twice-weekly fully supervised administration. The next steps for consideration include study of dosage and acceptability in greater detail and of a decrease in the frequency of administration to once weekly. Once-weekly regimens are now being investigated at this centre; if this frequency should prove successful, it would offer further advantages, in convenience for the patients, in economy, in applicability to mass treatment, and possibly in decreased toxicity.

SUMMARY

165 patients were allocated by a random procedure to an intermittent chemotherapeutic regimen of streptomycin plus isoniazid given together under supervision twice weekly (SHTW regimen, 83 patients) and to a standard regimen of P.A.S. plus isoniazid for daily self-administration (PH regimen, 82 patients). 15 patients (4 SHTW, 11 PH) have been excluded from the analysis because they had organisms resistant to streptomycin or isoniazid or both at the start of treatment.

This preliminary report gives the sputum-culture results at six and nine months.

The pre-treatment status of the patients in the two series was similar in respect of a number of factors examined—namely, age, sex, weight, radiographic findings and bacterial content of the sputum.

3 patients (2 SHTW, 1 PH) died of pulmonary tuberculosis. At six months all the cultures were negative for 84% of 77 SHTW patients compared with 85% of 68 PH patients. The corresponding proportions at nine months were 93% and 89%, respectively.

2 SHTW patients had isoniazid toxicity, treated with 6 mg. of pyridoxine twice a week without interrupting the regimen; in 5 SHTW patients the dosage of streptomycin was reduced because of giddiness; and 3 PH patients had their originally prescribed treatment terminated for P.A.S. toxicity. 6 uncooperative patients (5 SHTW, 1 PH) stopped treatment. This may have been partly due to streptomycin toxicity in 3 SHTW patients.

The encouraging results of twice-weekly supervised chemotherapy in this trial suggest that a change in orientation of drug administration for tuberculosis in developing countries may become possible.

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Excerpts from:

A CONCURRENT COMPARISON OF HOME AND SANATORIUM TREATMENT OF PULOMONARY TUBERCULOSIS IN SOUTH INDIA*

BY

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS

DISCUSSION

The present report is mainly concerned with the results of the comparison of treatment of patients for a period of 12 months at home or in sanatorium. It will be appreciated that there is comparatively little information, obtained from controlled clinical trials, on the value of chemotherapy either in the tropics or in under-developed countries, apart from the hospital studies reported from East Africa (Hutton et al., 1956; Fox et al., 1956; Howells & Swithinbank, 1957; East African/British Medical Research Council Sulphone Investigation, 1959), and from India (Frimodt-Møller, 1949, 1955; Frimodt-Møller et al., 1953, 1954). Furthermore, a review of the world literature has revealed that few controlled studies of the relative value of bed-rest and ambulation in the treatment of pulmonary tuberculosis have so far been reported. Wier et al. (1956, 1957) reported an eight-month comparison of modified bed-rest and ambulation in sanatorium patients in the USA. Tyrrell (1956) compared sanatorium treatment with ambulant treatment at home for a period of three to six months in patients from Glasgow. The Research Committee of the Tuberculosis Society of Scotland (1957) reported interim results of a study of chemotherapy and bed-rest at home or in hospital for a minimum period of three months, in comparison with the same chemotherapy in patients permitted to lead their normal working life. Acutely ill patients were not admitted to these studies, which are hardly comparable with the present investigation, in which the great majority of the patients had moderately advanced or far advanced disease, all had symptoms, and many were clinically ill, a number seriously so (see Appendix). Furthermore, treatment was for a period of 12 months and, in addition, is being continued at home for a second 12 months for patients in both series in order to investigate relapse and its pre-

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vention. Finally, the social conditions of our patients were very different from those in the American and British inquiries.

For the present study it was decided to use a standard form of oral chemotherapy—namely, isoniazid 200 mg daily together with PAS (sodium salt) 10 g daily, for patients weighing 100 lb. (45 kg) or more. The dosage was reduced for lighter patients, and ranged from 3.7 to 6.6 mg/kg bodyweight for isoniazid and from 0.19 to 0.33 g/kg for PAS (sodium). The drugs were given together in the same cachet and were prescribed in two doses daily. This combination was chosen because it is administered orally ; it is known to be efficacious ; it is not associated with a high incidence of side effects or toxic manifestations ; and because it has been used in controlled clinical studies, so that much is known about it in relation to other regimes (Great Britain, Medical Research Council, 1953b, 1955 ; Bowerman, 1957 ; East African/British Medical Research Council Sulphone Investigation, 1959). The combination was given to the patients in both series, so that the essential comparison was of treatment at home with treatment in sanatorium for 12 months, the patients receiving the same standard chemotherapy throughout this period.

In all, 96 patients were allocated to treatment at home and 97 to treatment in sanatorium, by a process of randomization. Of these, 82 at home and 81 in sanatorium form the basis of the main analysis in this report. These were the patients who had organisms sensitive to both drugs at the start of treatment, maintained that they had had no previous antituberculosis chemotherapy, or chemotherapy for less than two weeks (despite questioning on several occasions during treatment), and followed the prescribed course of treatment for the full 12 months.

Although the process of randomization was strictly observed, important pretreatment differences were, in the event, found between the two series of patients. The differences were in respect of the extent of cavitation and the total extent of disease radiographically, and in the bacterial content of the sputum. Although slight chance differences in pretreatment condition are to be expected in studies based upon random allocation of treatment, large differences in important criteria, as in the present study, represent a most unusual occurrence. The pretreatment differences have complicated the analysis of the present data. Since the disparity was greater for females than for males it has been necessary in this report to present the results separately for the males and females in the two series, and, in addition, to make special investigations of the influence of the pretreatment differences on the response to treatment in the two series. The risk of such differences might be reduced in future studies, especially if a wide range of disease types is being studied, by classifying the patients on the basis of the radiographic appearances and then allocating treatment at random within each class.

The most important finding is that even though the 49 *males* in the home series were at a disadvantage in respect of the radiographic features and bacterial content of the sputum when treatment started, as compared with the 50 males in sanatorium, there was little to choose between the progress of the males in the two series over the 12-month period. The sanatorium patients gained much more weight, as might have been expected, and the response of the erythrocyte sedimentation rate was greater. Nevertheless, the radiographic and bacteriological responses, which are the important assessments, show at most only a slight benefit to the sanatorium series. At the end of 12 months, 10% of the patients in each series had bacteriologically active disease, on the basis of very stringent criteria.

Because of the major pretreatment differences already referred to, it is less easy to interpret the direct comparison of the results of the treatment for *females* in the two series. These results showed definite radiographic and bacteriological disadvantages to the 33 treated at home, compared with the 31 in sanatorium. When allowance was made for pretreatment differences by statistical standardization, the radiographic responses were similar in the two series, but the bacteriological disadvantage to the females at home persisted. Taking these findings into consideration, it has been concluded that any difference which may exist between the response to treatment at home and the response to treatment in sanatorium for females in similar clinical condition before the start of treatment is small.

Summarizing the position for both sexes together, it is apparent that treatment at home gave results closely approaching those of treatment in sanatorium and that the differences between the results of home and sanatorium treatment were surprisingly small.

It should be noted that these satisfactory findings in the home patients have been obtained even though

the majority had major lesions, and that a high proportion had unfavourable clinical features when treatment began. The patients who did not attain bacteriological quiescence had, in the main, extensive disease and cavitation. It seems very likely that if it were possible, either as a result of mass radiography, or of propaganda directed at the general public and the medical profession, to diagnose the disease in its earlier stages, the results of domiciliary treatment might be even better than those reported here. It is also possible that better results could be obtained, even with a group of patients as ill as those in the present study, if the chemotherapy were changed to another combination when patients appeared unlikely to convert their sputum to bacteriological negativity on isoniazid plus PAS.

It has generally been considered that a good diet, satisfactory accommodation, adequate rest and nursing care together make an important contribution to the treatment of tuberculosis, and that they represent advantages of sanatorium treatment. In the present study, the patients treated at home were at a major disadvantage in all these respects but, despite this, they fared remarkably well; these factors appear to have had little influence on the results of treatment.

It has been established that there were major differences between the two series of patients in respect of diet during the course of the 12 months, the sanatorium diet being balanced and clearly superior. It will be possible, when the data have been analysed in detail, to study whether the attainment of bacteriological quiescence or the persistence of active disease is related to the diet of the patient. It is, however, already apparent that despite diets which were deficient in important factors, notably the protein content, the patients at home, as a group, made good progress. On the other hand, the control group in sanatorium, despite having a balanced diet, with an adequate protein content, and making substantial weight gains, derived surprisingly little additional benefit. The role of diet in the attainment of ultimate cure, however, has still to be investigated.

It has also been shown that the accommodation of the majority of the home patients not only before but during treatment was very unsatisfactory, a high proportion living in conditions of overcrowding. In addition, the home patients, especially the females, had less rest and returned to active work earlier. These further differences, which are usually regarded as predisposing to an unfavourable response to treatment, also do not appear to have affected the outcome to an appreciable extent.

An advantage of treatment in sanatorium is that the administration of medicines can be supervised, and, apart from major toxicity, no difficulty with the administration of medicine was encountered in the present study. However, an unexpected problem arose in persuading the home patients to take the medicine regularly, especially once they felt well. This occurred even though great emphasis was laid on the importance of regularity by all the clinical staff and although most patients attended the Centre regularly for their weekly supplies of medicine and their monthly examinations. In order to supervise the self-administration of the medicine, urine tests for PAS were introduced, and also counts were made of the patients' stock of cachets to see that the correct number remained. The most valuable checks by both methods were those made at surprise visits to the home. Although there was good evidence that a number of the patients were irregular in taking their medicine, it has not been possible to show that this was associated with clinical disadvantages during the 12-month period; however, the possibility of subsequent clinical disadvantages still remains to be studied. But even if moderate irregularities are ultimately shown to carry little long-term disadvantage, there must obviously be some level of intake below which irregularities do become important. Thus, in any scheme for domiciliary treatment depending on the self-administration of medicines, particular emphasis should be laid on the importance of regularity in taking them. Moreover, the present study has shown that mere regularity in attendance at a clinic does not necessarily mean that the patient is co-operating by taking his medicine. Difficulty with the self-administration of a combination of isoniazid and PAS in Britain has been reported by Simpson (1956), Dixon, Stradling & Wootton (1957), and Wynn-Williams & Arris (1958).

In contrast to these disadvantages of treatment at home, two unexpected advantages became apparent during the course of the study. The first advantage of treatment at home *in this study* was sociological. A detailed and careful sociological record was kept for each family. Whereas major problems were encountered in eight of the 96 home families, they arose in 20 of the 97 sanatorium families. Moreover, the sociological difficulties in the families of sanatorium patients were usually more serious than those in the families of patients treated at home. For example, there was one case

of infidelity in the home series, but in the sanatorium series there were six cases, anda suspicion of infidelity of a spouse in three more. There is little doubt that the long-term sanatorium treatment of patients *in this particular study* proved disruptive to family life, and this must be considered a disadvantage of treatment in the sanatorium series.

The second advantage concerns the co-operation of the patients. When this study was being planned, the general consensus of expert opinion, both in Europe and India, had been that it would be very difficult to obtain the co-operation of a high proportion of any group of patients in treatment at home, even for as long as three months, but that patients would welcome treatment in sanatorium. In the event, only one of the 96 patients allocated to treatment at home, compared with seven of the 97 patients admitted to sanatorium, was lost from treatment during the 12 months. In five more sanatorium patients there were interruptions in the sanatorium stay, although these did not necessitate the exclusion of the patients concerned from the main analysis. It proved much more difficult to persuade male patients to remain in sanatorium than female patients, 10 of the above 12 sanatorium patients being males. This difficulty in persuading patients to remain under treatment in sanatorium for a long period of time, despite a very active welfare service for the patients and their families, must be considered a major disadvantage of the sanatorium treatment. However, without the highly organized domiciliary service which concentrated on persuading patients to attend, especially when there were signs that they were becoming inattentive to treatment, it is certain that in this study a considerable proportion of the home patients would have stopped treatment.

In view of the poverty of the patients and their families and the need to keep their co-operation, a limited amount of financial assistance was given to more than half the families, as the main earner in the family often had to remain off work for several months or in sanatorium for a full 12 months. This financial assistance to the families was never above a modest level. As might have been expected, the families of male patients in both series needed more financial assistance than the families of female patients, and more assistance was required for the families of patients at home than for those of patients in sanatorium. It seems likely that this assistance contributed to the good co-operation of both series of patients, although it did not succeed in preventing the losses from sanatorium.

The conclusion from the present study that (except for some of the most severe cases) it is possible to obtain good results, at least for a period of 12 months, from treatment at home has practical implications. Provided it can be shown that relapse is infrequent and that there is no special risk to contacts if patients are treated at home, and provided that the results of this study would apply in other communities, there may be little to gain from admitting the general run of patients to sanatorium. There would still remain, however, a need to admit selected cases for in-patient care for example, gravely ill patients, patients suffering from complications such as haemoptysis or spontaneous pneumothorax and those needing special management, such as pregnant patients and those for whom it is decided that surgery is necessary. The management of the more seriously ill patients who were treated at home in this study would certainly have been easier in sanatorium, since this would have given greater control over the patient and his treatment. If domiciliary treatment is embarked upon on a large scale, it would also appear essential to have access to a small number of hospital beds for non-tuberculous conditions. In the present study it became necessary to admit 13 (13%) of the home patients to hospital, mostly for short periods only, for the investigation or treatment of such conditions.

It cannot be assumed that any routine tuberculosis clinic would automatically obtain results approaching those reported here. The experience of this Centre suggests that certain minimum facilities are necessary for the satisfactory organization of an efficient domiciliary service based on a tuberculosis clinic. Among these facilities are an adequate supply of medication, and alternative medicaments for patients who are not responding satisfactorily; enough staff to supervise the patients, including a social worker and a public health nurse; an efficient appointment system, so that it is known when patients have failed to attend; adequate transport for the senior clinical staff to visit ill patients, or patients whose co-operation is flagging; an ambulance for ill patients; a small number of hospital beds for special or emergency cases; an organized system of surprise visits to the home to collect specimens of urine to test for the presence of the drug and to check the stocks of medicine; a laboratory capable of performing, as a minimal requirement, large numbers of reliable smear examinations of sputum for tubercle bacilli; and the resources to give at least limited financial assistance in cases of

particular need, since a proportion of patients will present in a destitute condition. Without adequate facilities and close supervision of the patients, the results of domiciliary treatment might well fall far below those reported here.

Toxic and hypersensitivity manifestations were infrequent in this study, occurring in only 2.6% of the total of 193 patients; all were attributable to PAS. This accords with other experience with this combination of isoniazid and PAS (Great Britain, Medical Research Council, 1953b, 1955; Bowerman, 1957; Tuberculosis Society of Scotland, Research Committee, 1957). Although the incidence is low, the occurrence of manifestations which were possibly toxic in origin complicated the management of patients, especially under domiciliary conditions, since patients at home were only too ready to blame all untoward symptoms on their medicine. The only patient lost from the home series during the 12 months discharged himself because he developed jaundice, which he attributed to the medicine.

The patients and their relatives were interrogated about previous chemotherapy on several occasions during the course of treatment, and other detailed inquiries were often made. After excluding any patients who might possibly have had previous antituberculosis treatment, primary drug resistance was found to isoniazid in 3.6% of all the patients, to PAS in 2.6% of patients, and to streptomycin in 2.2% of patients. Despite the difficulty in establishing the facts with certainty, it is believed that no patient who had had previous chemotherapy is included in these percentages. The figures may be compared with those obtained in the National Drug Resistance Survey in Great Britain (Fox et al., 1957), which used the same methods of sensitivity testing and had the same criteria of resistance; that survey reported an incidence of primary drug resistance to isoniazid in 0.7% of patients, to PAS in 2.2% and to streptomycin in 2.3% in Great Britain in 1955-56. It should be noted that the incidence of isoniazid-resistant strains was considerably higher in Madras in 1956-57 in the patients under study. In addition to such patients with primary drug resistance, there are undoubtedly many patients who have had previous chemotherapy, and have drug-resistant organisms as a consequence, who would present themselves as new cases of the disease if a mass campaign were embarked upon. It is therefore of interest that there was evidence from a small number of cases in this study that patients who presented isoniazid-resistant organisms, whether primary or following previous treatment, fared rather l than patients who had had no previous therapy and had sensitive organisms.

There was a group of patients with initia sitive strains who repeatedly yielded positi tures in the later months of treatment, the being resistant to isoniazid. These 16 patient represented 10% of the survivors at 12 m should be regarded as a potential public healt The catalase activity of the strains from these p is of particular interest in view of the assoc between the catalase activity of tubercle bacil their virulence to the guinea-pig, and possibl to man (Middlebrook & Dressler, 1954; Schv & Vandra, 1958). The tests showed that the res strains from nine of the 16 patients had nc catalase activity, and so may have been virulent

The possibility that atypical mycobacteria– is, mycobacteria other than *Myco. tuberculo* might be occurring in the patients under study, might indeed be the cause of their disease, particularly investigated. A range of identifica tests was undertaken on a sample of the patie and these will be the subject of a separate rep In addition, the colonial appearances of the gro on Löwenstein-Jensen medium, the results of sensitivity tests and the catalase activity of the stra all of which were investigated as a matter of rou before and during treatment, provided evidence t the organisms were in fact tubercle bacilli. On basis of these findings it is believed that atypi organisms were not cultured before the start treatment from any patient in this study. Cultu containing small numbers of mycobacteria otl than tubercle bacilli were obtained occasiona during the course of treatment.

Smear-positive, but culture-negative, results, whi were very uncommon before the start of treatmer increased in frequency during the earlier months therapy, becoming less common again in the secor six months. A detailed analysis of the data sugges that these smear-positive culture-negative result obtained in patients on the combination of isoniazi and PAS, represented non-viable bacilli; they wer thus classed as bacteriologically negative results.

Information has accumulated during the cours of the study which suggests that Indian strains o tubercle bacilli differ from British strains in thei behaviour in PAS-sensitivity tests. It seems likel that it will prove necessary, in the case of Indiar strains, to use standards for resistance which are different from those in current use when classifying

British strains. Further work on this subject is in progress and will be reported later.

Finally, the results reported here relate only to a period of one year. A second year of treatment is being investigated in order to study relapse and its prevention, and these results will be reported later. Further, the study of the contacts of both series of patients, which is also in progress, will give information on whether the contacts of patients treated at home are exposed to special risk of infection. The Chemotherapy Centre is also undertaking further investigations into problems of domiciliary chemotherapy; a controlled study of the relative merits of different chemotherapeutic combinations in domiciliary patients is in progress, the contacts also being followed. It is hoped that these various studies will assist further in the planning of mass campaigns against tuberculosis.

SUMMARY

1. In all, 193 patients were admitted to a comparison of treatment at home (96 patients) with treatment in sanatorium (97 patients) for a period of 12 months, the patients being allocated at random to one of these two treatment series.

2. Patients in both series were given the same chemotherapy for the 12 months—namely, isoniazid 200 mg plus PAS (sodium) 10 g daily (given together in the same cachet in two doses) for patients weighing 100 lb. (45 kg) or more. The dosage was reduced for lighter patients, the range of dosage being from 3.7 to 6.6 mg isoniazid/kg body-weight and from 0.19 to 0.33 g PAS (sodium)/kg body-weight.

3. Although all the survivors were examined at 12 months, the main analysis in this report concerns the 82 home and 81 sanatorium patients who (*a*) had organisms sensitive to the two drugs, (*b*) had had little or no previous chemotherapy and (*c*) followed the allocated treatment regimen.

4. The intake of patients began on 24 September 1956 and ended on 24 September 1957.

5. On admission to treatment, and in spite of the random allocation of treatment, the home series had more severe disease than the sanatorium series in respect of extent of cavitation, total extent of the disease, and bacterial content of the sputum, although the series were similar in other respects; the pretreatment differences between the series were greater for the females than for the males.

6. When the 49 *males* at home were compared with the 50 males in sanatorium, it was found that the males in sanatorium had gained more weight and had shown the greater reduction in the ESR. On the other hand, the benefit in terms of radiographic change was only slight, and the two series had fared similarly in respect of cavity closure and reduction in cavity size. The two series had also responded very similarly bacteriologically, and at 12 months 9% of 44 home and 10% of 48 sanatorium patients yielded positive cultures; in terms of the total number of patients for whom cultures were examined, 9% of those at home and 4% of those in sanatorium yielded isoniazid-resistant cultures. Using very stringent criteria to assess the bacteriological status at the end of 12 months, 10% of the home and 10% of the sanatorium patients still had active disease bacteriologically; one patient in each series had died of tuberculosis.

7. The direct comparison of the 33 *females* at home with the 31 in sanatorium was less easy to interpret because of the pretreatment differences. The sanatorium series had gained more weight and had shown the greater response in the ESR. This series had also made better radiographic and bacteriological progress. At 12 months, using very stringent criteria, eight (24%) of 33 home and one (3%) of 31 sanatorium patients had active disease bacteriologically; one sanatorium patient (3%) had died of tuberculosis.

8. Statistical standardization of the results, to make allowance as far as possible for the pretreatment differences, suggests that the radiographic progress was similar for patients with similar pretreatment lesions, whether male or female, but the bacteriological disadvantage to the females at home persisted.

9. A study of prognosis in relation to the pretreatment clinical features suggests that a high ESR, extensive cavitation and widespread disease, and, to a lesser extent, a large bacterial content of the sputum, were relatively unfavourable prognostic signs.

10. The self-administration of the cachets was supervised both by tests on the urine and by counts of the stock of cachets, and this revealed a difficulty in obtaining the long-term co-operation of patients treated at home in taking their medicine. More irregularity in self-administration was found among female than among male patients.

11. Toxic manifestations attributed to PAS occurred in 2.6% of the 193 patients. No toxic effects were produced by isoniazid.

12. Thirteen home and six sanatorium patients were admitted to hospital in the course of the 12 months for the investigation or treatment of non-tuberculous conditions. Thus a small number of hospital beds proved to be necessary for the home series, and would be needed in any large-scale scheme for home treatment.

13. Infection with primary isoniazid-resistant organisms occurred in 3.6% of the patients, primary resistance to PAS in 2.6% and primary resistance to streptomycin in 2.2% of the patients.

14. A detailed analysis of smear-positive but culture-negative bacteriological findings has shown that these may be interpreted as negative bacteriological results.

15. There is evidence that different criteria of interpretation should be used for PAS-sensitivity tests on Indian strains of tubercle bacilli from those that apply to British strains.

16. At the start of treatment the great majority of patients had low incomes, by current Indian standards, and came from families with low total incomes.

17. The diet of the home and sanatorium series was similar before the start of treatment, but there were important differences during treatment, the sanatorium diet being clearly superior. Thus, in terms of animal protein, 84% of the males and 97% of the females at home had less than 30 g a day, compared with no patient of either sex in sanatorium.

18. The sanatorium patients had more rest: at 12 months, 19% of males and 10% of females were allowed up for four hours a day, whereas at home 80% of the males and 91% of the females had returned to part-time or full-time activity, both of which represent a greater degree of activity than four hours up for sanatorium patients.

19. The majority of the home patients were liv in overcrowded conditions, the families of 68% the males and 85% of the females having less t 45 sq. ft (4.2 m²) of living accommodation per pers 20% of the families of the males and 48% of females had less than 25 sq. ft (2.3 m²) per pers Two more males (4%) were homeless.

20. The income of the males in both series greatly reduced during treatment but a proport of the home patients had regained some earn capacity by the end of 12 months, when 55% the 47 males at home were earning.

21. A modest amount of financial assistance v given to the families of patients in both seri more being required for the families of male th of female patients, and more being required wh the patient was treated at home than when he w treated in sanatorium.

22. Whereas major social problems arose in 20 the families of the 97 patients in sanatorium, th occurred in only eight in the 96 home families, a were also less serious; thus, *in this study*, sanatoriu treatment proved more disruptive to family life.

23. Twelve of the 97 sanatorium patients we discharged during the 12 months (though fo were only temporary discharges) whereas only o of the 96 home patients discharged himself fro treatment. It proved easier to keep the co-operatic of the home patients.

24. It is concluded that the results of domicilia chemotherapy, as carried out in this study, approac sufficiently closely the results of sanatorium trea ment to suggest that it is appropriate to treat th majority of patients at home. In formulating th conclusion, consideration has been given to th manifest advantages of sanatorium treatment- namely, rest, diet, nursing and supervised medicin taking on the one hand, and the social disadvar tages, as represented by the disruption to family lif and the difficulty of persuading patients to remai in sanatorium, on the other. It is recognised tha the standards of medical care during this study wer very favourable, but it is considered that comparabl results should be obtainable from a domiciliar service which is being operated from a tuberculosi clinic, provided that certain minimum requirement are met. Among these are an adequate supply o antituberculosis drugs, enough staff, including a

public health nurse and a social worker, transport (including an ambulance), a small number of hospital beds for special cases, an efficient appointment system, a system of surprise checks on the co-operation of the patients in taking their medicines, reliable smear examinations of sputum for tubercle bacilli, and a welfare fund for especially needy patients.

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ABSTRACT

A long report was published in the *Bulletin of the World Health Organization* on some of the work of the Tuberculosis Chemotherapy Centre, Madras. The investigations recorded in it are of great interest and importance; they should be widely known. For those who cannot easily study the report in the original, the following abstract is published. The report itself (*Bull. Wld. Hlth. Org.*, 1959, **21**, 51) should, of course, be referred to for points of detail.

A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India*

Tnberculosis Chemotherapy Centre, Madras

'In India, as in most under-developed countries, the tuberculosis problem is aggravated by an acute shortage of sanatorium beds. The number of active cases of tuberculosis in the country has been estimated at 2½ million, but only 23,000 tuberculosis beds are available. In these circumstances great importance attaches to the possibility of applying mass domiciliary chemotherapy as a substitute for sanatorium treatment in cases of pulmonary tuberculosis. The findings of the present study, based on a comparison of the two types of treatment over a period of twelve months, show that despite the manifest advantages of sanatorium care – rest, adequate diet, nursing and supervised medicine-taking – the merits of domiciliary chemotherapy are comparable to those of sanatorium treatment, and that it would therefore be appropriate to treat the majority of patients at home, provided an adequate service were established.'

I. Introduction

The Tuberculosis Chemotherapy Centre, Madras, was set up in 1956 'under the joint auspices of the Indian Council of Medical Research (ICMR), the Madras State Government, the World Health Organization (WHO) and the Medical Research Council of Great Britain (MRC). The senior scientific staff of the Centre, who are responsible for the work reported here, are: Dr Wallace Fox (WHO), Senior Medical Officer; Drs R. H. Andrews (WHO), C. V. Ramakrishnan (ICMR), and S. Velu (Madras Government), Medical Officers; Dr S. Devadatta (ICMR), Assistant Medical Officer; Drs A. L. Bhatia (ICMR), D. A. Mitchison (WHO) and J. B. Selkon (WHO), Bacteriologists; Dr P. R. J. Gangadharam (ICMR), Assistant Bacteriologist; Miss E. Holst (WHO), Laboratory Technician; Mr T. V. Subbaiah (ICMR), Laboratory Research Assistant; Mr S. Radhakrishna (Madras Government), Statistician.

The research of the Centre is guided by a Project Committee consisting of three ICMR representatives (Drs P. V. Benjamin, Convenor, J. Frimodt-Møller and K. S. Sanjivi), the Director of the ICMR (Dr C. G. Pandit), the Director of Medical Services, Madras State (first Lt-Col Sangham Lal and then Dr V. R. Thayumanaswamy), a WHO representative (appointed for each meeting), an MRC representative (appointed for each meeting) and the Senior Medical Officer of the Centre (Dr Wallace Fox). The joint secretaries are Mrs K. Daniels and Mr B. S. Verma.

The MRC, through its Tuberculosis Research Unit, is responsible for the scientific direction of the research, in accordance with plans prepared by the Project Committee. Dr Wallace Fox of the Tuberculosis Research Unit has been seconded

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to WHO to serve as the Senior Medical Officer and the Director of Research at the Centre, and the laboratory was established by Dr D. A. Mitchison of the MRC Group for Research on Drug Sensitivity in Tuberculosis. Close contact is maintained between the Centre in Madras, the MRC Tuberculosis Research Unit (Dr P. D'Arcy Hart) and the Group for Research on Drug Sensitivity in Tuberculosis (Drs D. A. Mitchison, J. B. Selkon and J. G. Wallace) in London. Dr Ian Sutherland of the MRC Statistical Research Unit has advised on statistical aspects. In India, Drs Ida B. Scudder and J. Frimodt-Moller acted as independent radiological assessors, and Drs C. Gopalan and V. N. Patwardhan of the ICMR Nutritional Research Unit have advised on the dietary study referred to in this report.'

'The study was designed to yield information on the following aspects of the treatment of pulmonary tuberculosis among patients living in an adverse urban environment in India:

(1) The relative merits of home and sanatorium treatment with standard chemotherapy.

(2) The extent to which the infectivity of a series of patients treated at home can be reduced by standard chemotherapy.

(3) The prevalence of tuberculosis in family contacts at the time of diagnosis of the index case and the subsequent incidence of tuberculosis among them, with particular reference to the drug sensitivity of the strains.

(4) The identity and virulence of the causative organisms and their comparison with strains of tubercle bacilli from England.

(5) Some of the practical procedures involved in the mass application of chemotherapy – for example, methods of sputum collection, of checking the self-administration of medicines and of general supervision of patients.

(6) Diet and its relation to the response of chemotherapy.

(7) The causes and management of treatment failures.

The present report is concerned principally with the first two of these points. The others will be considered fully in later reports.'

II. General Plan and Conduct of the Study

Patients with pulmonary tuberculosis were selected from those attending local chest clinics in Madras City and living in a defined area, the final limits of which embraced a population of about 750,000. Most of the patients came from the poorest section of the community. They were selected for the study if they fulfilled all the following conditions:

(1) The patient had either had no previous antituberculosis chemotherapy, or antituberculosis chemotherapy had been administered for not more than two weeks.

(2) The patient was aged 12 years or more (sanatorium beds were not available for younger children).

(3) The sputum was positive for tubercle bacilli either on direct smear examination or on culture.

(4) The patient was living in Madras City in the defined area of intake (and was thus accessible for home visiting) and was likely to remain so for several years.

(5) The patient was prepared to:

(*a*) accept treatment either at home or in sanatorium for at least a year.

(*b*) accept treatment whether with pills or injections.

(*c*) permit home visiting.

They were ineligible if any of the following applied at the start of treatment:

(1) The patient was too ill for home treatment (e.g. was nearly moribund, had a spontaneous pneumothorax or had had a severe haemoptysis).

(2) The patient had a pleural effusion obscuring more than one-third of a lung field, as seen on a postero-anterior chest radiograph.

(3) The patient had a non-respiratory form of tuberculosis which it was considered would complicate treatment.

(4) The patient was known to have leprosy.

(5) The patient was known to have a serious concomitant disease such as diabetes.

(6) The patient was known to be pregnant.

A sample of 10 pre-treatment radiographs drawn at random from the group of patients treated at home (the group of especial interest) is illustrated in an Appendix.

Allocation of Treatment

Patients were allocated at random to two regimens of treatment. Both were to receive the same chemotherapy; one group was to be treated at home, the other in sanatorium.

Chemotherapy

Cachets, each containing 25 mg. isoniazid and 1·25 g. sodium PAS. The total daily dose varied with the patient's weight; for those less than 80 lb. (36·3 kg.) it was 150 mg. isoniazid and 7·5 mg. sodium PAS (3 cachets morning and evening) and for patients of 100 lb. (45·4 kg.) or more 200 mg. isoniazid and 10 g. sodium PAS (4 cachets morning and evening). The dose of isoniazid was greater than 4 mg./kg. body weight in all but a very few patients.

Home Treatment

'In this study home treatment meant the treatment of patients in their own homes, with clinic supervision of their progress. Chemotherapy was started immediately after allocation of the treatment and the majority of the home patients attended the Centre weekly throughout the twelve months for supplies of medicine. In addition a visit was usually paid to the home each week during the first month by a health visitor, and less regularly by a doctor or a public health nurse. Less frequent home visits were made in later months. It was rare for fewer than two home visits to be made each month, because one was made to deliver a sputum specimen bottle and one – an unexpected visit – to collect a specimen of urine to be tested for the presence of PAS, as a check that the patient was taking the medicine. Patients initially too ill to attend weekly rested at home for the first month and were then brought up by ambulance for re-examination and assessment. As soon as they had improved sufficiently they were changed to the ordinary routine of visits to the Centre and the home.' They were encouraged to stop work and rest. The majority were up and about much of the time and quite often not at home when visited. When medically fit to return to work they were encouraged to do so.

Sanatorium Treatment

Patients allocated to this group were admitted with a minimum of delay to the Government Tuberculosis Sanatorium, Tambaram. They rested in bed in the early months, being up only for toilet. After three to four months they were usually allowed up two hours a day and by six months were up four hours a day. After six months they were allowed to go home for one day, if fit, once a month.

III. Bacteriological Procedures

Sputum was examined before treatment and at monthly intervals throughout treatment; from the fourth month two laryngeal swabs were also examined each month. Efforts were made to ensure that, as far as possible, identical procedures were used for both home and sanatorium patients.

The bacterial content of the sputum was estimated by examination of smears

by fluorescence microscopy with grading according to the density of bacilli, and by culture on Löwenstein-Jensen medium, the results also being graded.

Sensitivity tests to streptomycin, PAS and isoniazid were carried out on two pre-treatment cultures and on one culture every month throughout treatment. The tests were set up from the primary cultures on to Löwenstein-Jensen medium slopes containing known concentrations of the drugs. 'Growth' was defined as meaning 20 or more colonies on any slope. The results of streptomycin and PAS tests were expressed as 'resistance ratios' – namely, the minimal drug concentration inhibiting growth of the test strain divided by that inhibiting growth of H37Rv, which was set up with each batch of tests. The results of isoniazid tests were expressed as the minimal drug concentration inhibiting growth of the test strain.

Definitions of Resistance

Isoniazid: Growth on 1 μg./ml. or a higher concentration, or growth on 0·2 μg./ml. provided that a repeat test on the same strain yielded growth on 0·2 μg./ml. or a higher concentration.

PAS: Pre-treatment tests: a resistance ratio of more than 8, or if there were 2 tests, resistance ratios of 8 and 4 or more, or if three ratios of 4 were obtained from among the tests on the two pre-treatment cultures and the two repeat tests on these cultures. Post-treatment tests: either a resistance ratio of 8 or more, or a resistance ratio of 4, followed by a ratio of 4 or more in a repeat test.

Streptomycin: A resistance ratio of 8 or more, or a ratio of 4 followed by a ratio of 4 or more in a repeat test.

IV. The Patients Allocated to Treatment

Altogether 193 patients were allocated to the two groups, 96 to home treatment and 97 to sanatorium, between September 1956 and September 1957. For various reasons 30 (14 home – 16 sanatorium) could not be used for the main analysis (9 had isoniazid-resistant cultures before treatment and 6 PAS-resistant; 4, although having sensitive cultures, were found on further enquiry to have had more than two weeks chemotherapy in the past; 2 died from non-tuberculous diseases that influenced the course of the tuberculosis; 2 had prolonged or intractable PAS sensitization; 8 were prematurely discharged from treatment (1 home, 7 sanatorium); and 3 patients being treated at home were admitted to hospital or sanatorium for periods of more than six weeks). For the main analysis, therefore, there were 163 patients (82 home, 81 sanatorium), who had organisms sensitive to isoniazid and PAS, had had little or no previous chemotherapy and followed the allocated treatment regime.

Pre-treatment Comparison Between the Groups

In spite of the random allocation procedure being rigorously observed, there were important differences in the pre-treatment state between the home and sanatorium groups.

Radiographic. – All radiographic assessments of initial state and of change were made by independent assessors unaware of the treatment group of the patient. Among the male patients the home treated group initially had 39 per cent with extensive cavitation and 55 per cent with five or six lung zones involved. The corresponding proportions for the sanatorium males were 32 per cent and 38 per cent. Among the females, the proportions for the home group were 58 per cent and 55 per cent and for the sanatorium group 23 per cent and 39 per cent.

Bacteriological. – Of the males, 59 per cent of those treated at home had 3-plus (heavy) direct smears initially, compared with 44 per cent of those admitted to

sanatorium. The corresponding proportions for the females were 45 per cent and 26 per cent.

Thus, the two groups were not equivalent in some important factors before treatment began, the home groups in both sexes having more severe disease, and the difference being greater among the females than the males.

V. Comparison of Home and Sanatorium Treatment in Males

Deaths: There were two deaths among the 49 in the home series (1 from tuberculosis in the eighth week; 1 from an accident at work) and 1 (from tuberculosis) in the 50 of the sanatorium series.

Change of chemotherapy. – One patient at home deteriorated after initial improvement and treatment was changed after nine months to streptomycin and pyrazinamide. There were minor modifications of dosage or short interruptions of chemotherapy in a few patients in both series, insufficient to justify removing them from the main analysis.

Clinical changes. – At the end of twelve months the sanatorium males had gained more weight (17·8 lb. compared to 10·6 lb.) and had lower ESRs, both differences attaining statistical significance.

Radiographic changes. – The differences between the series were small, though those treated in sanatorium had slightly more with considerable radiographic improvement over the twelve months period (50 per cent sanatorium, 39 per cent home). Among the sanatorium group a higher proportion were judged to have no x-ray evidence of cavities (on tomography) at twelve months (50 per cent sanatorium, 38 per cent home), having had cavities initially. The home series did, however, have more severe disease before treatment and when allowance was made for this the progress of the two groups of patients showed an even closer similarity.

Bacteriological changes. – There was a striking decline in the bacterial content of the sputum in both series, with little difference between them. With single specimens taken at monthly intervals the proportions still positive on culture at three, six, nine and twelve months in the two groups were: home – 36 per cent, 13 per cent, 13 per cent, 9 per cent; sanatorium – 26 per cent, 4 per cent, 6 per cent, 10 per cent. The disease was considered to be 'bacteriologically quiescent' at twelve months if *all* the cultures for at least the last three monthly examinations had been negative. The total cultures set up for each patient each month from the third month onwards could be 4 – two sputum specimens and two laryngeal swabs. Thus, the definition of 'bacteriological quiescence' was a very stringent one. 'Bacteriological quiescence' was reached by 38 (78 per cent) of the 49 home patients and 41 (82 per cent) of the sanatorium patients. There was a tendency for sputum conversion to occur earlier in the sanatorium group: 68 per cent of those who attained 'bacteriological quiescence' had negative cultures by three months compared with 50 per cent of the home patients.

Isoniazid sensitivity. – At six months 5 of the 7 positive cultures in the home group were resistant, compared with all of the 4 positive cultures in the sanatorium group. At twelve months the proportions of the total patients with resistant cultures were 9 per cent of the home series and 4 per cent of the sanatorium. Four patients (2 in each group) still had sensitive cultures.

VI. Comparison of Home and Sanatorium Treatment in Females

The pre-treatment differences were greater in the females than in the males. Differences in response during the treatment period should therefore be interpreted with great caution (see section VII).

Deaths. – One patient in sanatorium died of tuberculosis after five days' treatment.

Change of chemotherapy. – In 1 patient treated at home treatment was changed at eleven months to streptomycin and pyrazinamide because of deterioration after initial improvement. The few patients with modifications or interruptions are included in the analysis.

Clinical changes. – At the end of twelve months the sanatorium group had gained more weight and had lower ESRs.

Radiographic changes. – Of the 33 treated at home 42 per cent had considerable improvement by twelve months, compared with 51 per cent of the 31 treated in sanatorium. The proportions with disappearance of cavities were 38 per cent of the home series and 61 per cent of the sanatorium.

Bacteriological change. – The proportions with positive cultures from single specimens at six and twelve months were: home 12 per cent and 13 per cent, sanatorium 0 per cent and 0 per cent. 'Bacteriological quiescence' was reached at twelve months by 67 per cent at home and 94 per cent in sanatorium.

Isoniazid sensitivity. – At six months 3 of 4 cultures from the home series were resistant and there were no positive cultures in the sanatorium series. At twelve months the proportions of total patients with resistant cultures were 19 per cent at home and 3 per cent in sanatorium. One patient still had a sensitive culture.

VII. The Influence of the Pre-treatment Differences between the Series on the Results of Treatment

Special analyses were undertaken to investigate the influence of the pre-treatment differences, statistical standardization being applied to various measures of progress. The principle is a comparison of the progress of patients in the two series with similar disease characteristics before treatment.

For all patients the unstandardized proportions showing considerable radiographic improvement at twelve months were 40·4 per cent for those at home and 51·0 per cent for those in sanatorium, the former being 79 per cent of the latter. When both the extent of cavitation and the lung-zone involvement were taken into account this ratio of home to sanatorium improvement increased to 90 per cent. Similarly with closure of cavities, the ratio of home to sanatorium rose from 68 per cent to 89 per cent.

With the males the pattern was very similar to that of the whole group, namely a small residual advantage in radiographic change to the males treated in sanatorium, who had fared a little better than those at home. With females, on the other hand, standardization for the same two pre-treatment differences simultaneously reversed the position in terms of considerable radiographic improvement at six months, the proportions changing from 30·3 per cent for those at home and 43·3 per cent for those in sanatorium to 32·1 per cent and 30·4 per cent respectively. At twelve months the corresponding standardized figures were 44·3 per cent and 39·9 per cent. With cavity closure the contrast between the series almost disappeared, the standardized proportions at twelve months being 49 per cent at home and 51 per cent in sanatorium. In summary, there was little to choose between the two groups of females after allowance had been made for pre-treatment radiographic differences.

Similar analyses concerning the bacteriological response showed that taking into account the pre-treatment radiographic condition almost removed the bacteriological disadvantage to the males treated at home; but the disadvantage to the females at home remained. Thus, the proportions of males with 'bacteriologically quiescent' disease at twelve months changed very little with standardization, from 89·4 per cent home and 99·8 per cent sanatorium to 91·4 and 86·6 per cent respectively. But the difference with the females remained large and almost unaltered, the standardized proportion being 75·5 per cent home and 100 per cent sanatorium.

The same measures of radiographic and bacteriological response were also standardized both for the extent of cavitation and the bacterial content of the sputum initially, with similar conclusions.

It is emphasized that standardization has been undertaken for only *some* of the important pre-treatment differences. Moreover, if, as with the female series, pre-treatment differences are large and the number of patients small, no standardization process is likely to be completely successful in taking into account all differences in response arising from pre-treatment differences.

VIII. Prognostic Value of Various Clinical Features before the Start of Treatment

The results suggest that a high ESR, extensive cavitation and widespread disease, and, to a less extent, a large bacterial content of the sputum, were relatively unfavourable prognostic signs.

IX. Further Bacteriological Findings

Smear-positive Culture-Negative Results

The occurrence of smear-positive culture-negative results before the start of treatment was rare. Such results increased to a maximal frequency in the middle months of treatment, and subsequently decreased. The result was an isolated observation in the majority of patients, and it was very uncommon for it to occur frequently, or over a long period of time. It was thought justifiable to conclude from these and other findings that the bacilli in these specimens were non-viable.

Isoniazid Resistance

Twenty-seven patients had one or more isoniazid-resistant cultures during treatment. Eight of these were consistently positive bacteriologically with persistently resistant cultures; another 8 had intermittently positive cultures which were consistently resistant. The 16 patients (9·8 per cent of the whole group) may have been a source of danger to the public health during the study and perhaps subsequently.

Of the 130 who attained 'bacteriological quiescence' at the end of twelve months, 126 (97 per cent) had yielded only isoniazid sensitive results and 4 isolated resistant results. Ten had disease of 'doubtful' status and of these 7 had yielded resistant results; and of the 19 classed as 'active', 16 (84 per cent) had had resistant cultures. No patient remained consistently bacteriologically positive with isoniazid-sensitive cultures throughout the whole twelve months.

PAS Sensitivity

At six months 3 of the 15 strains tested were resistant to PAS and at twelve months 9 of 17. Cultures remained positive, and sensitive to the companion drug, for a longer period after the emergence of isoniazid resistance than after the emergence of PAS resistance. This suggests that a finding of isoniazid resistance is associated with a greater tendency to persisting subsequent positivity than a finding of PAS resistance. The development of PAS resistance was less likely to be followed by resistance to isoniazid than the development of isoniazid resistance by resistance to PAS. When resistance emerged, the isoniazid sensitivity results were highly consistent, whereas the PAS results were more variable.

'PAS sensitivity tests, as carried out and interpreted in this study, were considered less useful than isoniazid sensitivity tests, being inconsistent and less indicative of a poor response to treatment or the likelihood of resistance to the other drug emerging.

X. Toxicity and Other Complications

Gastro-intestinal side effects were completely unimportant in both series. It was not necessary to reduce the dosage of the drugs for any patient on account of them.

At most only 5 (2·6 per cent) had hypersensitivity or other toxic reactions to PAS. There was no suspicion of isoniazid toxicity in any patient.

It was necessary during the twelve months to admit to hospital 19 of the patients being treated at home; 6 had complications of the pulmonary tuberculosis or of treatment, 13 had non-tuberculous conditions.

XI. Self-administration of the Medicine

Two methods were used to check regularity of self-administration – urine testing for PAS and counts of the patient's stock of cachets. Among the men, 40 per cent of those at home gave positive urine tests in each of the twelve months and 96 per cent of those in hospital. Twenty-six per cent of the male patients at home gave one or more negative tests in at least three of the months. Among the women only 27 per cent of those at home gave positive results throughout and only 63 per cent of those in hospital. Thirty-three per cent of the female patients at home gave one or more negative results in at least three of the months.

Cachet counts at surprise visits to the patient's home showed inaccuracies in the number of cachets that should have remained from the prescribed stock in 6·6 per cent of the checks on men and 9 per cent on women. In 5 patients the inaccuracy was large enough to suggest that the patient had completely stopped taking the drugs.

There was no clear-cut evidence that those patients who had negative urine tests during treatment or inaccurate cachet counts fared less well than the remainder.

XII. Various Social Factors

The diet of the patients was investigated to discover differences between those treated at home and those at sanatorium. Before the start of treatment the diets of both groups were similar. During treatment, however, there were major differences. The daily intake was less than 2,000 calories in 42 per cent of home male patients, compared with only 4 per cent of those in sanatorium. For females the corresponding proportions were 61 per cent and 3 per cent. Forty-four per cent of the males and 61 per cent of the females at home were receiving less than 50 g. of protein a day, compared with none of those in sanatorium. The animal protein content of the diet was less than 30 g. in 84 per cent of the males and 97 per cent of the females at home, compared with none in sanatorium. The home series appear, therefore, to have been at a very considerable dietetic disadvantage.

The majority of the home patients were living in overcrowded conditions, the families of 68 per cent of the males and 85 per cent of the females having less than 45 sq. feet (4·2 sq. metres) of living space per person; 20 per cent of the families of the males and 48 per cent of the females had less than 25 sq. ft. (2·3 sq. metres). The income of the males in both series, already low by current Indian standards, was greatly reduced during treatment but a proportion of the home patients had regained some earning capacity by the end of the twelve months, when 55 per cent of the 47 males at home were earning.

A small amount of financial assistance was given to families of patients in both series, more being required for the families of male patients and more when the patient was treated at home than in sanatorium.

Great attention was paid by the clinical staff of the Centre to the welfare of the patients and their families; and a great deal of sociological information was obtained and recorded in the social workers' records. There were major sociological problems in 8 per cent of the families in the home series: in the sanatorium series the proportion was 21 per cent. In the home series 5 families split and there were 3 serious family quarrels. In the sanatorium series there was temporary or continued desertion or family split in 20 cases and serious home difficulties in 5. There is little doubt that

in this study treatment of patients in a sanatorium for twelve months carried sociological disadvantages.

XIII. Subsidiary Groups of Patients Not Included in the Main Analysis

Patients with Resistant Organisms Before Treatment

Of the 9 with initially isoniazid resistant cultures it is considered that 7 (3·6 per cent of the 192 with pre-treatment results available) had been infected with resistant organisms; the other 2 patients had had previous chemotherapy: they fared badly and both developed PAS resistance. Two of the 7 with primary resistance also fared badly, but 3 responded well: 1 died shortly after starting treatment and the other received triple drug therapy following an early complication.

Of 6 patients with initially PAS-resistant cultures 5 (2·6 per cent of the 192) are thought to have been infected with resistant organisms. The one who had had previous chemotherapy did well. Three of the 5 with primary resistance also fared well; 1 developed isoniazid-resistance and 1 eventually did well after receiving streptomycin and isoniazid.

Pre-treatment resistance to streptomycin was found in 5 cultures. It is likely that in 4 of these cases (2·2 per cent of 183 patients) there had been infection with a resistant strain.

Premature Discharge from Treatment

Much difficulty was encountered in persuading many of the patients to remain in sanatorium for the full twelve months. In spite of all the efforts of the staff 9 patients absconded and 3 had to be discharged for disciplinary reasons. Five of those who absconded returned after a short interval and have been included in the main analysis. All of the remaining 7 patients not included were examined at the end of the twelfth month: 3 were still infectious, 2 with resistant organisms.

Only 1 patient absconded from treatment in the home series. He had developed jaundice which he attributed to the treatment.

Contrary to all expectations, it was, therefore, more difficult to ensure that patients continued treatment in sanatorium than to persuade patients to remain under treatment at home.

Conclusion

'It is concluded that the results of domiciliary chemotherapy, as carried out in this study, approach sufficiently closely the results of sanatorium treatment to suggest that it is appropriate to treat the majority of patients at home. In formulating this conclusion, consideration has been given to the manifest advantages of sanatorium treatment – namely, rest, diet, nursing and supervised medicine-taking – on the one hand, and the social disadvantages, as represented by the disruption to family life and the difficulty of persuading patients to remain in sanatorium, on the other. It is recognized that the standards of medical care during this study were very favourable, but it is considered that comparable results should be obtainable from a domiciliary service which is being operated from a tuberculosis clinic, provided that certain minimum requirements are met. Among these are an adequate supply of antituberculosis drugs, enough staff, including a public health nurse and a social worker, transport (including an ambulance), a small number of hospital beds for special cases, an efficient appointment system, a system of surprise checks on the co-operation of the patients in taking their medicines, reliable smear examinations of sputum for tubercle bacilli and a welfare fund for especially needy patients.'