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REALISTIC CHEMOTHERAPEUTIC POLICIES FOR TUBERCULOSIS IN INDIA

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A SERIES of controlled studies carried out at the Tuberculosis Chemotherapy Centre have revealed that ambulatory chemotherapy for tuberculosis based on a well-organized clinic service for a year, is virtually as effective as sanatorium treatment for the same period, not only in the immediate therapeutic response in terms of overall radiographic improvement, cavity closure and sputum conversion (Tuberculosis Chemotherapy Centre, Madras, 1959) but also in the likelihood of relapse in a subsequent 4-year period of follow-up (Dawson *et al,* 1966). Further, principally owing to the rapid sputum conversion of patients receiving effective chemotherapy there was no increased risk of contracting the disease to close family contacts of the patients treated at home, the main risk to them being before treatment had begun (Andrews *et al,* 1960; Kamat *et al,* 1966). These studies also clearly showed that the traditionally held virtues of sanatorium treatment *namely,* prolonged bed-rest, good diet, good airy accommodation, nursing and isolation were remarkably unimportant provided adequate chemotherapy was administered. There have been 5 other controlled trials based on random allocation . reported in the world medical literature which compared either sanatorium treatment with clinic treatment (Tyrell, 1956 ; Bell, 1960) or rest with ambulation (Kay, 1957 ; Tuberculosis Society of Scotland, 1960; Wier *et al,* 1957 ; Wynn-Williams and Shaw, 1960) and not one demonstrated any advantage either of sanatorium treatment over clinic treatment or of rest over ambulation. Because of these findings and because of the gross shortage of hospital beds for tuberculosis, ambulatory chemotherapy for the major or the entire period of treatment has become the accepted practice in the tuberculosis control programmes in India as well as in many other developing countries of the world.

Chemotherapeutic regimens.-The great progress made in the chemotherapy of pulmonary tuberculosis during the last few years has made it possible for the economically developed countries to treat all newly diagnosed patients with chemotherapeutic regimens which are potentially 100% effective. But unfortunately in our country the most effective triple-drug regimens cannot be applied on a large scale at present due to cost, shortage of drugs and difficulties in application. For instance, a triple-drug regimen of streptomycin, isoniazid and PAS given daily for 6 months followed by a dual-drug regimen of isoniazid plus PAS for the rest of the year, although virtually 100% effective, is clearly too expensive and unsuitable for general

application to treat the estimated 1½ million infectious cases. Further, there is a general shortage of all anti-tuberculosis drugs and particularly of PAS. It is therefore necessary for us, to evolve regimens which are not only effective but also inexpensive and capable of application on a mass scale through the existing health facilities in the country. Let us now consider the progress we have so far made in this direction :

At the Tuberculosis Chemotherapy Centre, Madras, a series of controlled clinical studies based on random allocation have been undertaken to assess the merits of different chemotherapeutic regimens in the ambulatory treatment of patients with bacteriologically confirmed pulmonary tuberculosis. Patients selected for these studies were all drawn from the poor sections of the community in Madras City and were referred to the Centre from the local chest clinics where they had reported because of symptoms. They were all aged 12 years or more and were judged to be co-operative and likely to remain in the city for a period of at least five years. They all had newly diagnosed previously untreated (some had previous treatment upto 2 weeks) pulmonary tuberculosis with sputum-positive on direct smear or on culture, the great majority having advanced and cavitated disease with positive direct smears.

We shall now consider the chemotherapeutic regimens studied so far :

Daily oral regimens.–*Isoniazid alone compared with isoniazid plus PAS:*– Isoniazid is the most effective, least toxic and least expensive of the antituberculosis drugs, and a large body of medical opinion had considered that isoniazid, administered by itself, was the best available chemotherapy for developing countries. Indeed it was being used by itself on a large scale for ambulatory treatment of tuberculosis in India. In order to assess the value of isoniazid alone in comparison with a standard dual drug regimen of isoniazid *plus* PAS in the ambulatory treatment of pulmonary tuberculosis, a controlled study based on random allocation was undertaken. In this study 3 regimens of isoniazid alone, were compared with a standard regimen of isoniazid plus PAS. The regimens and the daily dosages of drugs for a patient weighing 100 lbs. were :–

PH– Isoniazid 200 mg. *plus* PAS (sodium) 10 g. in 2 divided doses
H– Isoniazid alone 200 mg. in 2 divided doses.
HI-2– Isoniazid alone 400 mg. in 2 divided doses.
HI-1– Isoniazid alone 400 mg. in one single dose.

The regimens and their therapeutic efficacy assessed at one year are set out in Table I, *p. 3,* and it will be seen that 91% of patients on isoniazid *plus* PAS attained bacteriologically quiescent disease (i.e., all cultures, usually 3 each month, negative at 10, 11 and 12 months) at one year compared with 44%, 58% and 73%. respectively on the 3 isoniazid alone regimens (Tuberculosis Chemotherapy Centre, Madras, 1960). Further, it gave the first definite evidence

that isoniazid in a daily dosage of 400 mg. (approximately 9 mg./kg. body-weight) was more effective when given in a single dose than when given in two divided doses. This was due to the fact that in these patients the therapeutic response was related to the peak level of isoniazid attained in the serum rather than to the continuous inhibitory level of the drug throughout the day (Gangadharam *et al*, 1961). We shall refer to this important finding again.

Since treatment with isoniazid alone in a single dose of 400 mg. daily resulted in favourable response in 73% of patients, it was conceivable that increasing the single daily dose with consequent raising of the peak level of isoniazid in the serum might improve the results still further. Unfortunately, however, toxic manifestations of isoniazid, principally peripheral neuropathy, occurred in 19% of patients receiving 400mg. in a single dose daily (see Table I, below) and it could be expected to occur more frequently, if the dosage was increased. Therefore, a double blind trial was designed principally to find an inexpensive prophylactic for peripheral neuropathy and also to determine the therapeutic effect of increasing the single daily dose of isoniazid. This investigation showed that a single daily dose of 650 mg. did not improve the therapeutic response attained by 400 mg. in a single daily dose. It however, showed that as small a daily dose as 6 mg. of pyridoxine could prevent the neurological complications of high dosage isoniazid therapy while other constituents of B complex were practically ineffective (Tuberculosis Chemotherapy Centre, Madras, 1963a, 1963b).

TABLE I

Isoniazid Study.: Daily Dosages of Drugs, Efficacy and Complications of Regimens

Chemotherapy regimens	Isoniazid		PAS (Sodium)		No. of doses a day	Therapeutic efficacy * in the first year	Neuropathic complications
	mg.	mean mg/kg	g.	mean g/kg.			
Isoniazid alone (daily)	200	4.4	–	–	2	44%	0%
	400	8.8	–	–	9	58%	9%
Isoniazid plus PAS (daily)	400	8.8	–	–	1	73%	19%
	200	4.4	10	0.22	2	91%	1%

*** Assessed as the percentage of patients with bacteriologically quiescent disease at 1 pear—that is, all cultures (usually 3 each month) negative at 10, 11 and 12 months.**

The best available regimen of isoniazid alone is therefore clearly inferior to the dual-drug regimen of isoniaiid *plus* PAS, a point which emphasizes the need to prescribe a dual-drug regimen for all newly diagnosed patients with positive sputum.

Isoniazid *plus* thioacetazone*– Since isoniazid alone even in its optimal single daily dose is not sufficiently effective, and isoniazid

*Thioacetazone is the recommended international non-proprietary name (WHO, 1969) for 4'- formylacetanilide thiosemicarbazone (thiacetazone ; Tb1-698). .

plus PAS is too expensive for mass application, a relatively inexpensive regimen of isoniazid *plus* thioacetazone was compared concurrently with isoniazid *plus* PAS in a controlled trial of patients treated at home (Tuberculosis Chemotherapy Centre, Madras, 1966). Table II shows the two regimens and the daily dosages of drugs for a patient weighing 100 lbs. The two regimens compared were :–

TH : Isoniazid 300 mg. (mean 6.9 mg./kg. body-weight) and thioacetazone 150 mg. (mean 3.4 mg./kg. body-weight) both drugs given together in a single dose daily.

PH: Isoniazid 200 mg. (mean 4.5 mg./kg. bodyweight) and PAS (sodium) 10 g. (mean 0.22 g./kg. body-weight) both drugs given together in *two* divided *doses.*

The results of treatment at one year with each regimen are set out in Table III, *below*. It will be seen that the therapeutic response was the same with both regimens. 89% of patients on each regimen attaining bacteriologically quiescent disease at one year. The overall incidence of major toxicity was also similar in the two series being 12% in TH and 11% in the PH series (*see* Table IV, p. 5.) However, of the 5 patients who had cutaneous hypersensitivity

TABLE II

Regimens

Regimen	Daily dosage of drugs for 100 lb. patient	Daily dosage of drugs mean mg/kg	Rhythm
PH	PAS (sodium) 10 g	220	In two doses
	plus		
	Isoniazid 200 mg	4.6	
TH	Thiacetazone 150 mg	3.4	In a single dose
	plus		
	Isoniazid 300 mg	6.9	

TABLE III

Status of patients at 12 months

Status	PH No.	PH %	TH No.	TH %
Quiescent disease	54	*82*	53	*82*
Active disease	11	*17*	11	*17*
Death from Tuberculosis	1	*2*	1	*2*
All patients	66	*100*	65	*100*

reactions in the thioacetazone series, 3 had exfoliative dermatitis compared with none of the 4 in the PAS series. It is therefore important to be cautious and to withdraw the drug promptly as soon as skin lesions occur. Hæmatological and liver function studies did not reveal any evidence of suppression of hæmopoiesis or derangement of liver function. Minor side-effects which did not require an interruption or change of chemotherapy, such as anorexia, vomiting, diarrhœa or giddiness occurred more commonly in the thioacetazone series than in the PAS series. Further, the average gain in weight and rise in the hæmoglobin level over the year of treatment were less in the thioacetazone series than in the PAS series. Even so, it may be concluded that thioacetazone 150 mg. *plus* isoniazid 300 mg. daily has emerged in this study as an effective yet inexpensive regimen suitable for ambulatory chemotherapy- Further, there is evidence from East Africa (East African/

BMRC third thioacetazone investigation) that an initial supplement of streptomycin daily for the first two months enhances its efficacy to 90 or 93%.

Intermittent regimens.–The success of ambulatory chemotherapy depends almost entirely on the patient actually taking the prescribed drugs regularly for at least one year. When daily oral regimens are prescribed, reliance is placed on the co-operation of patients in self-administering the drugs at home. But prolonged self-administration of drugs often results in serious irregularities in drug taking and consequent failure of therapy which can be prevented only by supervising the administration of drugs. Although daily supervision, as a general policy, is an impossible task, it may be possible to organise supervised administration of drugs intermittently once or twice a week.

TABLE IV

Incidence of major toxicity (thioacetazone study)

Toxic manifestations	PH		TH	
	No.	%	No.	%
Cutaneous hypersensitivity	4	6	5	7
Jaundice	2	3	2	3
Intractable vomiting ...	2	3	2	3
Total major toxicity ...	8	11	9	12
All patients in study	71		75	

TABLE V

Regimens in intermittent chemotherapy study

Regimen	SHTW	PH
Drugs	Streptomycin 1 g. (for all patients) plus	Sodium PAS, 220 mg./kg. plus
dosages	Isoniazid, 14 mg./kg.	Isoniazid, 4.5 mg./kg.
Rhythm	Twice a week together	Daily in two doses

As mentioned earlier, there was evidence from the isoniazid studies that a high peak level of isoniazid in the serum each day influenced the therapeutic response more than a continuous inhibitory level of the drug in the serum throughout the day. This finding suggested a rational basis for intermittent chemotherapy with a regimen containing a high dose of isoniazid in which the interval between peak serum levels, and therefore the doses, was extended. An investigation was, therefore, undertaken to assess the therapeutic efficacy of a high dose of isoniazid in combination with another potent drug, streptomycin, given intermittently under supervision twice a week, the minimum interval considered to offer substantial practical advantage over daily chemotherapy. This intermittent regimen was compared concurrently with a standard oral regimen of isoniazid *plus* PAS (Tuberculosis Chemotherapy Centre, Madras, 1964).

The two regimens are summarized in Table V, *see* above.

SHTW :–Streptomycin (Sulphate) by intramuscular injection in an uniform dose of 1 g. (mean 27 mg./kg. body-weight) irrespective of patient's weight, *plus* isoniazid in a single oral dose of approximately 14 mg./kg. body-weight (a patient weighing **100** lb. receiving 650 mg.) both drugs given together, under supervision. twice weekly, at intervals of 3 and 4 days alternately.

PH :–Isoniazid 44 mg./kg. body-weight *plus* PAS (sodium) 220 mg./kg. body-weight (a patient weighing 100 lb. receiving isoniazid 200 mg. *plus* PAS 10 g.) the two drugs given together in 2 divided doses daily.

Patients on the intermittent (SHTW) regimen attended the clinic twice a week and received an injection of streptomycin and took a dose of isoniazid under direct supervision of the clinic staff. Those on the daily (PH) regimen attended the clinic once a week to collect a week's supply of the drugs which were to be taken twice daily by themselves at home.

Over the year of treatment, the therapeutic response, in terms of overall radiographic improvement, cavity closure and sputum conversion, in the SHTW series was at least as good as in the PH series. Thus 94% of patients on the intermittent (SHTW) regimen had bacteriologically-quiescent disease at one year compared with 85% on the daily (PH) regimen *(see* Table VI, *below).*

TABLE VI
Status at 1 Year

Status	SHTW	PH
Quiescent	94%	65%
Active, relapsed or deteriorated	3%	14%
Death from TB.	3%	2%
Tots1 patients	72	66
Toxicity	0	3
Uncooperativeness	7	1
Non-tuberculous death	0	1
All patients	79	71

TABLE VII
Regimens

Drugs and dosage	Rhythm	
	SHTW	SHOW
Streptomycin lg. plus Isoniazid 14 mg./kg.	Twice weekly	Once weekly

It may, therefore, be concluded that streptomycin *plus* isoniazid given together twice weekly under supervision has emerged in this study as a very valuable regimen which is not only at least as effective as a standard daily oral regimen but has the advantage that no reliance need be placed on the co-operation of patients in self-administering their drugs at home.. This regimen, therefore, offers a practical method of supervised chemotherapy, which is of particular value in ambulatory chemotherapy.

Once-weekly regimens of chemotherapy.- The encouraging results of the twice-weekly regimen suggested the possibility of a longer interval between the doses and therefore a once weekly regimen of isoniazid *plus* streptomycin has been compared with the twice weekly regimen.

The two regimens being compared in this study are set out in Table VII, *above.* In both the regimens the drugs and doses remain the same, *namely* streptomycin 1 g. *plus* isoniazid 14 mg./kg. body-weight, the only difference between the two being the interval between the doses - twice weekly in one (SHTW) and once weekly in the other (SHOW).

The interim results at 6 months, in terms of overall radiographic improvement, cavity-closure and sputum-conversion, reaffirmed the efficacy of the twice-weekly regimen but showed that the once-weekly regimen was unsatisfactory. Thus, at 6 months all cultures (usually 3) were negative in 89% of patients in the twice-weekly series as compared with only 66% in the once-weekly series (Menon, 1965).

The failure of the once-weekly regimen in this study does not necessarily imply that once-weekly intermittency has no therapeutic potentialities. Indeed, there is some evidence from the interim results of a, current study, still in progress, that the addition of a third drug to the once-weekly regimen or an initial short course (say for 1 month) of daily chemotherapy enhances its efficacy.

These findings on the fully-supervised intermittent chemotherapy have opened up a new approach to chemotherapy of pulmonary tuberculosis in general and ambulatory chemotherapy in particular, with highly effective regimens at a relatively low cost.

Table VIII, *below,* summarises, the best available regimens, their maxims1 effectiveness and the approximate cost of drugs (based mainly on the Madras Government Medical Stores prices) for a year of treatment.

TABLE VIII

Best available regimens, maximal effectiveness and cost of drugs for one year

Regimens		Drugs	Maximal Effectiveness %	Cost in rupees
Triple-drug		SPH (6m) —> PH	100	269
		STH (2m) —> TH	93	59
Dual Drug	Daily oral	PH	90	180
		TH	(?) do.	29
	Inter-mittent	S H T W	96	59
		SH (1m) —> SHOW	(?) do.	42
Single-drug		H400	70	17

Priorities of chemotherapy.–Considering the meagre resources available to treat the estimated 6 million tuberoulosis patients in the country of whom 1½ to 2 millions are in the infectious stage, the need for a careful order of priorities is obvious. The first priority clearly is to give effective chemotherapy for a year to all newly diagnosed patients with active tuberculosis. The choice of the regimen would depend upon the resources available, but the general policy should be to choose regimens which would give the maximum benefit to the maximum number of patients. For example; if the resources of drugs

are limited, the first priority for double-drug regimens should go to patients whose sputum smears are positive, those *negative on smear* being prescribed isoniazid *alone* in a single daily dose of 400 mg. (approximately 9 mg./kg.) preferably with 6 mg. of pyridoxine. However, all efforts should be made to administer a double-drug regimen for a year for every newly diagnosed patient and to educate the patient and the family regarding the importance of regular treatment for at least a year. The intermittent regimens would permit greeter control over the amount of chemotherapy the patient actually receives and ensure maximum therapeutic benefit. They are of particular value in urban tuberoulosis-control progrsmmes where facilities for injections can be organised.

Although the aim is to give chemotherapy for one year to every patient, it is necessary to assess response to treatment by sputum smear examination as frequently as possible, or at least at the end of 6 months of regular chemotherapy in order to decide whether or not the same chemotherapy should be continued for the second six months. If sputum smears are consistently positive at 6 months after regular chemotherapy, it may be predicted with confidence that bacteriological quiescence will not be attained with the regimen and there will be no virtue in continuing with it and the regimen has to be changed. On the other hand, if all smears at 6 months are negative it can be predicted that bacteriological quiescence will be attained at 12 months if the same chemotherapy is continued up to 12 months.

TABLE IX

Influence of Isoniazid on the Relapse-rate (first study)

At start of follow-up (at 19 months)			Relapses in follow-up	
Cavitation status	**Treatment series**	**Total patients**	**First year**	**Second, third and fourth years**
Cavitated	**Isoniazid (200 mg. for 1 year)**	52	4	0
	Calcium	44	8	4
Non-Cavitated	**Isoniazid (200 mg. for 1 year)**	196	1	1
	Calcium	116	11	6
	Total ...	337	19	11

Second year of chemotherapy for patients with quiescent disease at one year.–There is evidence from the Madras studies that if chemotherapy is limited to one year, the likelihood of relapse in patients with quiescent disease, over a subsequent 4-year period of follow-up is in the order of 15% and that this can be reduced to 5% by isoniazid alone given for the second year. There is further evidence

that isoniazid alone given for a second year was effective in preventing almost all relapses in patients with quiescent disease who had *no* residual cavitation at one year, for only 2 of 125 who received isoniazid for the second year had a relapse over a 4-year period of follow-up compared with 17 of 116 who received no chemotherapy (see Table IX, page 8). On the other hand, in patients with quiescent disease and residual cavitation at 1 year ("open negative syndrome") isoniazid was of doubtful value, for 4 of 52 patients who received it had a relapse compared with 7 of 44 who received no chemotherapy after the first year. Even if all relapses could be prevented by a second year of combined chemotherapy, it would be unrealistic to treat 100 patients for a second year to prevent 15 relapsing unless, as the first priority, every newly diagnosed patient with active disease could be also brought under effective chemotherapy.

When resources become adequate it will be logical to give a second year of chemotherapy with isoniazid alone to those with no residual cavitation and continue double-drug chemotherapy to those with residual cavitation.

Reserve regimens for "failure cases." –Reserve regimens used for patients who fail on initial chemotherapy and have resistant organisms, are expensive and are not available at present for use on a large scale. The best method to tackle the drug-resistant problem is to prevent emergence of drug-resistant organisms by giving effective chemotherapy initially, a point which underlines the need for ensuring that patients do take the prescribed drugs regularly.

Patients who fail on thioacetazone *plus* isoniazid or isoniazid alone pan be retreated with a regimen of streptomycin *plus* PAS daily. The reserve regimens tested under domiciliary conditions at this Centre for patients who failed on the initial regimens are:-

1. Streptomycin sulphate 1 g. *plus* pyrazinamide 1 to 1.5 g. daily.
2. Ethionamide 500 mg. *plus* cycloserine 500 mg. daily.

Over the year of treatment 58% of patients on each regimen attained bacteriologically quiescent disease and toxicity was not a serious problem with either regimen.

Summary and conclusions. –In formulating chemotherapeutic policies for tuberculosis we have to take into consideration the availability of funds, the cost of chemotherapy, the availability of drugs and the facilities for the application of the regimens. Under the existing state of our medical sources. the first priority should be to give an effective double-drug chemotherapy to every newly diagnosed patient for one year. Irregularities in self-administration of drugs should be prevented as far as possible by careful and repeated explanation to patients and their families concerning the importance of regularity in drug-taking for atleast one year. If injection facilities can be provided a supervised intermittent regimen either preceded by a short initial course of daily chemotherapy (say for 1 month) or for the entire period of 12 months is the best, because it permits a precise knowledge of, and therefore greater control over the amount of chemotherapy the patient actually receives. If the drug supply is inadequate to give a double-drug regimen

for all patients for a year, those with *negative sputum* but with clear-cut radiographic evidence of active or probably active tuberculosis may be given isoniazid alone in a single daily dose of 400 mg. (approximately 9 mg./kg.). When resources sufficiently improve, chemotherapy with isoniazid alone may be given for the second year for patients with quiescent disease and no residual cavitation and the double-drug regimen continued for those *with* residual cavitation ("open negative syndrome"). The reserve regimens are expensive, relatively more toxic and laboratory facilities for culture and sensitivity-testing are required to make effective use of these regimens.

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