INTRODUCTION

Ever since the discovery of Streptomycin, the first anti-tubercular drug, a long chain of drugs have been made available, inspite of having these chemotherapeutic agents, the sage of pre-chemotherapeutic era continued for some time, Patients would be treated by TB Specialists only, Management of patients was individualised and according to the fancies of the Specialist, a cocktail of drugs was prescribed. Very soon it was realised that this practice cannot make any dent on the tuberculosis problem. Two revolutionary findings of late fifties are considered more crucial than even the discovery of the drugs by itself. These are feasibility of domiciliary treatment and development of highly effective drug regimens through controlled clinical trials. Evolution of Chemotherapy further led to development of drug regimens which were more suitable for self-administration at home by the patient himself. This standardisation and simplification of treatment will make it possible for the treatment of tuberculosis to step out of Specialist fold to general physician, as that any person suffering from tuberculosis will have a chance of effective treatment in any medical institution.

To achieve the objective of chemotherapy i.e, early bacteriological conversion, prevention of drug resistance, prevention of relapse and relief from physical suffering some principles have been laid down. They are:

- Use of standard drug regimen
- Optimum duration
- Optimum drug regularity

WHAT IS A DRUG REGIMEN?

The following six components put together make-the term “drug regimen”:

1. Drugs
2. Combinations
3. Dosage
4. Duration
5. Rhythm
6. Mode of administration

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and not merely just combination of drugs, a mis-conception quite prevalent among the members of medical community.

A standard drug regimen is one which has been found effective and least toxic in controlled clinical trials. Thus, depending upon the duration of treatment they can be classified into two categories - conventional regimens (12-18 months) and short-course regimens (6-9 months).

**CHEMOTHERAPY POLICY**

Decisions taken with regard to chemotherapeutic management of tuberculosis patients under the National Tuberculosis Programme (NTP), is based on technical, sociological, operational and organisational considerations and is referred to as chemotherapy policy. The policy is liable to change for the same reasons from time to time. At present, the policy comprises of:

- Domiciliary treatment
- Use of standard drug regimens
- Duration of treatment, 12-18 months
- Priority to sputum positive cases
- Treatment free of cost
- Priority to newly diagnosed patients over previously, treated patients
- Treatment organisation:
  - Fully decentralised
  - Efficient defaulter retrieval system
  - Mostly self-administered regimens
  - Timely follow-up
- Short-course chemotherapy has not yet become a part of DTP but in some Districts it is being implemented on pilot basis
- Chemoprophylaxis is not recommended as it is impractical

**ANTI-TB DRUGS**

Seven most commonly used drugs in conventional and short-course drug regimens are listed below in Table 1 which their dosage, abbreviations and adverse reactions:

(Table 1)
(Please see next page)

**SELECTIVE ACTION OF DRUGS ON BACILLARY POPULATION IN TUBERCULOSIS**

**LESSON OF MAN**

The understanding of selective action of drugs is based on experimental work done in vitro and vivo by many works and subsequent measuring of contribution of individual drugs by well designed controlled clinical trials. This is being summarised as below:

There are three different types of bacterial population on which drugs act (Fig 1), Majority of the bacterial population falls in the
### Table 1
**Drugs used in Conventional Short-course Chemotherapy**

<table>
<thead>
<tr>
<th>Sl No</th>
<th>Name and Abbreviation</th>
<th>Dosage &lt;50 Kg</th>
<th>Dosage &gt;50 Kg</th>
<th>Adverse Reactions</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ISONIAZID (H)</td>
<td>300 mg</td>
<td>300 mg</td>
<td>Peripheral Neuritis</td>
<td>Pyridoxine 10 mg Daily</td>
</tr>
<tr>
<td>2</td>
<td>RIFAMPICIN (R)</td>
<td>450 mg</td>
<td>450 mg</td>
<td>Anorexia, Vomiting, pain abd. itching all Over body With rashes or without Rashes, Clinical Jaundice</td>
<td>To take drugs after Meals Symptometica treatment/Desensitize patient, with-hold all drugs till complete recovery Terminate R</td>
</tr>
<tr>
<td>3</td>
<td>STREPTOMYCIN (S)</td>
<td>0.75g</td>
<td>0.75g</td>
<td>Vertigo, Atazia, Giddiness</td>
<td>Discontinue drug till complete recovery Reduce the dosage to 0.5g</td>
</tr>
<tr>
<td>4</td>
<td>ETHAMBUTOL (E)</td>
<td>800 mg</td>
<td>1200 mg</td>
<td>Optic Neuritis</td>
<td>Terminate the drug</td>
</tr>
<tr>
<td>5</td>
<td>PYRAZINAMIDE (Z)</td>
<td>1.5g</td>
<td>2g</td>
<td>Arthralgia Hepatitis</td>
<td>Symptomatic treatment Same as above</td>
</tr>
<tr>
<td>6</td>
<td>THIOACETAZONE (T)</td>
<td>150mg</td>
<td>150mg</td>
<td>Gastro-intestinal itching all over body Exfoliative dermitis</td>
<td>Same as in R</td>
</tr>
<tr>
<td>7</td>
<td>PAS (P)</td>
<td>10 g</td>
<td>10 g</td>
<td>Gastro-intestinal cutaneous Hepatitis</td>
<td>Same as in R</td>
</tr>
</tbody>
</table>
FIG. 1

SELECTIVE ACTION OF DRUGS ON SPECIAL PORTIONS OF
THE BACTERIAL POPULATION IN LESIONS OF MAN

ACTIVE GROWTH

INTERMITTENT GROWTH

VERY SLOW GROWTH

DORMANT

A

B

C

D

HRS

NEUTRAL pH

Z

ACID pH

?

pH
the category of (a) actively Multiplying tubercle bacilli which are acted upon by Isoniazid, Rifampicin and Streptomycin, (b) extracellular bacilli which multiply slowly and intermittently and the drug effective against this type of bacilli is Rifampicin and (c) intracellular and slow multiplying bacilli and the drug effective against this group is Pyrazinamide.

There is also a fourth group of dormant bacilli which do not multiply at all and hence no drug acts upon them. Their size or site is not known.

Relapses after the end of Chemotherapy are likely to derive from residual organisms in semi-dormant population groups rather than from the dormant group.

Thus, as summarized by Fox5, it can be stated that:
1. Isoniazid is the key bactericidal drug.
2. Rifampicin and Pyrazinamide have special sterilizing roles, acting on the different bacterial populations.
3. The most potent sterilizing combinations are isoniazid plus pyrazinamide and isoniazid plus Rifampicin.
4. Adding Streptomycin or Ethambutol makes little or no contribution to the sterilizing capacity of either of the above two combinations.

STANDARD CONVENTIONAL DRUG REGIMENS UNDER NTP

It has been well established that chemotherapy with Standard (first line) anti-TB drugs is potentially cent percent effective in the treatment of newly diagnosed sputum positive tuberculosis patients. It is effective when administered at home on ambulatory out-patient basis as in a Sanatorium provide adequate Chemotherapy is administered.

The following regimens of proven value are recommended for the National Tuberculosis Programme of which District Tuberculosis Programme is a Major part (Table2). Any one of these regimens may be employed, depending upon the availability of drugs and operational feasibility. The dosage, mode of administration and other instructions are given below. The dosage given is for adults and would need adjustment for children on the basis of their age/weight.

(Table 2)
(Please see next page)

Whenever possible, biphasic drug regimen (R5) with initial intensive chemotherapy should be given for seriously ill tuberculosis patients as it has a substantial influence on the outcome of treatment.

DURATION OF TREATMENT

All patients should be treated for a minimum of 1 year irrespective of their disease status or drug regimen prescribed. Patients put on R1 and R3 even if they are regular at the end of 1 year should be encouraged to continue treatment upto 18 months in order to prevent
Table 2

Standard conventional drug regimens adopted under NTP

<table>
<thead>
<tr>
<th>DTP Code</th>
<th>Regimen with dosage of drugs</th>
<th>Duration in months</th>
<th>Efficacy %</th>
<th>Relapse %</th>
<th>Overall Efficacy %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R1 TH (150mg + 300 mg) daily.</td>
<td>18</td>
<td>82</td>
<td>5</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>R2 SH tw (0.75g + 650 mg) twice weekly</td>
<td>12</td>
<td>94</td>
<td>9</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>R3 PH (10g + 300 mg) daily</td>
<td>18</td>
<td>86</td>
<td>5</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>R4 EH (1g+300mg) daily</td>
<td>12</td>
<td>96</td>
<td>15</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>R5 S+TH/PH/EH/Daily for 2m, TH/PH/EH daily or SH tw for 10 m</td>
<td>12</td>
<td>96</td>
<td>6</td>
<td>90</td>
</tr>
</tbody>
</table>

relapses. Treatment can be continued up to 2 years after review at the end of 18 months but continuation beyond two years has no added advantage.

PRINCIPLE OF SHORT-COURSE CHEMOTHERAPY REGIMENS

In the standard conventional chemotherapy regimens, the principle was to employ a combination of drugs with the primary object of prevention of emergence of drug resistance and to treat for a sufficiently long period to eliminate the entire bacterial population. The aim of short-course chemotherapy, while helping to achieve a similar end point is also to achieve rapid sterilization of the lesson.

INDICES OF THE EFFICACY OF SHORT-COURSE CHEMOTHERAPY REGIMENS

The success of a short-course chemotherapy regimen can be judged by the sputum conversion by culture at the end of two months of treatment and the rate of post-treatment relapse. The conversion at the end of 2 months is termed as the “early index” while the relapse rate as the “best index”.

EVOLUTION OF SHORT-COURSE CHEMOTHERAPY

The duration of chemotherapy could be shortened and this has become possible with the advent of Rifampicin and Pyrazinamide.
The first report of effective short-course regimens came from East Africa. The efficacy of 6 months regimens have been investigated both by East African and British studies and they have been summarized in the Table 3.

### Table 3

**Role of Rifampicin & Pyrazinamide in short-course chemotherapy**

<table>
<thead>
<tr>
<th>Sl.no</th>
<th>Regimen duration (6 Months)</th>
<th>Culture conversion at 2 months</th>
<th>Bacteriologic relapse at 24 Months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 SH</td>
<td>49</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>6 SHT</td>
<td>49</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>6 SHZ</td>
<td>66</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>6 SHR</td>
<td>75</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>2 SHRZ/4HR</td>
<td>95</td>
<td>0-2</td>
</tr>
</tbody>
</table>

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

As shown in Table 3, first regimen which consisted of Streptomycin and isoniazid daily for 6 months, had culture conversion in 49% of cases at 2 months and 29% relapses at the end of 24 months. In second regimen addition of Thioacetazone did not enhance the efficacy of the regimen from the first one. But, in third regimen which consisted of Streptomycin, Isoniazid and Pyrazinamide daily for 6 months, had culture negatively at 2 months in 66% of cases and a relapse rate of only 8%. This difference is both indices was highly significant and thus suggested that Pyrazinamide might have something to offer in short course chemotherapy. In the Fourth regimen of Streptomycin, Isoniazid and Rifampicin daily for 6 months culture conversion at 2 months increased to 75% and relapse rate of only 4% at 24 months which did not increase during a five year follow up in this I East African Study.

The fifth regimen consisting of Streptomycin, Isoniazid, Rifampicin and Pyrazinamide daily for initial 2 months followed by Isoniazid and Rifampicin daily for 4 months showed 95% culture conversion at 2 months and 0-2% relapse rate at 24 months in subsequent studies conducted at East African and Britain. Thus, achieving almost 100% cure rate by this regimen.
DURATION OF SHORT-COURSE CHEMOTHERAPY

Following the favourable results of East African, British and Singapore studies of the 6 month Streptomycin, Isoniazid and Rifampicin regimens, the studies will still shorter periods ranging from 5-2 months were investigated. Intermittent regimens in continuation phase or from the start of treatment were also investigated in Hong Kong and Madras. Amalgamated findings from British, East African, Singapore, TRC Madras and Hong Kong Study are summarized in Table 4.

Table 4

Duration of Chemotherapy in Short-course Chemotherapy

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Total duration (in months)</th>
<th>Bacteriological Relapses follow-up 24th month(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2 SHR/10HR</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>2 SHR/7HR</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>2 SHR/4HR*</td>
<td>6</td>
<td>3-8</td>
</tr>
<tr>
<td>2 SHRZ/4HR</td>
<td>6</td>
<td>0-2</td>
</tr>
<tr>
<td>6 S3H3R3Z3 ***</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>2 SHRZ/3HRZ</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>3 SHRZ/2S2H2Z2***</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>2 SHRZ/2HRZ</td>
<td>4</td>
<td>16(12 M)</td>
</tr>
<tr>
<td>3 SHRZ</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>2 SHRZ</td>
<td>2</td>
<td>32</td>
</tr>
</tbody>
</table>

Note: For abbreviations see Table 3.

*Replacement of S with E in all 3 drug regimens did not have any effect on relapse rate.
** SHRZ three times a week for total duration.
*** SHZ twice a week for 2 months in continuation phase.

It will be seen from the table that as the duration decreased upto six months is very low, but as the duration goes below six months the relapse rate rises sharply. Hence, at present it is not possible to reduce the total duration of chemotherapy to less than 6 months.
There is not much difference in the recommended duration of treatment of culture positive and suspect cases from that of smear positive cases, even though these two categories of cases differ widely in their bacillary content from smear positive cases.

**STANDARD SHORT-COURSE REGIMENS FOR TUBERCULOSIS PROGRAMME**

Considering all important factors, some of the drug regimens are listed in table 5. Levels of efficacy of drug regimens suggested here range from 90% to 98%. The approximate cost has been calculated on the present market rate. However prices keep fluctuating and thus the cost calculation is suggestive only.

<table>
<thead>
<tr>
<th>Sl No</th>
<th>Regimens *</th>
<th>Duration (in month)</th>
<th>Relapse Rate %</th>
<th>Cost in rupees</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2SHRZ/4HR</td>
<td>6</td>
<td>0-2</td>
<td>1,000/-</td>
</tr>
<tr>
<td>2</td>
<td>2SHRZ/4H₂R₂</td>
<td>6</td>
<td>0-3</td>
<td>750/-</td>
</tr>
<tr>
<td>3</td>
<td>2SHR/4HR</td>
<td>6</td>
<td>3-8</td>
<td>725/-</td>
</tr>
<tr>
<td>4</td>
<td>2H₂R₂Z₂/4H₂R₂</td>
<td>6</td>
<td>3-8</td>
<td>465/-</td>
</tr>
<tr>
<td>5</td>
<td>2HRZ/4HR</td>
<td>6</td>
<td>0-3</td>
<td>650/-</td>
</tr>
<tr>
<td>6</td>
<td>2SHRZ/6TH</td>
<td>8</td>
<td>6</td>
<td>700/-</td>
</tr>
<tr>
<td>7</td>
<td>1SHRZ/7TH</td>
<td>8</td>
<td>10</td>
<td>350/-</td>
</tr>
</tbody>
</table>

*Dosage and abbreviations are given in Table 1.

In all the above mentioned regimens `S' can be replaced by `E', Cost will be slightly lower.

**DOSAGE SCHEDULE**

With present pharmacokinetic knowledge about the drugs it is necessary to administer all the drugs in single dose in a bolus one a day in order to ensure range.

**BASIS OF SELECTION OF A DRUG REGIMEN**

Selection of one of these drug regimens will depend upon the availability of drugs, patient’s convenience, acceptance and clinical condition. Very ill patients may be motivated to accept one of the
drug regimens containing Streptomycin. Change of Regimen should be made only if there is major toxicity to drugs or inability to continue treatment by the patient due to operational or financial reasons.

CONCLUSIONS

Rifampicin and Pyrazinamide are even more effective when used together in the intensive phase. Intensive phase is particularly important. 4 drug combination renders the sputum culture negative very quickly. Two months duration of intensive phase with 4 drug combination renders the sputum culture negative very quickly. Two months duration of intensive phase with 4 drug combination is ideal. Pyrazinamide administration beyond 2 months does not confer any additional benefit.

Continuation phase in short-course chemotherapy is also important. Rifampicin continues to make important contribution even during continuation phase. At present it is not possible to reduce the total duration of chemotherapy less than 6 months. When Rifampicin is limited to intensive phase the total duration of chemotherapy should be 8 months.

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REFERENCES