I am indeed privileged to stand before you to deliver the prestigious P.V. Benjamin oration bestowed to me by the Andhra Pradesh Tuberculosis Association. I pay my tributes to this great visionary in the field of tuberculosis (TB). Dr Benjamin was regarded as the father of anti-TB movement in India. Among his great contributions are that he was the founder member of almost all the leading Tuberculosis Research Institutions in the country. The Tuberculosis Chemotherapy Centre (later re-designated as Tuberculosis Research Centre [TRC]) was established in 1956, and I feel proud to be associated with this institute that has made enormous contributions in understanding the principles of chemotherapy for TB and through this to the various control programmes during the past 3 decades. When the National Tuberculosis Institute, Bangalore (NTI) was established, Dr Benjamin remarked, "This institute will contribute a lot for the control of TB". True to this, we are aware of the contributions made by NTI to the control of TB. The Madanapalle centre for which he was the superintendent for 10 years, has been responsible for the study on protective efficacy of BCG vaccination and many more studies on epidemiology of TB. He is also a founder member of the largest voluntary organization fighting the cause of TB i.e., Tuberculosis Association of India. He initiated the National Sample Survey in 1956 and several other research programmes. While saluting this great personality I have chosen a topic dear to his heart for my oration "Chemotherapy of tuberculosis : Challenges, Solutions".

To quote Kevin de Cock, 'Tuberculosis for which effective interventions exist, remains an orphan, and the world should be ashamed'. What is the present situation with regards to TB? Why are we in this state of a situation? Let us take a deeper look into the problems.

**TUBERCULOSIS: A GLOBAL BURDEN**

The major challenge facing the world is the magnitude of TB. Considering the Global scenario, 1.7 billion people are infected with tubercle bacilli, 8 million cases of TB occur every year and 3 million people die of TB every year. Most of these occur in the developing world. In the developed world where the disease was under control in early 1980s, there has been a re-emergence of TB in the late eighties and nineties. Due to the magnitude of the problem, the WHO declared TB as a Global Emergency in 1993.

**Burden of tuberculosis: India**

Considering the magnitude of the problem in India, about 40% of our population is infected with tubercle bacilli, about 3.5 million of 14 million diseased are sputum positive cases. About 1.5 million new cases are added every year. Half a million people die every year due to TB in India.

**Socio economic burden**

Since TB affects and kills the persons belonging to the most economically productive age group, its share to the economic loss is considerable. One sputum positive patient if left untreated can infect 10 to 15 individuals every year increasing the infected pool and producing more cases. TB is one of the leading causes of maternal mortality and hence produces more orphans.

**Impact of HI Von TB**

On this already bleak scenario on TB, we now have another threat posed by the co-infection with Human Immunodeficiency Virus (HIV). As you are aware, the break down rate of TB among co-infected with HIV is about 10% per year compared to 10% during lifetime among those infected only with tubercle bacilli. In addition, HIV poses a problem in diagnosis since patients are more likely to be smear negative and have atypical pulmonary shadows on X-ray. Due to this increased
breakdown, the incidence of Multi drug resistant TB (MDR-TB) is also likely to increase. This will further lead to an increase in burden on the already loaded health care facilities.

THE PARADOX AND CHALLENGES IN TB CONTROL

This grave situation of TB continues even though tubercle bacilli, as a causative organism of the disease was discovered more than a century ago and effective chemotherapeutic regimens have been available for more than 40 years. TB is a typical example where affordable and effective regimens have been made available through well conducted controlled clinical trials. Still one patient dies of TB every minute, in our country. Why is this happening? What are the challenges?

Let us examine the challenges in TB control one after the other.

Mycobacterial properties

Unique properties of the mycobacteria are that it is very slow growing in nature compared to other organisms. The generation time of tubercle bacilli is 12 to 18 hours. The bacterial wall is unique in nature, making it difficult for the drugs to penetrate. In a lesion, the bacilli occur in different types, with different locations and metabolic activity. In addition, they have the unique ability to survive in a dormant state for a long period and start multiplying at any time. They also have the ability to develop resistance to the drugs. Naturally resistant mutants occur in any bacillary population. For every $10^6$ bacilli, there is one bacillus resistant to Isoniazid (H), 1 in $10^6$ to Streptomycin (S), 1 in $10^8$ to Rifampicin (R) and 1 in $10^7$ for Ethambutol (E). The frequency with which a naturally occurring resistant mutant to 2 drugs namely H and R is 1 in $10^{14}$.

Bacilli present at different locations with different metabolic activities. Fig. 1 shows the different types of bacterial populations and actions of anti-TB drugs. One group of bacilli is extra-cellular in location and multiplies very rapidly. Some bacilli do not multiply ordinarily but show spurts of metabolism and the third group within the macrophages in the acidic medium multiply slowly. There is yet another group of organisms, which lie dormant and do not show any metabolic activity. Considering the drug action on different bacillary populations: H, R, S, Para-Amino Salicylic-Acid (PAS) and E have action on extra-cellular rapidly multiplying organisms. R also acts on extra-cellular bacilli which are slowly multiplying or show spurts of metabolism. Pyrazinamide (Z) can penetrate into macrophages and kill the intracellular bacilli. Before the discovery of R and Z, there was no drug that could act so fast on these two groups of bacilli and the treatment had to be for a duration of 12-18 months for H to decimate these two groups of sub-population. There is no drug, which has got action against the dormant group of bacilli which can lie dormant for any length of time and get activated causing relapse.

Emergence of resistance

When S was introduced in the treatment of TB and patients were treated with that drug alone, 57% of patients had emergence of resistance to the drug. Subsequently, when the second drug PAS was given in addition, this emergence of resistance was reduced to 69c. This was the first demonstration of combined therapy being more effective than single drug. This finding has been confirmed by other studies also.

With the proper use of Short Course Chemotherapy (SCC) regimens, the emergence of drug resistance could always be prevented. With the advent of R and use of 3-4 drugs in SCC, the chances of emergence of resistance are very low. The Directly Observed Treatment Short course (DOTS) strategy in Revised National Tuberculosis Control Programme (RNTCP) ensures drug consumption preventing emergence of drug resistance to any drug i.e., <1% (Table 1). Development of drug resistance to H and R is known as MDR-TB. It can be seen that MDR-TB is a man-made problem.

Once MDR-TB occurs, the treatment is very difficult because we have very few alternative drugs available. They are less effective and more costly. So the best way to
manage MDR-TB is to prevent it from occurring, by judiciously choosing the regimens and giving them under direct observation.

The drugs available in managing MDR-TB are Cycloserine, Quinolones, Aminoglycosides, Thioamides like Ethionamide and Prothionamide, PAS and Thioacetazone (T). The main principle in management is to pick and choose the drug which the patient has not received before and one should take care to include at least 2 or 3 new drugs that the patient has not received. We should never add a single drug to a failing regimen.

ANTTI-TB DRUGS

Development of drugs

The development of drugs for TB has been accidental and sporadic. 1940s saw the introduction of S and PAS for treating TB. This was followed by H, T and Ethionamide in 1950s. E and R were added in 1960s. Subsequently there have been no new drugs for treating TB. Even though 1980s saw the epidemic of HIV deteriorating TB situation around the world and in 1993, WHO declared TB as a global emergency, no new drugs have become available. This is because of the very high cost and prolonged testing time required to come out with a new drug compared to an antibiotic against rapidly multiplying bacilli. Once the drug is made available, to get the clinical benefits takes much longer duration compared to other drugs.

Duration of treatment

The adequate duration of treatment of TB is very critical. In the earlier days when attempts were made to reduce the duration by giving SH only for 6 months, 29% of patients had a bacteriological relapse. With the addition of T to SH regimen, the relapse rate was reduced to 22%. When the duration was increased to 12 months, the relapse rate was further reduced to 12 -19%. With 3 drugs in the initial phase followed by 2 drugs in the continuation phase, the relapse rate was only 3% (Table 2). Thus the duration of treatment when R and Z are not included in the regimen should be 12-18 months.

With SCC regimen the duration of treatment is critical though shorter. When 4 drugs namely H, R, Z and S were given daily for a period of 3 months (90 doses), 20% had relapsed. When the duration was increased to 6 months with the same drugs even with lesser number of doses, the relapse rate was only 3-7% (Table 3). Thus the duration of treatment has to be 6 months with the SCC drugs.

Role of hospitalisation

In 1950s, the total number of hospital beds available for treating TB was 23,000 and the burden of TB was 1.5 million sputum positive cases in the country. Thus many patients were being treated at home for want of beds. This raised considerable alarm among the public health authorities about the spread of disease. The TRC undertook a controlled clinical trial by randomly allocating sputum positive pulmonary TB patients to be treated either in the Sanatorium or in their homes. The outcome of treatment in terms of favourable response at the end of treatment and relapse over a follow up period of 4 years was similar in both the groups. Apart from the patients, the centre also investigated the risk of close family contacts developing the disease. We followed up 245 contacts of patients treated at home and 264 contacts of patients who were isolated to Sanatorium for the period of 5 years. The attack rate of TB in both the groups of contacts was similar. There was no additional benefit by bed rest and good food, which were available only for patients admitted in Sanatorium. This study showed that domiciliary chemotherapy was as effective as Sanatorium chemotherapy (Table 4).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Critical duration of treatment (non-SCC)</th>
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<tbody>
<tr>
<td>Regimen</td>
<td>Duration (months)</td>
</tr>
<tr>
<td>SH</td>
<td>6</td>
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<tr>
<td>SHT</td>
<td>6</td>
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<tr>
<td>TH</td>
<td>12</td>
</tr>
<tr>
<td>PH</td>
<td>12</td>
</tr>
<tr>
<td>EH</td>
<td>12</td>
</tr>
<tr>
<td>(SH)&lt;2</td>
<td>12</td>
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<tr>
<td>2STH / TH</td>
<td>18</td>
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<tr>
<th>Table 3</th>
<th>Critical duration of treatment (SCC)</th>
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<tr>
<td>Regimen (%)</td>
<td>Duration (months)</td>
</tr>
<tr>
<td>3HRZS</td>
<td>3</td>
</tr>
<tr>
<td>2(HRZS)&lt;2 / 4(HR)&lt;2</td>
<td>6</td>
</tr>
<tr>
<td>2(HRZS)&lt;2 / 4(HR)&lt;2</td>
<td>6</td>
</tr>
<tr>
<td>2(HRZE)&lt;3 / 4(HR)&lt;2</td>
<td>6</td>
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<thead>
<tr>
<th>Table 4</th>
<th>Favourable response with domiciliary chemotherapy</th>
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<tbody>
<tr>
<td>Series</td>
<td>Total No. of patients</td>
</tr>
<tr>
<td>Home</td>
<td>82</td>
</tr>
<tr>
<td>Sanatorium</td>
<td>81</td>
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Genesis of intermittent chemotherapy

Domiciliary chemotherapy necessitates patients to take the drugs by themselves regularly for a prolonged period. Studies at TRC have shown that there was some amount of concealed irregularity in drug intake by the patients. It was also proved that Isoniazid given in a single dose was more effective than when given in divided doses. There was also experimental evidence to suggest that drugs given thrice weekly were as effective as daily consumption. These formed the basis of studying intermittent chemotherapy for the treatment of pulmonary TB. The very first intermittent chemotherapy trial was done by comparing PAS and INH daily self administered with a regimen of S and H given twice a week under supervision in the clinic, both regimens were given for a duration of one year. The efficacy of the regimens and the relapse rates were similar in both the study groups thus showing that intermittent chemotherapy was as effective as daily chemotherapy (Table 5). Subsequently, more intermittent regimens were evolved to be given under supervision. These regimens have the benefits that the concealed irregularity can be avoided.

### Table 5 Efficacy of intermittent chemotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients</th>
<th>Favourable response (%)</th>
<th>Relapse (%)</th>
</tr>
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<tbody>
<tr>
<td>PH</td>
<td>79</td>
<td>85</td>
<td>12</td>
</tr>
<tr>
<td>(SH)₂</td>
<td>71</td>
<td>94</td>
<td>8</td>
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The scientific basis of intermittent chemotherapy was developed on the basis of long generation time of tubercle bacilli and lag period after chemotherapy. When a culture of mycobacterium TB was exposed to an anti-TB drug, there was a reduction in the number of organisms. When the drug was washed away after 24 hours, the organisms did not start multiplying immediately. Their numbers continued to fall for some more time before starting to multiply. This period when the drug is not available and before organisms start multiplying is called "Lag Phase" (Fig.2). Most of the anti-TB drugs except Thioacetazone have a lag phase and can be given intermittently.

**CHALLENGES IN IMPLEMENTATION OF CHEMOTHERAPY**

The standard as well as SCC regimens have been found to be 85-95% effective under controlled clinical trials. However, their efficacy in the field is less than 50%. Why this gap has occurred between controlled clinical trials and the field conditions? There is a lot of talk about compliance. We have to see whether the lack of compliance is by the patients, the providers or the health system. This is mainly because of poor case holding.

"To default is the natural reaction of normal, sensible people. The person who continues to swallow drugs or have injections with complete regularity in the absence of encouragement and help from others is the abnormal one" ANNIK ROUILLON

**Non-compliance: reasons**

We have investigated the reasons for patient non-compliance in 2 districts in south India by visiting patients who have defaulted for treatment. 38% of patients did not attend due to reason related to their work, 25% because they had abatement of symptoms, 19% due to adverse reaction to the drugs and 17% due to domestic pre-occupation. It can be seen that most of these reasons are correctable by motivating the patient and decentralizing the drug supply.

When the chest symptomatics attend seeking relief for their symptoms, it has been observed that there is a delay in diagnosis. Even though there is definite streamline procedure for diagnosis and treatment in government sector, still this delay occurs. In the Private Sector, both diagnosis and management are fully individualized. In addition, there is an error in prescribing the regimens, as shown in various studies.

**Decentralization**

In few studies conducted by TRC, it was observed that only 43% of patients were cured and 23% died when uninterrupted drug supply was ensured. Even though patient motivation, prompt defaulter retrieval action and continuous drug supply were carried out by trained medical social workers, the cure rate was only 60%. The main drawback of these studies was that the patient had to attend to the centralised clinic for getting their treatment...
under supervision. This brings the needs for decentralizing the drug supply.

Thus the main reasons for the poor case holding are inadequate and irregular drug supply, inadequate motivation of health staff and patients and inconvenient timings and place of treatment. The ultimate outcome of all these are that the drugs do not reach the patients. The associated dangers are increase in the pool of chronic excretors causing an increase in the transmission of disease and thereby increasing the burden of TB in the country. Irregularity in chemotherapy also leads to development of MDR-TB. Till recently there has been a very poor political commitment towards TB programme.

Directly observed treatment short course

Understanding these problems, the Government of India has revised the National TB Control Programme and is implementing it in the country in a phased manner since 1993. The main strategy of the RNTCP is "DOTS".

DOTS is a strategy with 5 components:

* Political commitment
* Diagnosis by sputum microscopy
* Uninterrupted supply of quality drugs for treatment
* Directly observed treatment and
* Accountability

One may wonder why DOTS is necessary. We know that only one third of the patients are regular in their drug intake and it is not possible to predict which patients will be regular. Hence the DOTS is a solution to provide the full course of treatment to all the patients and is an accepted strategy around the world. Experience in India shows that 80% of the patients put on DOTS complete the treatment and 75% of them get cured.

THE CURRENT CHALLENGES

The challenge at present is to make DOTS acceptable to the community and the medical profession. This requires a good advocacy. We are aware that as much as 50% of our patients are approaching private providers for the treatment of TB. There is a need to involve the private sector into the programme if any epidemiological impact has to be felt. The other challenges are expansion of implementation of DOTS in the country, identifying the correct DOTS provider, involvement of the community and proper monitoring and evaluation of the system.

BIBLIOGRAPHY


