

# The Indian Journal of Tuberculosis

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Vol. 42

New Delhi, October 1995

No. 4

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## Editorial

### CHEMOTHERAPY - NEW STRATEGIES?

The present day management of mycobacterial diseases revolves round chemotherapy. Most infective diseases, of course, are treated and cured by the use of appropriate drugs, mostly antibiotics. Whereas acute diseases need drug treatment for short periods only, tuberculosis and some other chronic diseases have to be treated by prolonged chemotherapy.

In this issue, we have papers highlighting some of the issues and problems that are encountered in delivering the chemical/antibiotic treatment, and one of the papers presents an alternative approach to drug delivery. Whether that approach is feasible in the NTP is a moot point.

After the reappraisal of the apparent failure of the NTP in this country, WHO and IUATLD have recommended a new strategy, now under implementation in some pilot projects. The principal stress in this strategy is on direct supervision of drug intake by the patient. The patient attends the drug distribution centre thrice a week and is asked to take the medicines, Rifampicin 450 mg, INH 300 mg, Pyrazinamide 1500 mg and Ethambutol 1000 mg, in the presence of a member of the staff. After two months, the drugs are reduced to Rifampicin and INH only, for another four months.

Two or three issues need consideration if the new strategy is to succeed. Firstly, can we ensure that the patients will be attending regularly for their medicines? If they do not, will we have to chase them all over the place to bring them back? It may be feasible to ensure treatment regularity in urban pilot projects, but the same may become difficult or even impossible when the programme adopts this strategy for the entire country.

The second issue is that the drugs are given in a fixed dosage, irrespective of the patients' weight. This may result in overdosage with attendant side effects, or under-dosage leading to treatment failure and development of drug resistance. On an all India basis, our patients are likely to weigh anything from < 30 kg. to >60 kg.

Current knowledge of the pharmacokinetics of the important anti-tuberculosis drugs suggests that ingestion, specially of Rifampicin, on a full stomach may mean a fall of as much as 20% in the bioavailability of the drug. Can the new strategy ensure that the drugs are taken on empty stomach? The answer, regrettably, has to be in the negative.

In a previous issue (October, 1994) we had highlighted some of the success stories of SCC in this country, both under study conditions and in the field. We also pointed out that intermittent chemotherapy did not lead to significant diminution of results. The most important component of the campaign against tuberculosis is ensuring that the patient takes the drugs, regularly, in adequate dosage and combination, and for the required length of time.

The NTP has always envisaged the involvement of the general health services personnel. PHIs have a large number of auxiliaries, delivering various programmes and services. Each one of them can be allotted a specific area, trained to detect symptomatics for sputum examination, collect sputum and for those who turn out to be sputum positive, deliver the medicines and ensure their consumption on an everyday basis. All the tasks should be handed over to this auxiliary for his/her allotted area, with the NTP forming just one of the programmes. It might even be feasible to arrange that this auxiliary resides in or very near the area she serves. The corps of supervisors assigned to the PHI could easily supervise all the activities of the auxiliaries, after they have been properly oriented. Technical supervision would then be exercised by the DTC with its specialists and health visitors, etc.

Earlier, we have referred to the dosage problem. Proper dosage can be ensured by allowing the DTO to make individual variations after taking into account the patient's weight. As most of the side effects are related to Rifampicin, the DTO should also be supplied 150 mg and 300 mg tablets of Rifampicin, as also small quantities of other drugs, the bulk of his stock being the fixed dosage combined tablets/capsules or kits. The prerogative about varying the dosage will lie only with the tuberculosis specialist in the DTC who should also be allowed to start alternative (or additional) drugs in clinically suspected cases of drug resistance, while waiting for laboratory confirmation. Small stocks of one of the quinolones and P.A.S. may be of considerable use in such cases.

S.C. KAPOOR

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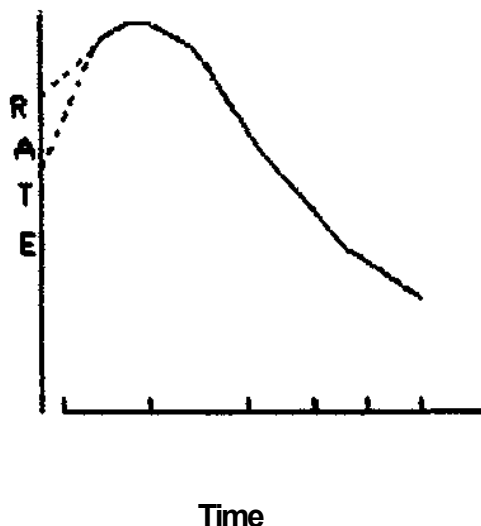
## EPIDEMIOLOGY OF TUBERCULOSIS WITH PARTICULAR REFERENCE TO INDIA

I have been four times to India; I was here in 1971, working as a short-term WHO consultant at the National Tuberculosis Institute in Bangalore. Dr. Karel Styblo was the other short-term consultant and we worked closely together and produced a joint report. In the 1980s, I had the privilege of having two assignments to the Tuberculosis Research Centre in Madras. On each occasion, I learnt a great deal about tuberculosis from the Indian research workers. Indeed, I think it is fair to say that Indian research in tuberculosis has been most important in the world and that much of the knowledge derived from Indian research is used extensively in all countries of the world.

INDIA'S CONTRIBUTION TO TUBERCULOSIS CONTROL	
Therapy	- Proof that home treatment is as good as hospital treatment. - Development of supervised intermittent regimens.
Diagnosis	- Importance of bacteriological examination.
BCG	- Largest BCG trial in south India.

Coming to epidemiology of tuberculosis, Graph I shows the usual tuberculosis epidemiological curve. On the ordinate are tuberculosis rates (mortality or morbidity) and on the abscissa are years. It will be noticed that in this curve the ascending limb is fairly steep followed by the peak, and then there is a gradual descent. There is really nothing original in this curve. Dr. Gothi in his Wander TB Association of India oration - in 1977 discussed very ably a similar model published by Dr. Grigg of the United States.

The duration of the tuberculosis epidemic is often measured in hundreds of years. For instance, in Britain and parts of western Europe, the epidemic began in the middle of the 18th century, reached its peak in the first half of the 19th century and then gradually declined. It is still declining, some 250 or 300 years after its beginning, although it has reached quite low levels. As my work was mainly in England and



Graph I. Model of Tuberculosis Epidemic

later in Canada, I have only observed the steady natural decline of this disease. The speed of this natural decline is about 2% per annum. However, in the 1960s, I was fortunately able to study tuberculosis among the Eskimos, a relatively small group of people occupying northern Canada, Alaska and Greenland. There, for the first time, I met with the peak of the epidemic. I never thought I would be able to observe the ascending part of the tuberculosis epidemic curve; however, some eight months ago, I was asked to go to South Africa to look for the reasons why in one of the groups of population - "the coloured" - the rate of tuberculosis was rising quite alarmingly. Although the story is not completely told, yet I believe that this group of South Africans is actually experiencing the early phase of tuberculosis epidemic.

What I will try to do now is to convince you that the current tuberculosis epidemic in India started probably in the mid 19th century, reached its peak some 50 years later, at the beginning of this century, and that it has been naturally declining slowly ever since. There is evidence that there was little tuberculosis in most parts of India in the early 19th century.

Evidence can be found in the writings of English physicians working in India then. Thus, according to Young in the Transactions of Calcutta

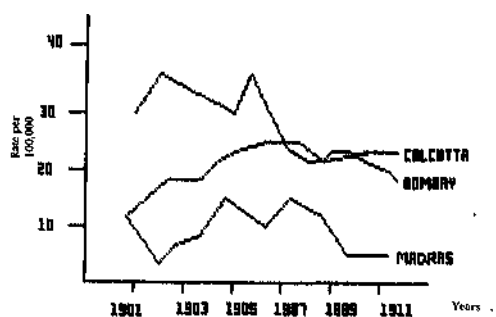
Medical Society; 1823, IV, 36) and Murray (Trans, Bombay Med. Soc. 1838,11,45), tuberculosis was extremely rare in the upper plateau of the Western Ghats, Nilgiri hills and on the northern and southern slopes of the Himalayas. And Chevers, after 36 years of service in India, observed in the "Commentary on the Diseases of India (1886)" that phthisis was comparatively rare as was scrofulous affection of glands, bones and joints. We must remember that these authors were quite familiar with tuberculosis as it was a very common disease in Britain at that time. Possibly, the British brought tuberculosis infection to India and it spread in the second half of the 19th century. Towards the end of that century, tuberculosis had become quite common in the Indian population. Graph 2 shows mortality from tuberculosis in three Indian cities - the peak occurred at the turn of the century. Tables 1 and 2 show how the disease rose and then started falling in India. The rate gradually fell among the British soldiers while it rose among Indian soldiers serving in the Indian Army. In the 1890s, the line representing incidence among the British soldiers, which was steadily going down, crossed the line representing the incidence of tuberculosis among Indian soldiers in whom the incidence was rising.

**Table 1. Admission Rates Among Prisoners in Jails, Bombay Presidency for Tubercle of the Lungs (Per 1000)**

Year	Rate
1891	1.0
1893	0.8
1895	7.8
1897	7.1
1899	5.9
1901	5.6
1903	6.3
1905	5.0
1907	5.8
1909	3.7
1911	3.7

The peak of the epidemic in India occurred probably in the first two decades of this century and since that time, the disease has been gradually declining.

1901-1911



Graph 2. Deaths from Phthisis in Madras, Calcutta & Bombay per 10,000 Population 1901-1911

**Table 2. Admission Rates in Army in India for Tubercle in Lungs (Per 1000)**

Year	Indian Troops	European Troops
1891	1.7	3.2
1893	1.6	3.0
1895	2.3	4.8
1897	2.6	4.2
1899	3.3	3.1
1901	4.2	3.4
1903	5.9	3.4
1905	3.1	2.1
1907	2.5	1.6
1909	2.3	1.1
1911	2.1	0.0

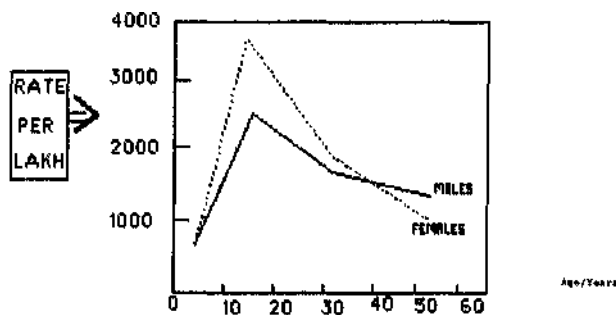
Source: E. Wilkinson. RSM Proceedings. 1914 Vol.7, 195-226

There is other evidence of the natural decline of tuberculosis in India. In Table 3 we can see the characteristics of the two stages of the epidemic: at its peak and during the period of decline. One of the main differences between the two is the change in the age-specific rates of mortality or morbidity. For example, graph 3 shows the incidence rate of tuberculosis in Eskimos during the height of the epidemic. You will notice that the rates are highest in young people, the highest being in women aged around 20 years.

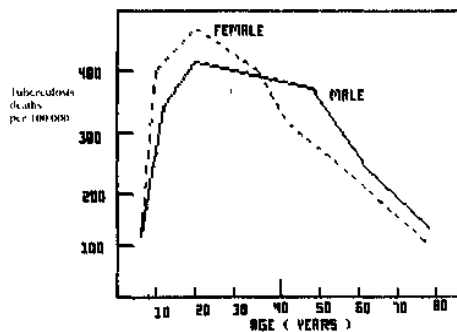
Graphs 4 shows the mortality rate in England and Wales in the 1850s. As tuberculosis declines, the age and sex: specific curves change. A practically identical situation can be seen in the

**Table 3. Main Characteristics of Tuberculosis Epidemic**

	At the Height	During Decline
Morbidity	Very high	Lower & falling
Rates Highest in	Young adults	Elderly men
Fatality	High	Lower & falling

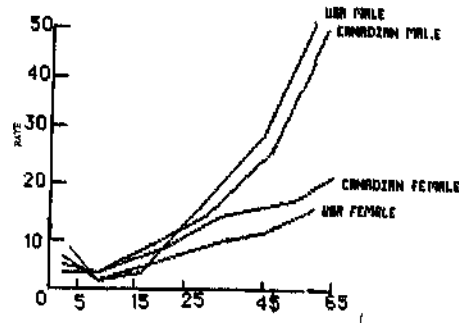


**Graph 3. Mean Annual Morbidity - Bacillary Active Tuberculosis - In Inuit (Alaska) 1967-69**



**Graph 4. Mean Annual Mortality from all Forms of Tuberculosis in England & Wales in Decennial Periods Among Males & Females, 1851-60**

incidence rates in Canada and the United States (Graph 5). The curves drawn for Canada and U.S.A are practically identical, the shape of these curves, with the men's rates becoming increasingly greater with advancing age while the women's rate staying relatively flat after reaching a certain level, is characteristic of tuberculosis in decline. I always tell my students that this shape is as diagnostic of declining trend as bronchial breath



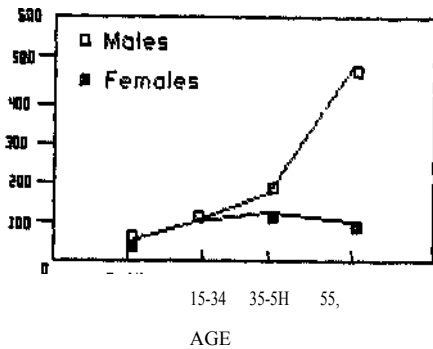
**Graph 5. Tuberculosis Incidence Rate/1,00,000 by age and sex, Canada & U.S.A. 1977**

sounds are diagnostic of consolidation in the underlying lung.

Let's now look at India. Graph 6 shows incidence of tuberculosis in the longitudinal study conducted by the NTI, Bangalore and Graph 7 of that in Chingleput study area. You will see clearly that this pattern of decline is seen in both these areas.

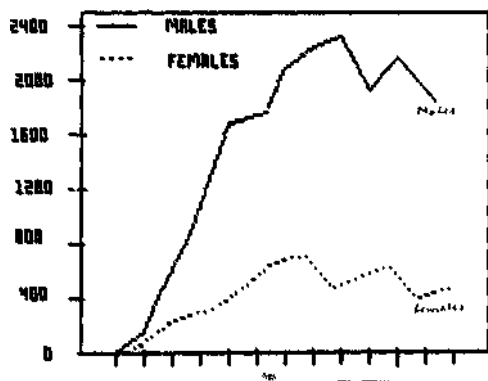
To summarize, I would like to say that India's experience with tuberculosis in modern times started probably in the middle of the 19th century; that it reached its peak in the early years of this century, and since that time, it has been declining quite slowly. The rate of this natural decline can be accelerated by good treatment programmes as seen in some of the so-called developed countries in which the speed of decline accelerated from 2 per cent natural decline to about 10 per cent. Indeed, I have observed, in Eskimos, an achievement of 14 per cent annual decline with a very thorough but extremely expensive programme.

However, a poorly operating treatment programme may result in slowing down of the natural rate of decline, although I doubt if it ever would be able to actually reverse the downward trend (Graph 8). I discussed the epidemiological impact of a treatment programme at the National Conference in Lucknow in the 1980s, and that contribution was published in the Indian Journal of Tuberculosis. It is, therefore, unnecessary to



Graph 6. Average Annual Incidence Rate of Pulmonary Tuberculosis NTI Longitudinal Study (1961-66)

discuss this problem in detail now. I would like to say, however, that the tuberculosis programme in India can justly claim a most important achievement. It saves lives and reduces suffering. Graph 9 shows that even a very poor treatment programme, such as, mono-therapy, or poorly taken treatment which is so common in many third world countries, reduces very substantially the number of deaths from tuberculosis. It also leads to cure of many patients who would otherwise succumb to this disease. Many tuberculosis treatment programmes, however, do not contribute to the reduction of tuberculosis problem. This is simply due to the fact that these programmes frequently produce chronic cases of tuberculosis, the chronic bacillary excretors. Therefore, the actual number of sources of



Graph 7. Prevalence of Culture positive cases (Chingleput Trial Area)

infection in the community becomes even greater, than would have been if no treatment was given. And the epidemiological situation is not improved.

Another facet of this situation lies in the fact that in many places half or more than half of the smear positive cases of TB are accounted for by those who have been treated unsuccessfully. They are either chronics or relapses. In the prevalence survey in China (Table 4), more than half of the smear positive cases gave history of previous treatment.

In India, data are available from the Chingleput BCG trial area (Table 5). Only 29 per cent of the total bacteriologically proven cases were truly new cases; the others had been discovered before. This, however, was a very artificial situation because pretty well all die cases in the community studied in the BCG trial area, were found, the case finding being perfect. Treatment, however, was the same as given in the National Tuberculosis Programme. This situation in which half or more than half of smear positive cases in the country are treatment failures, chronics or relapses gives us an opportunity to design a really effective programme. Dr. Kan in Beijing has shown that it is not too difficult to cure most of those cases. Therefore, this problem of chronic cases may be solved rather quickly, leading to appreciable epidemiological improvement in a short space of time. To sum up, poor chemotherapy prevents deaths but often keeps large numbers of chronic excretors alive. And the epidemiological situation depends mainly on the number of sources of infection.

I would like to conclude by suggesting that perhaps India, like so many other so-called third world countries, could be considered a low incidence but high prevalence country, the high prevalence being due to large numbers of treatment failure, chronic and relapse cases produced by ineffective treatment programmes.

I would now like to look at the future of tuberculosis in India. Were it not for HIV infection, the future would look fairly bright provided that special programmes to find and cure chronic bacillary cases are established. HIV infection has indeed a very profound effect on

**Table 4. History of Chemotherapy in Sputum Positive Cases discovered In the First Prevalence Survey in China (1979)\***

	Number	Percent
Previous treatment "Old"	379	63
No previous treatment "New"	222	37
<b>Total</b>	<b>601</b>	<b>100</b>

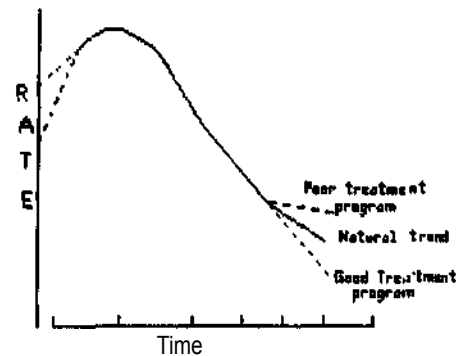
\*Beijing, Shanghai and six provinces

**Table 5. Previous Status of 778\* Culture Positive Cases Seen At Round 5 in Chingleput Area**

Status at previous rounds	Culture Positive 10 years after intake	
	No.	%
Culture positive	473	61
Active on X-ray	77	10
Normal X-ray	228	29
<b>Total</b>	<b>778</b>	<b>100</b>

\* There were 837 cases but 59 were excluded as they were seen for the first time

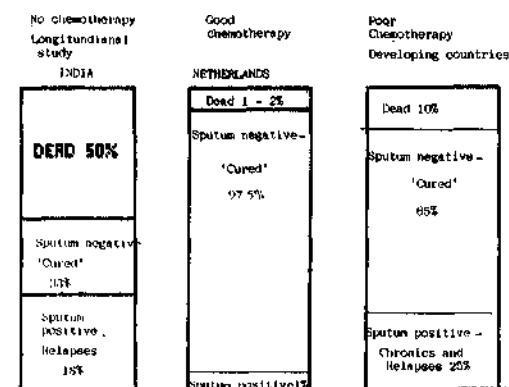
tuberculosis. The epidemiological impact of HIV infection comprises (i) increased risk of infection (ii) increased risk of disease among die infected and (iii) increased fatality among the diseased. This is simply due to the fact that the lowered resistance brought on by this virus makes people who are dually infected, i.e., infected with both HIV and tubercle bacillus, very susceptible to. develop tuberculosis. One facet of it is shown in Table 6. The overall risk of dually infected persons who were first infected with tuberculosis and later with HIV, probably reaches 50 percent. The risk is concentrated in the last two or three years of life with two-thirds of the cases occurring a year or two before other AIDS manifestations. These cases, incidently, do not often differ very much from ordinary cases of tuberculosis. One-third occur when the immunity is very low, after



**Graph 8. Model of a Tuberculosis Epidemic in the Context of Control Programme**

the onset of other manifestations of AIDS. At this time, rather unusual clinical and radiological features such as large glands, etc., are common. Little is known about the situation in which individuals get infected with HIV first and later with tubercle bacillus; this has not been studied well. There are two studies in which sources of tuberculosis infection were introduced into the hostels for AIDS victims. In this situation, the morbidity was extremely high. It must be pointed out that this situation of HIV first-TB second is, extremely uncommon in the United States and Western countries. It is probably quite common in sub-Saharan Africa and it will possibly be fairly common in a country like India.

In Vancouver, I work closely with Michael Schultzer, a professor of mathematics. With his help and with the assistance of Mrs. Radamani



**Graph 9. Fate of Smear Positive Cases**

**Table 6. Risk of Pulmonary Tuberculosis**

(a) Following TB Infection in HIV Negative Persons

Immediate	Remote
First 2 years	5 per cent
After 2 years	5 per cent

Assumptions

- (1) In 15-49 age group, in 1993:
  - (a) Prevalence of HIV infection was 0.5 per cent
  - (b) Prevalence of TB infection was 50 per cent
- (2) HIV was introduced to India in 1986

(b) In HIV Infected Persons

	TB Infection first/ HIV second	HIV Infection first/ TB second
Risk	50 per cent	80 per cent (?)
Time of development of TB	1-2 years before other AIDs Mani- festations (2/3) and during AIDS (1/3)	Unknown, possibly immediately following TB infection

(c) Prediction for the year 2006 (15-49 age group)

Incidence of smear positive tuberculosis will triple - from 28 to 88 per 1,00,000  
28 per cent of these patients will be HIV positive.

from Tuberculosis Research Centre, Madras, we have constructed a mathematical model to predict the size of the future impact of HIV on tuberculosis. We published one paper on die sub-Saharan Africa and Dr. Schultzer's second paper with Mrs. Radamani and others on this model is going to be published in shortly the International Journal of Epidemiology. I have asked Dr. Schultzer to put the figure for India in this model. I have assumed that the first year in which HIV entered India was 1986, that the prevalence of tuberculosis infection in those between 15 and 49 years of age is 50 per cent and that prevalence of HIV infection in this group is 0.5 per cent. It was seen that by the year 2006, the incidence

of tuberculosis in the 15-49 years age group will rise threefold, which probably means that it will double in the total population.

I hope that by that time India will be prepared to meet this grave new challenge. It can be done by organising special treatment programmes for treatment failures, chronic bacillary excretors and relapses, and by improving the organization of treatment of new active cases

**Stefan Grzybowski**  
Emeritus Professor of Medicine  
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## INTERIM FINDINGS ON THE EVALUATION OF SPLIT DRUG REGIMENS FOR PULMONARY TUBERCULOSIS - A RANDOMIZED CONTROLLED CLINICAL TRIAL\*

TUBERCULOSIS RESEARCH CENTRE, MADRAS

**Summary:** A randomized controlled clinical trial of three fully oral short course chemotherapy regimens of 6 month duration is being conducted to evaluate split-dose double drug combinations for the treatment of sputum positive pulmonary tuberculosis. Split I and Split II regimens consist of Rifampicin and Ethambutol on one day and Isoniazid and Pyrazinamide on the next day, each combination given thrice a week during the initial intensive phase of 2 or 3 months, respectively, followed by Rifampicin and Isoniazid given twice a week during the continuation phase for the next 4 and 3 months, respectively. The control regimen consists of all the four drugs, Rifampicin, Isoniazid, Pyrazinamide and Ethambutol; given together in a single dose thrice a week during the intensive phase of first 2 months, and Rifampicin and Isoniazid twice a week during the continuation phase of next 4 months. Drugs were given under full supervision during the entire chemotherapy period of 6 months. The findings upto the end of chemotherapy for 750 patients suggest that the response is similar in split and control regimens among patients with sensitive organisms and those with resistance to Isoniazid alone. Among patients with organisms resistant to both Isoniazid and Rifampicin, almost all had an unfavourable response. Adverse reactions were low and similar in both split and control regimens!

### Introduction

Several highly effective short course chemotherapy regimens have been evolved for

the treatment of sputum, positive pulmonary tuberculosis. In most of these regimens, four drugs, viz, Rifampicin(R), Isoniazid(H), Pyrazinamide(Z) and Streptomycin(S) or Ethambutol(E) are given together in a single dose either daily or intermittently in the initial phase. The bulk of the drugs to be consumed in a single dose is, therefore, large and may affect patient compliance. Further, the incidence of adverse reactions such as arthralgia and jaundice is higher with daily regimens.

Hence, a study is being conducted wherein the four drugs are split into two 2-drug combinations, each combination given on alternate days, thus making each combination intermittent. The advantage of the split regimens is that the bulk of the drugs in a single dose is less and adverse reactions are expected to be low. These two factors together will presumably help in improving patient compliance.

### Study Subjects

The patients were residents of either Madras or Madurai, and had come to the out-patients chest clinics because of symptoms. Patients were eligible for inclusion in the study irrespective of previous chemotherapy, if they were aged 12 years or more, had at least 2 sputum cultures positive for *M. tuberculosis*, even though admission to the study was based on smear positivity, and were willing to attend the centre for supervised chemotherapy for a period of 6 months. Patients with diabetes, hypertension, bleeding diathesis and extra pulmonary tuberculosis were not eligible for the study.

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The report was prepared by Dr. A.M. Reetha, Mr. P.V. Krishnamurthy, Dr. T. Santha Devi and Dr. R. Prabhakar of Tuberculosis Research Centre, (Indian Council of Medical Research), Madras

\* Paper presented at the 49th National Conference on Tuberculosis and Chest Diseases, Pondicherry: 6th - 9th October, 1994

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### Regimens

Patients were randomly allocated, stratified on the basis of duration of previous chemotherapy and degree of sputum positivity, to one of the following three fully supervised regimens of 6 months' duration.

In the first regimen, 2RE3HZ3(alt)/4RH2 (split I), during the initial phase, Rifampicin and Ethambutol were given on one day and Isoniazid and Pyrazinamide on the next day, thrice a week for 2 months followed by Rifampicin and Isoniazid twice a week for the next 4 months. The second regimen, 3RE3HZ3 (alt)/3RH2 (split II), was similar to regimen 1, but the initial phase was for 3 months, followed by 3 months in the continuation phase. The third regimen, (2REHZ3/4RH2), was the control regimen where all four drugs were given together in a single dose thrice a week for 2 months followed by Rifampicin and Isoniazid twice a week for next 4 months. The dosages were same for all the three regimens in both the phases. For patients weighing 40 kg or less, rifampicin 450 mg, Ethambutol 1000 mg and Pyrazinamide 1.5 g were given. For patients weighing more than 40 kg, the dosages were 600 mg, 1200 mg and 2 g, respectively. Isoniazid was given in a flat dose of 600 mg, irrespective of body weight.

### Results

The findings of the interim analysis upto the end of chemotherapy are presented here. The

population consisted of 750 patients of whom 124 were excluded for various reasons like negative culture on admission, early death, death due to non-tuberculous causes and for having missed 25% or more of chemotherapy. There remained a total of 626 patients in the analysis. Of these, 80% had organisms sensitive to Isoniazid and Rifampicin, 16% of patients had resistance to Isoniazid alone, 0.3% had resistance to Rifampicin alone and 3% of patients had resistance to both Isoniazid and Rifampicin (Table 1).

During chemotherapy, 3 sputum specimens from each patient were examined by culture for *M. tuberculosis* every month. The proportion of patients with negative culture at first month was 28% and 30% in split I and II regimens, respectively and 28% in the control regimen. By second month, it had gone up to 80-83%. From 3rd to 6th month it was 95 - 99%. Thus the speed of sputum conversion was similar in all the 3 regimens (Table 2).

Proportion of patients who received more than 80% of their prescribed chemotherapy was 82% and 85% in split I and II regimens, respectively and 82% in the control regimen. Even though patients had to attend daily for the initial 2 to 3 months in the split regimens, the drug regularity was similar to that of control regimen where they had to attend thrice a week during this period. (Table 3).

A favourable bacteriological response at the end of chemotherapy was defined as all cultures

*Table 1. Study population*

	2RE3HZ3(alt)/ 4RH2 (Split I)	3RE3HZ3(alt)/ 3RH2 (Split II)	2REHZ3/ 4RH2 (Control)	Total
Total patients	251	250	249	750
Exclusions	43	38	43	124
Total in analysis	208	212	206	626
Sensitive to H and R	173	169	162	504 (80%)
Resistant to H alone	27	36	38	101 (16%)
Resistant to R alone	1	1	0	2 (0.3%)
Resistant to H and R	7	6	6	19 (3%)

**Table 2. Culture negativity (%) during treatment among patients with initial drug sensitive organisms**

Months after start of treatment	2RE3HZ3(alt)/	3RE3HZ3(alt)/	2REHZ/
	4RH2 (Split I)	3RH2 (Split II)	4RH2 (Control)
1	28	30	29
2	80	83	82
3	97	96	96
4	97	99	98
5	95	98	96
6	97	95	98
Range of Patients	171 - 173	168 - 169	161 - 162

**Table 3. Percentage of chemotherapy received during phases I & II**

Treatment received(%)	Number of patients		
	2RE3HZ3(alt)/4RH2 (Split I)	3RE3HZ3(alt)/3RH2 (Split II)	2REHZ3/4RH2 (Control)
>80	195(82)*	204(85)	200(82)
50 - 79	28(12)	24(10)	22(9)
< 50	1(<1)	0(0)	1(<1)
Missed continuously for >1 month	14(6)	13(5)	20(8)
Total	238	241	243

\* Percentages in parenthesis

**Table 4. Response at the end of chemotherapy among patients with initial drug sensitive organisms**

Response	Number of patients		
	2RnZH3(alt)/4RH2 (Split I)	3RE3IIZ3(alt)/3RH2 (Split II)	2REHZ3/4RH2 (Control)
Favourable	163(94)*	158(93)	152(94)
Doubtful	6(3)	9(5)	10(6)
Unfavourable	4(2)	2(1)	0(0)
Total	173	169	162

\* Percentages in parenthesis

negative in the last two months of chemotherapy. An unfavourable bacteriological response was defined as 2 or more cultures being positive in the last two months of treatment including one culture in the last month and a least one culture growing 20 colonies or more. In addition, patients who had a change of treatment for persistent

culture positivity, or radiographic or clinical deterioration and those who died of tuberculosis were also classified as having had an unfavourable response. Those who did not fit into these criteria were classified as having doubtful response.

At the end of chemotherapy, among patients

with drug sensitive organisms, a favourable response was obtained in 94% and 93% in split I and II regimens, respectively and 94% in the control regimen. It can be observed that the response at the end of treatment is not very much affected by splitting the drugs. All those with doubtful response converted by 7th month without additional chemotherapy. Only 2% and 1% of patients, respectively in the split I and II regimens had unfavourable response (Table 4).

Among those with organisms resistant to Isoniazid alone, favourable response was seen in 78% and 81%, respectively in split I and II regimens and 74% in the control regimen, while unfavourable response was seen in 19%, 14% and 21% respectively in the three regimens. Out of these patients with unfavourable response, one died and all the others had change of treatment for persistent culture positivity (Table 5).

There were 19 patients with organisms

resistant to both Isoniazid and Rifampicin. Except one, all the others had an unfavourable response. Two patients who had resistance to Rifampicin alone had a favourable response.

#### Adverse reactions

Adverse reactions encountered during chemotherapy were mainly gastro-intestinal symptoms, arthralgia, hepatitis and cutaneous reactions. Proportions of patients reporting with any of these complaints were 11%, 18% and 17%, respectively, in the 3 regimens. The difference between split regimens and control regimen was not statistically significant (Table 6). Majority of the adverse reactions were managed symptomatically. Modification of chemotherapy had to be done only in 14 patients. One patient (split I) developed hypersensitivity reaction during the third week of treatment in the form of severe burning all over with hot flushes, when he was receiving Isoniazid and Pyrazinamide. Attempts

**Table 5. Response at the end of chemotherapy among patients with initial H resistant organisms**

Response	2RE3HZ3(alt)/4RII2 (Split I)		3RE3HZ3(alt)/3RII2 (Split II)		2REHZ3/4RH2 (Control)	
	No.	%	No.	%	No.	%
Favourable	21	78	29	81	28	74
Doubtful	1	4	2	6	2	5
Unfavourable	5	19	5	14	8	21
Total	27		36		38	

**Table 6. Adverse reactions**

Regimen	Total No. of patients	Patients with complaints						
		Any	Gastro- intestinal	Arthr- algia	Cutan- eous	Giddi- ness	Hepa- titis	Others*
2RE3HZ3 (alt)/ 4RH2 (Split I)	243	27(11)*	9	7	7	3	2	1
3RE3HZ3(alt) 3RII2 (Split II)	244	43(18)	13	19	6	4	-	3
2REHZ3/4RII2 (Control)	244	41(17)	20	7	9	6	1	4

Percentages in parenthesis

\* Includes "flu" syndrome, hypersensitivity reaction and peripheral neuropathy

for desensitization for both Isoniazid and Pyrazinamide failed and the drugs were terminated. Rifampicin was terminated in three patients. One patient (control) developed itching with purpuric rashes during the third week of treatment, second patient (control) had 'flu' syndrome from the second dose of treatment (this patient had received Rifampicin outside before admission to the study) and the third patient (split II) had fever and breathlessness after receiving Rifampicin and Ethambutol combination, developed hypersensitivity reaction while under observation in the clinic after receiving Rifampicin. Nine patients had interruption of drugs, seven for jaundice (2 split I, 4 split II, 1 control). Of these, five patients developed jaundice during the initial intensive phase. Rifampicin and Isoniazid (and Pyrazinamide in the initial phase) were withheld temporarily and reintroduced after subsidence of jaundice without any problem. The other two patients had interruption of the offending drug for severe glossitis in one and itching in the other. For these two patients also, drugs were reintroduced without any problem. One patient (control) had severe gastrointestinal problem and the dosage of the drugs had to be reduced.

### Discussion

Several studies have shown that short course regimens using the four drugs viz, Rifampicin, Isoniazid, Pyrazinamide and Streptomycin or Ethambutol during the intensive phase are effective in the treatment of sputum positive pulmonary tuberculosis<sup>1,3</sup>. However, in these regimens patients find it difficult to consume the drugs given either daily or intermittently because of the bulk. An *in vitro* study done at our centre has demonstrated that splitting the 4 drugs REHZ into 2 split drug combinations of RE and HZ may not affect the bactericidal action of the regimens<sup>4</sup>. Further, it has already been reported from experimental murine tuberculosis that split dose alternating regimens are as effective as giving all the 4 drugs together<sup>5</sup>. Thus, it was assumed that anti-tuberculosis drugs given in split combination would be effective in human beings as well.

Hence, the Tuberculosis Research Centre conducted a controlled clinical trial in sputum positive pulmonary tuberculosis where the 4 drug

combination was split into two 2-drug combinations, combination given on alternate each days, thus making each combination intermittent.

This study, as far as we are aware, is unique because split drug combinations were used in a controlled clinical trial in sputum positive pulmonary tuberculosis patients for the first time.

The results indicate that in patients with initially drug sensitive organisms, the split regimens have a high sterilizing activity, producing sputum conversion in 80 to 83% by 2 months, which is similar to that in the control regimen. This result compares well with the findings of 80 - 87% conversion in East African patients treated with short course chemotherapy<sup>6-7</sup>. At the end of chemotherapy, a favourable response (all cultures negative in the last two months of chemotherapy) was observed in 93 - 94% in split regimens which is again similar to that in the control regimen (Table 4). This finding is in conformity with the observations from *in vitro* studies, animal experiments and *in vivo* studies<sup>4,8</sup>.

Among patients with bacilli resistant to 'H' alone, favourable response was observed in 78% and 81%, respectively, in split I and II regimens which is similar to the 74% in control regimen, whereas in patients with organisms resistant to both Isoniazid and Rifampicin almost all had an unfavourable response.

Adverse reactions were generally low and similar in both split and control regimens. Patients were not questioned about symptoms of drug toxicity, but every spontaneous complaint was recorded after careful questioning by a physician. Main adverse reactions encountered were gastrointestinal symptoms, arthralgia, hepatitis and cutaneous reactions. Proportions of patients with any of these complaints were 11% and 18% in split regimens and 17% in the control regimen. This is much lower than that observed at the centre in earlier SCC regimens with daily treatment in the initial intensive phase<sup>1</sup>. Modification of chemotherapy (termination, interruption, reduction) were necessary in only 14 cases.

Thus, there does not appear to be any difference either in the efficacy of regimens or toxicity when drugs are administered as split regimens (alternately) compared to giving all the 4 drugs together. All patients are being followed-up to assess the efficacy of the double drug combination regimens with long term follow up for possible relapses. It may be presumed that the relapses would be minimal since the culture negativity rates at the end of 2 months of intensive chemotherapy are of the order of 80 to 83%".

#### Acknowledgement

The scientific staff with major responsibility for the work are as follows: Dr. R. Prabhakar, Director; Clinic - Dr. T. Santha Devi, Dr. V.K. Vijayan, Dr. Padma Ramachandran, Dr. Rajeswari Ramachandran, Dr. Rani Balasubramanian, Dr. M.S. Jawahar, Dr. Soumya Swaminathan, Dr. K. Rajaram, Dr. Rema Mathew, Dr. A.M. Reetha, Dr. Paulin Joseph, Dr. K. Palanimurigan, Dr. R. Balambal, Dr. K.C. Umopathy, Dr. Usha Ramanathan and Dr. Rajani Ramachandran, Mrs. Parvathy Raghavan, Mrs. Ambujam Ganesh, Mrs. Sudha Ganapathy and Mr. K.N. Gopilingam; Laboratory - Dr. C.N. Paramasivan, Dr. N. Selvakumar, Dr. Vanaja Kumar, Mr. P. Venkataraman, Mr. B.N. Gopalan, Mrs. Sara Mathew, Dr. Daniel Herbert, Dr. G. Raghupathy Sarma, Dr. Rajiswamy, Dr. Prema Durumurthy, Dr. V.D. Ramanathan; Statistics - Mr. P.R. Somasundaram, Mr. P.V. Krishnamurthy, Mr. S. Sivasubramanian, Mrs. Fathima Rahman, Dr. P. Venkatesan and K. Sivarmaniam. Special thanks are due to Dr. K. Jagannath, Director, Institute of Thoracic Medicine, Madras for independent radiographic assessment.

The writers thank the Dean of Government Rajaji Hospital, Madurai and Dr. Kumaravel, Medical Officer, for their enthusiastic cooperation in conducting the study at Madurai. We are grateful to the entire staff of TB Research Centre, Madras and the TRC unit at Madurai for their enthusiastic co-operation. The nursing staff and social workers made particularly valuable contributions. The secretarial assistance of Mr. J. Stanly Gnanadhas is gratefully acknowledged.

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## DIAGNOSTIC YIELD FROM FLEXIBLE FIBEROPTIC BRONCHOSCOPY IN SPUTUM NEGATIVE PULMONARY TUBERCULOSIS CASES\*

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**Summary:** In our tertiary referral hospital, 100 smear' negative suspected cases of pulmonary tuberculosis were subjected to flexible fiberoptic bronchoscopy for diagnostic evaluation. Visible endoscopic abnormalities were present in 56 patients. Out of these, bronchogenic carcinoma was confirmed in five and suppurative lesions in six. Bronchoscopic lavage fluid showed AFH in 12 (12/100) and post bronchoscopy sputum was positive for AFB in another 13 (13/100) by smear examination. Thus, the total immediate positive yield for AFB was 25 patients. Granulomata were detected in 10 cases on histopathology of biopsy material. Pulmonary tuberculosis could be confirmed bacteriologically in 36 patients after culture for mycobacteria. Thirty six patients included 11 positive by culture alone. Thus, bronchoscopy provided diagnostic yield in 46% cases in our series.

### Introduction

Sputum smear and culture examinations still remain the gold standard in the diagnosis of pulmonary tuberculosis<sup>1-3</sup>. It is also known that in many patients, this stringent criterion cannot be satisfied due to factors like:

- (a) lack of sputum production,
- (b) low bacterial yield, and
- (c) incorrect or improper sampling.

In most of the tuberculosis centres, even after meticulous search, the bacteriological positive yield from sputum is around 16 to 50%<sup>2-4</sup>. Anti-tuberculosis treatment (ATT) is frequently started

empirically, leading many a time to avoidable risk of drug toxicity, and infructuous expenditure. Diseases like bronchogenic carcinoma and diffuse lung diseases are sometimes missed because cases are put within the grey area of "tuberculosis suspects". On the other hand, if not treated, 64% of sputum negative suspects could need chemotherapy within 12 months<sup>3</sup>.

Flexible fiberoptic bronchoscopy (FOB) is a tool which gives access to the diseased area and better bacteriological and histological yield, leading to a definitive diagnosis.

### Material and Methods

One hundred consecutive smear negative suspect cases of pulmonary tuberculosis underwent FOB under topical anaesthesia at the Cardio-Thoracic Unit, Military Hospital, Pune. All these were fresh cases who did not receive any anti-tuberculosis treatment before transfer to our centre. Instrument used was flexible fiberoptic bronchoscope (Olympus BF IT-20 or Karl Storz adult type bronchoscope).

All patients were referred cases where pulmonary tuberculosis was suspected by a General Duty Medical Officer, and corroborated by a physician. Chest X-ray and 3 sputum smears were undertaken in all these patients before they were transferred to our centre where another three early morning spot and overnight specimens were examined. One specimen was also put up for culture in all these cases. If sputum was found to be negative, they were subjected to FOB. After an overnight fast, they were premedicated with inj. atropine 0.6 mg and morphine 7.5 mg IM. Topical lignocaine 4% was sprayed in the nostrils and later into the throat limiting the quantity

\* Paper presented at 49th National Conference on Tuberculosis and Chest Diseases, Pondicherry, 6-9 October, 1994.

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sprayed to 5cc, though in a majority just 4cc was sufficient to induce local anaesthetic effect. Bronchial lavage was taken from the affected segments and biopsy was taken from any endoscopically visible lesion.

The aspirate was cultured on LJ medium and put up for pyogenic culture and stained by IIE stain to obtain bacteriological and cytological characteristics. Biopsied material was also stained with HE stain and examined for histological characteristics.

### Observations and Results

Out of the 100 patients, 60 had unilateral (upper or lower lobe) radiological shadows, 31 had bilateral lesions, 4 had miliary lesions, 2 had the so called "coin lesion" and in 3 cases no abnormality was seen.

On FOB, 44 cases had absolutely no abnormality while in 56 cases one or more observations were made (Table 1). Histopathological examination of the material obtained by FOB confirmed the diagnosis of malignancy in 5 cases; finding pus led to the diagnosis of bronchiectasis in 6 cases, while acute inflammatory cells were seen in 21, chronic inflammatory cells in 6 and tuberculous granuloma in 10 cases. Diagnosis of bronchiectasis was further corroborated by high resolution contrast tomography findings.

**Table 1. Bronchoscopy findings in 100 suspected cases of pulmonary tuberculosis**

Normal appearance	44
Abnormalities seen* :	
Growth	5
Unhealthy mucosa/granuloma	21
External compression	3
Discharge from bronchus	35
Bleeding from bronchus	3

\* Multiple findings in some cases

Bronchoscopic lavage fluid when examined by smear and culture for AFB showed that 12 cases were positive by smear and 19 by culture including 2 by smear alone and 9 by culture alone. Post bronchoscopy secretions were also

examined bacteriologically. Thirteen more cases were positive by smear and 17 by culture including 3 which were positive by smear alone and 7 by culture alone.

In 6 cases, sputum collected initially grew *M. tuberculosis* on culture subsequently.

Overall, shortly after FOB and examination of secretions and biopsied material the final diagnostic situation is shown in Table 2.

**Table 2. Immediate\* diagnostic yield after FOB**

Malignancy	5
Pyogenic infections	6
Bronchoscopy lavage smear positive	12
Post-bronchoscopy sputum smear positive	13
Granuloma	10
Total	46

\* Excludes addition by culture subsequently

### Discussion

In this study, early diagnosis of bronchogenic carcinoma in 5 cases was the most important achievement. We could stop ATT and offer appropriate therapy to them avoiding unnecessary delay. Demonstration of frank pus and growth of pyogenic organisms in 6 patients of bronchiectasis was also helpful. The diagnosis could be further corroborated by high resolution tomographic findings. Thus, in 11 cases we could avoid ATT immediately after FOB.

Pulmonary lesion with sputum production is the common manifestation of most respiratory ailments. And tuberculosis being the commonest entity, ATT is prescribed in most of these patients even when sputum examination is negative for AFB. That other conditions have to be excluded before making the diagnosis of tuberculosis has been highlighted by some authors<sup>57</sup>.

Cytologically, demonstration of acute and chronic inflammatory cells in 21 and 6 patients respectively could be related bacteriologically to

11 (40%) who showed AFB. (If we exclude cases of bronchiectasis, 11 out of 21 (52%) had a positive bacteriological yield out of those who had acute inflammatory cells). In bronchial secretions, one case showed granuloma and one both granuloma and AFB. A total of 13/21 i.e. 62% revealed findings diagnostic of tuberculosis. Out of the 6 patients who showed chronic inflammatory cells, 4 showed bacteriological and/or histological evidence of tuberculosis, indicating that these findings point towards a diagnosis of tuberculosis.

Out of 12 patients whose bronchoscopic lavage showed AFB, 2 did not show growth on culture. Simultaneously, out of the 13 additional cases where post bronchoscopy sputum showed AFB, in 3 *Mycobacterium tuberculosis* could not be grown on culture. The use of 4% lignocaine (5cc or more) could be the reason in these cases for failure of culture.

Tuberculosis could be confirmed by smear examination of bronchoscopy lavage fluid in 12 and, subsequently, 13 more were found positive by post bronchoscopy sputum examination. In another 10 cases, granuloma was demonstrated histologically. Thus, in 35 cases, we could get immediate diagnosis of tuberculosis. Culture added 11 more cases of tuberculosis. The diagnostic yield of 46% is comparable to that of Jaiswal<sup>6</sup> and slightly less than the figure quoted by Wallace<sup>8</sup>.

Thus, out of total 100 suspected cases of pulmonary tuberculosis we could exclude 5 cases of lung cancer and 6 of bronchiectasis; 35 patients showed evidence of tuberculosis either by smear examination or by histological evidence, and another 11 cases were added by culture for AFB.

This makes FOB an essential requisite for respiratory work-up not only in confirming tuberculosis but also in establishing diagnosis of non-tuberculous pathology.

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## BIOAVAILABILITY OF RIFAMPICIN, ISONIAZID AND PYRAZINAMIDE IN PATIENTS WITH INTESTINAL TUBERCULOSIS WITH MALABSORPTION\*

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**Summary;** Malabsorption is commonly observed in patients with intestinal tuberculosis which may impair blood levels of drugs and thus, may affect the outcome of anti-tuberculosis therapy. To determine the effect of malabsorption, we estimated the plasma concentrations of Rifampicin, Isoniazid and Pyrazinamide in 10 patients with pulmonary tuberculosis, 10 patients with intestinal tuberculosis and 7 patients with intestinal tuberculosis with malabsorption. The patients received Rifampicin 600 mg, Isoniazid 300 mg, and Pyrazinamide 1500 mg, as a single dose on empty stomach. The peak levels of Rifampicin, Isoniazid and Pyrazinamide were reached at 90-180 minutes, in all the patients in the three groups. The differences in the mean serum concentrations of the drugs between the three groups were statistically not significant suggesting that absorption of antituberculosis drugs is not impaired in patients with intestinal tuberculosis, not even in those with malabsorption and, thus, there is no need to modify the chemotherapy regimes in such cases.

### Introduction

The efficacy of antituberculosis chemotherapy depends to a large extent on the blood and tissue concentration of drugs. Rifampicin, Isoniazid and Pyrazinamide are potent and most widely used antituberculosis drugs which readily get absorbed from the proximal gastrointestinal tract. Malabsorption is commonly observed in patients with gastrointestinal tuberculosis; upto 40% of them may have abnormal D-xylose absorption

and/or faecal fat balance tests. The proportion may go upto 75% in patients with intestinal obstruction, requiring surgery.<sup>1</sup> The pathogenesis of malabsorption in GI tuberculosis is not clear. Though the "blind loop" syndrome seems to be the most important cause; mucosal ulceration, involvement of lymphatics, and fistula formation are other contributing factors.<sup>2</sup> Malabsorption due to any of these factors may lead to decreased absorption of antituberculosis drugs and, thus, may affect the outcome of chemotherapy. Wasson and Harris et. al<sup>3</sup> observed that absorption of Rifampicin was decreased in patients with jejuno-ileal bypass done for obesity.

With the aim to find out the effect of malabsorption on blood concentration of antituberculosis drugs, we studied blood levels of Rifampicin, Isoniazid and Pyrazinamide in patients with intestinal tuberculosis with and without malabsorption and pulmonary tuberculosis.

### Material and Methods

Twenty seven patients (15 male and 12 female) attending the gastroenterology clinic of G.B. Pant Hospital and New Delhi Tuberculosis Centre, were included in the study. Of them, ten had pulmonary tuberculosis (PT), ten, intestinal tuberculosis (IT) and seven, intestinal tuberculosis with malabsorption (ITM). The mean age ( $\pm$  SD) of patients was  $28 \pm 12$  years (range 22-48 years). All patients were subjected to routine biochemical and haematological investigations. Patients with evidence of renal or hepatic dysfunction were excluded. The diagnosis of intestinal tuberculosis was made on the basis of clinical picture, radiological features, endoscopic examination and histopathological as well as bacteriological studies, when required. Pulmonary tuberculosis was

\* This study received financial assistance from the Tuberculosis Association of India department of Gastroenterology & Biochemistry, G.B. Pant Hospital, New Delhi and New Delhi Tuberculosis Centre

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diagnosed on X-ray chest and positive sputum for AFB on two occasions in the IT group; 3 patients each had jejunal and ileal involvement and 4 had ileocaecal disease. In the intestinal tuberculosis with malabsorption (ITM) group, there were 2 patients each with ileal and jejunal disease and 3 had ileocaecal involvement.

Two patients in the IT group and 3 in the ITM group had evidence of healed pulmonary tuberculosis. One patient in the IT group had tuberculous cervical lymphadenitis. The diagnosis of ileal and jejunal tuberculosis was based on clinical and radiological evidence. Colonoscopy with biopsy confirmed the diagnosis of ileocaecal tuberculosis in 6 patients. In one patient in the ITM group, the diagnosis of ileocaecal tuberculosis was based on clinical and radiological features. Malabsorption was documented by impaired D-xylose (less than 25 mg/dl of D-xylose in serum at 1 hr after an oral 25 g dose)<sup>4</sup> and/or abnormal faecal fat excretion (> 6 g/day on 100 g fat diet)<sup>5</sup>.

All patients received a combination of Rifampicin 600 mg, Isoniazid 300 mg and Pyrazinamide 1500 mg as a single dose on empty stomach. Venous blood samples were drawn before administration of the drugs and, thereafter, at 30 and 90 min, and 3, 5 and 7 hours. Plasma was separated and assayed for concentration of each drug by high performance liquid chromatography<sup>6,7</sup>. The peak levels of each drug in the three groups were compared.

## Results

### Malabsorption Studies

Blood D-xylose and faecal fat balance tests were normal in all the patients in the PT and

IT groups. Of 7 patients in the ITM group, 3 had isolated D-xylose malabsorption and 3 had abnormal faecal fat balance whereas one patient had both the tests abnormal.

### Plasma levels of drugs

Findings relating to plasma levels of Rifampicin, Isoniazid and Pyrazinamide are shown in Table 1.

#### Rifampicin

The peak level of Rifampicin was reached between 90-180 minutes in all the three groups. The mean ( $\pm$  SD) concentration ( $\mu$ g/ml) was  $11.0 \pm 3.2$  (range 8.6-13.4) in the PT group,  $9.1 \pm 2.8$  (range 8.2-12.4) in the IT group and  $9.8 \pm 2.4$  (range 8-13.6) in the ITM group. The differences were not statistically significant.

#### Isoniazid

The peak level of Isoniazid was attained between 90 to 180 minutes in each group. The mean drug level ( $\mu$ g/ml) was  $6.9 \pm 4.2$  (range 3.4-7.9) in the PT group,  $5.8 \pm 4.1$  (range 2.8-7.3) in the IT group and  $6.2 \pm 3.8$  (range 2.8-7.4) in the ITM group. The differences, again, were statistically not significant.

#### Pyrazinamide

The peak level of Pyrazinamide, like Isoniazid and Rifampicin, was achieved between 90 to 180 minutes in each of the three groups. The mean drug level (ng/ml) was  $26.7 \pm 5.2$  (range 15.2-36.4),  $22.2 \pm 8.3$  (range 16.4-32.6) and  $25.2 \pm 7.7$  (range 17.4-35.5) in the PT, IT and ITM groups respectively. The differences, again, were not statistically significant.

Table 1. Peak levels ( $\mu$ g/ml.) of Rifampicin, Isoniazid and Pyrazinamide in the three groups

		PT (n=10)	IT (n=10)	ITM (n=7)	Peak time
Rifampicin	(Mean $\pm$ SD)	$11.0 \pm 3.2$	$9.1 \pm 2.8$	$9.8 \pm 2.4$	90-180 mins
Isoniazid	(Mean $\pm$ SD)	$6.9 \pm 4.2$	$5.8 \pm 4.1$	$6.2 \pm 3.8$	90-180 mins
Pyrazinamide	(Mean $\pm$ SD)	$26.7 \pm 5.2$	$22.2 \pm 8.3$	$25.2 \pm 7.7$	90-180 mins

### Discussion

Absorption of a drug across the mucosal surface is largely through the process of passive diffusion. High lipid solubility and less degree of ionisation facilitate absorption. Equally important are the molecular weight, configuration and solubility of the drug in body fluids. Anti-tuberculosis drugs are lipid soluble and have low molecular weight and are weak electrolytes. These drugs are, therefore, readily absorbed after oral administration.

That in intestinal tuberculosis malabsorption due to any mechanism may be associated with impairment of absorption of a drug is a distinct possibility. Wasson & Harris et al<sup>3</sup> have shown that jejunio-ileal bypass decreases the peak level of Rifampicin in serum. On the other hand, it has been shown that sub-total or total gastrectomy, coeliac disease or small bowel diverticulosis may delay but not affect the peak serum concentration of Rifampicin<sup>8</sup>. Further, surgical procedures such as partial gastric and duodenal resection and jejunio-ileal bypass do not alter the absorption of Isoniazid<sup>9</sup>. Data regarding Pyrazinamide absorption in such conditions are lacking.

Because of the small number of cases studied, the statistical tests of significance mentioned earlier may be said to lack 'power'. Subject to this limitation, our study appears to suggest that the orally administered antituberculosis drugs are well absorbed in patients with intestinal tuberculosis with or without malabsorption. There is neither delay in absorption nor differences in peak plasma concentration of drug(s) when compared with patients with intestinal tuberculosis without malabsorption and patients with pulmonary tuberculosis only. Perhaps, because of the focal nature of disease, the damage in most patients with gastrointestinal tuberculosis is not extensive enough to affect absorption of drugs. Gurumurthy et al<sup>10</sup> also reported similar findings in patients with intestinal tuberculosis. However, none of their patients had malabsorption. It would be reasonable to conclude that the blood concentration of orally administered anti-tuberculosis drugs- Rifampicin, Isoniazid and Pyrazinamide - is not

impaired in patients with intestinal tuberculosis, not even in those with malabsorption, and that there is no need to modify the chemotherapy regimens.

### Acknowledgements

The authors wish to thank Tuberculosis Association of India for providing the grant, Lupin Laboratories for supply of Rifampicin and Pyrazinamide and Pfizer for supply of Isoniazid.

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## A COMPARISON OF PERFORMANCE OF X-RAY CENTRES, MICROSCOPY CENTRES AND REFERRING CENTRES UNDER DISTRICT TUBERCULOSIS PROGRAMME

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(Original received on 10.1.95; Revised version received on 6.3.95; Accepted on 14.3.95)

**Summary:** Analysis of the functioning of peripheral health institutions in DTPs has revealed that the X-ray Centres are functioning more satisfactorily in respect of quality of case-finding compared to Microscopy Centres. With regard to Referring Centres, their poor performance needs a detailed investigation. Overall, the performance of PHIs in DTPs needs to be studied and the key factors identified so that these can be made use of in strengthening the DTP functioning.

### Introduction

The District Tuberculosis Programme (DTP) was formulated in 1962 with the objective of diagnosing maximum number of tuberculosis patients among the out-patients attending general health institutions (GUIs)<sup>1</sup>. Since the Indian population is predominantly rural, health institutions in the rural areas were expected to play a major role. An average Indian district has a net-work of health institutions. At the time of implementation of DTP, rural GUIs - Peripheral Health Institutions (PHIs)- are assigned different types of activities depending on the facilities available and classified into (i) X-ray Centres (XCs), (ii) Microscopy Centres (MCs) and (iii) Referring Centres (RCs). While all such centres provide treatment, XCs offer chest X-ray and sputum microscopy examination; MCs offer only sputum microscopy examination and sputum slides are prepared in RCs and sent to the nearest MC or XC for examination or the patients are referred there for sputum examination.

In the prescribed reports on the performance of DTPs, the activities of District Tuberculosis Centre (DTC) and PHIs (i.e. XCs, MCs & RCs collectively) are reported. It has been observed that PHIs are contributing about 70% towards total sputum examinations and 50% in respect of tuberculosis cases. However, the contribution of XCs, MCs and RCs, separately, has not been reported so far. Understanding the performance of these centres, separately, may provide insight into the performance of DTPs which in turn may help in developing a strategy for improving the performance of the national tuberculosis programme.

### Material

In all, 208 quarterly reports for the period October to December 1993, received at the National Tuberculosis Institute (NTI) have been analysed to compare the performance of the three types of PHIs. This period was selected because of the latest periodic DTC reports being available. In all, 315 reports had been received, but only 208 could be taken for analysis as these were complete in respect of their Pills i.e. XCs, MCs and RCs. An attempt was made to cross check the findings of the same 208 districts during the subsequent quarter i.e. January to March, 1994 but was found impracticable because of incompleteness of reports. However, in respect of the 170 complete reports for that quarter, a separate analysis showed that the findings of 2 separate quarters were consistent.

### Results

DTP is operational in 390 out of the 438

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**Table 1. Reporting by PHIs according to category**

Category	Reports expected No.	reports Received		Correct reports		Reporting efficiency % (Col 5/2)
		No.	%	No.	%	
1	2	3	4	5	6	7
XC	1447	1308	90.4	1209	92.4	83.6
MC	5160	4680	90.7	4427	94.6	85.8
RC	3495	2170	62.1	1892	87.2	54.1
Total	10102	8158	80.8	7528	92.3	74.5

districts in the country (89 per cent). The numbers of XCs, MCs & RCs are given below:

Functioning DTPs	XC	Implemented PHIs		
		MC	RC	Total
390	2393 (13.4%)	8717 (48.8%)	6740 (37.8%)	17850 (100.0%)

#### Reporting

PHIs are required to report their activity to DTC every month. During the period under study, 90% of the expected reports were received from XCs and MCs as compared to 62% from RCs. Of these, 90% of the reports received from XCs and MCs could be considered satisfactory, bringing the efficiency of reporting to about 85%, whereas the efficiency of reporting of RCs was 54% (Table 1).

#### Out-patients Attendance

Out of about 33.1 million out-patients seeking medical relief from various health institutions, 35% attended XCs, 43% MCs and 22% RCs (Table 2).

**Table 2. Out-patients Attendance at various PHIs**

Category	Out-patients attendance* (In million)	%
XC	11.63	35
MC	14.20	43
RC	7.28	22
Total	33.11	100.0

\*Corrected for non-receipt of reports

#### Sputum Examination

Out of the total 5,29,000 sputum examinations performed during the period under study, XCs examined 39%, MCs 52% and RCs 9% (Table 3). XCs examined sputa of 204,000 patients out of the 11.63 million who attended. Selection of chest symptomatics for sputum examination worked out to 1.8% compared with the expectation of 2.5% (Baily et al<sup>2</sup>); the corresponding figures for MCs and RCs were 2.0% and 0.7% respectively.

#### Case Detection

Out of the total 28,654 sputum positive cases diagnosed, 56% were diagnosed by XCs, 37% by MCs and 7% by RCs (Table 3). It is seen that XCs diagnosed 56% of the total cases by doing 39% of the total sputum examinations. The sputum positivity rate at XCs (7.8%) is almost double that of MCs (3.8%) and RCs (4.4%). This could be due to several factors such as quality of selection for sputum examination, instructions given to patients, quality of laboratory procedures and selection of ineligible patients in order to achieve the target of sputum examination, etc. This suggests further probing and appropriate corrective actions.

#### Efficiency of Sputum Examination & Case Detection

Efficiency is defined as percentage of achievement compared with the expectation. The expected number of chest symptomatics among die out-patients attendance and the number of cases that could be diagnosed compared with the actual number of symptomatics examined by

**Table 3. Quality of Sputum Examination According to Category of PHIs**

Category of PHIs	*Sputum exams	(OOOs)	*Sputum	cases	Sputum positivity
	No.	%	No.	%	rate (%) (Col 4/2)
1	2	3	4	5	6
XC	204	39	16024	56	7.8
MC	277	52	10514	37	3.8
RC	48	9	2116	7	4.4
Total	529	100	28654	100	5.4

\* Corrected for non-receipt of reports

**Table 4. Efficiency of Sputum Examination & Sputum Case Detection**

Category of PHIs	Expected*	Sputa	Efficiency	Expected	Cases	Efficiency
	symptomatics (OOOs)	examined (OOOs)	%	Cases (OOOs)**	diagnosed (OOOs)	%
1	2	3	4	5	6	7
XC	243	170	70.0	19.4	13.4	69.1
MC	305	238	78.0	24.4	9.0	36.9
RC	98	26	26.5	7.8	1.1	14.1

\*Expectation according to Baily et al<sup>2</sup>      \*\*8% of Col. 2

sputum and the cases diagnosed have been shown in Table 4. Statewise, efficiency of sputum examination and case detection is presented in Annexure 3.

The sputum examination efficiency (SEE) of XCs & MCs was 70% & 78% respectively as compared to only 26.5% in RCs. The case detection efficiency (CDE) of MCs (36.9%) was slightly above half that of XCs (69.1%) and more than double that of RCs (14.1%). The fairly high SEE of MCs (78%) combined with low CDE (36.9%) indicates the liberal selection of symptomatics by them for sputum examination. It may be observed that the sputum positivity rate of RCs (4.4%) is not different from that of MCs (3.8% - Table 3), indicating that though the quality of selection of symptomatics is on a par with that in MCs, RCs could put in more efforts to refer more chest symptomatics for sputum examination to XCs/MCs.

#### Work Load in PHIs

PHIs are required to perform DTP activities along with those pertaining to other health

programmes. The work load involved per month/ per PHI in respect of out-patients attendance, sputum examination and detection of cases is presented in Table 5.

**Table 5. Work Load Per PHI per Month For Out-patients, Sputum Examination and Cases**

Category of PHI	Attendance	New sputum examinations	Cases detected
XC	2829	50	3.9
MC	1009	20	0.7
RC	784	5	0.2

The work load was calculated on the basis of total PHI months. It is observed that work load is low, for all the three categories of PHIs, to allow the expectation of 2.5% of out-patients attendance being chest symptomatics to be selected for sputum examination and 8% of the examined detected as cases (Baily et al<sup>2</sup>).

#### Discussion

DTCs and PHIs (XCs, MCs & RCs) are the working components of a DTP. During the period

review of quarterly reports, XCs, MCs & RCs collectively contributed 75% to the total sputum examinations done and 55% in respect of detection of cases. The role played by each category of PHIs separately is depicted in Annexures 1 and 2.

Of the total out-patients, 35% had attended X-ray centres; the reporting efficiency of XCs, was 84%, their sputum examination efficiency was 70% and sputum positivity rate of 7.8% indicates satisfactory selection of chest symptomatics and procedures of sputum examination. Hence, it appears that XCs are functioning satisfactorily in DTPs. It is possible that some chest symptomatics prefer attending XCs because of the availability of X-ray facility there and some XCs might do smear examination after ascertaining the result of X-ray (though this is not the procedure recommended). Therefore, it appears worthwhile to further critically examine the situation and performance at XCs before coming to a firm conclusion about the role of XCs in DTP.

Microscopy centres attended to 43% of the out-patients, had reporting efficiency of 86% but had tuberculosis case-finding efficiency of 36.9% and a low sputum positivity rate of 3.8%. Unsatisfactory case-finding activity, both qualitatively and quantitatively at MCs suggests that there is large scope for improvement.

Referring Centres constituted nearly 1/3rd of the total PHIs, catered to about 20% of the total out-patients, had reporting efficiency of 50%, sputum examination efficiency of 9% and case detection efficiency of 7%, revealing a great need for their supervision and extending them technical support. However, only 30% of RCs had been supervised as compared to 50% of XCs & MCs (Table 6).

**Table 6. Supervision**

Category of PHIs	Number for which supervision details available	Supervised	
		No	%
XC	1341	711	53.6
MC	4724	2439	51.6
RC	3201	937	29.3
Total	9296	4087	44.1

It was further observed from the reports that in 56% of the RCs not a single sputum examination had been done and in 83% of the RCs not a single case was detected. Greater attention in respect of supervision, reporting, etc. is needed so that their functioning can be improved. A detailed analysis of the performance of PHIs may lead to a better understanding of the programme and emergence of new measures to improve the functioning of PHIs.

#### ACKNOWLEDGEMENTS

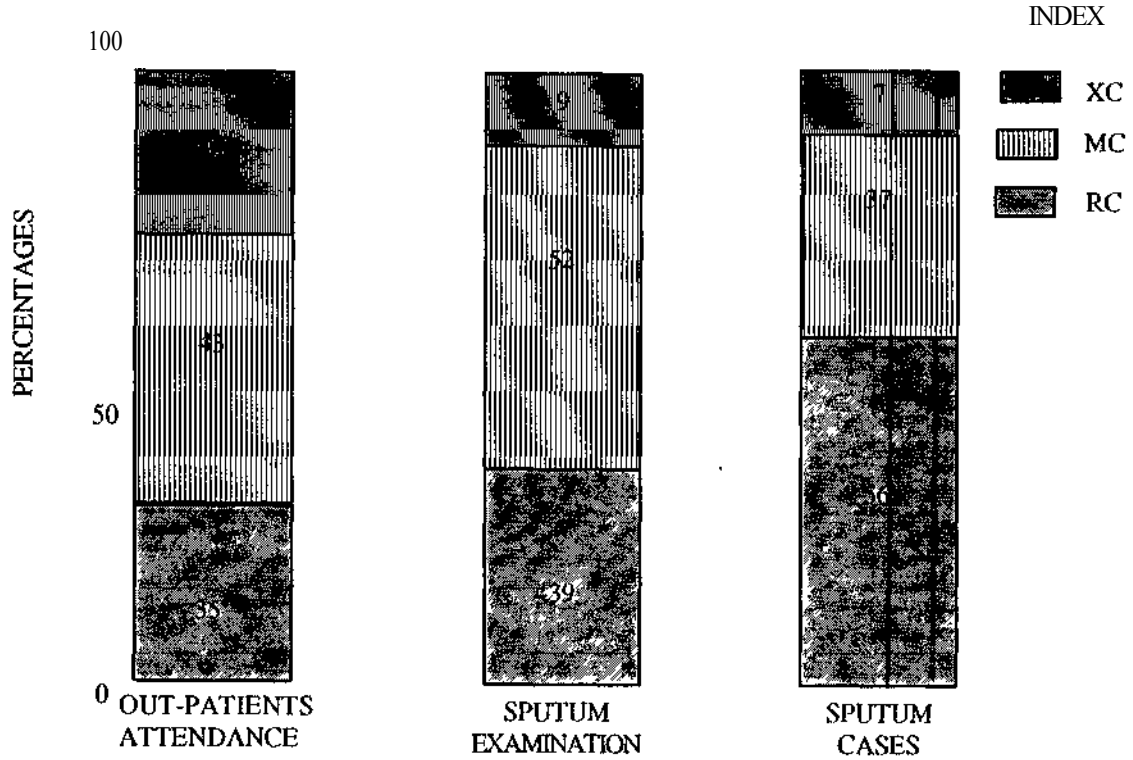
The authors acknowledge the contribution made by Dr L Suryanarayan, Mr K. Vembu, Mr C. Satyanarayana, Mr S.G. Radliakrishna and Miss T.I. Alamelu.

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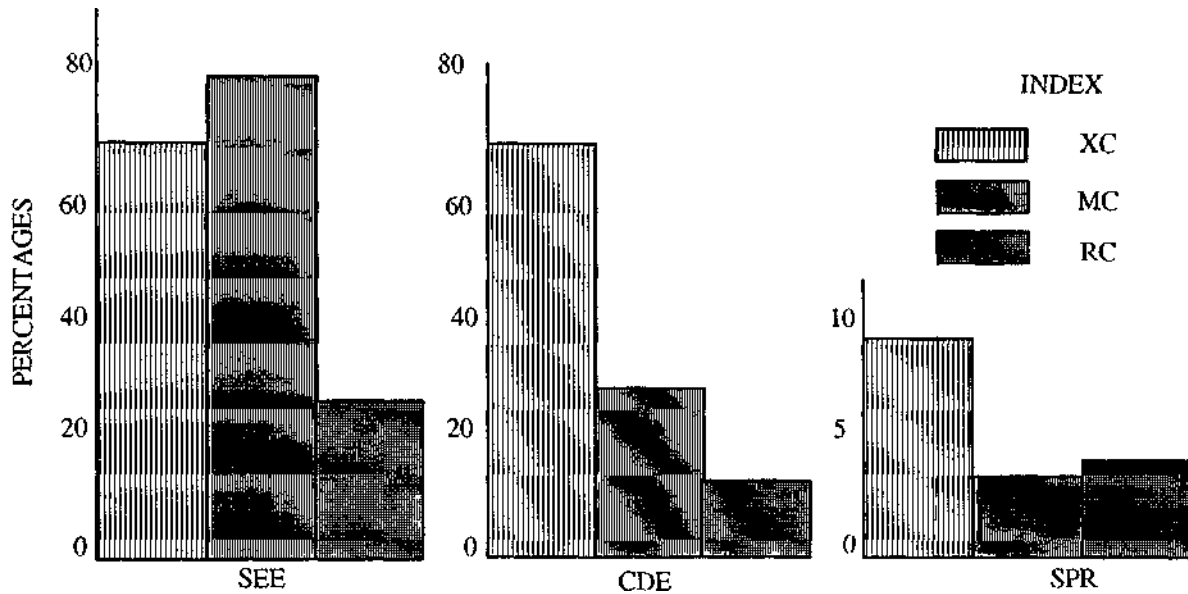
*Annexure 1*

Percentage contribution by XCs, MCs & RCs with respect to Out-patients Attendance, Sputum Examinations and Sputum cases



*Annexure 2*

Category-wise percentage efficiency of sputum examination (SEE), Case detection (CDE) and sputum positivity rate (SPR)



Average Efficiency of Sputum Examination for Different States

Efficiency (%)	XC	MC	RC
0	-	-	HP,AR,PR,GOA,MZ, TR,CH,PO
1-25	A&N	AP,AS,KE,AR PR, TR.A&N	AP,AS,KE,MP,OR, RA,TN
26-50	AP,J&K,KE,OR,RA, TN,AR PR,TR,CH	HP,WB,MZ,PO	J&K,KA
51-75	HA,HP,KA,MP,PO	HA,J&K,KA,OR,RA,TN	H A
76-100	MZ	ME	GU
100+	AS,GU,MII,PU,UP, WB,GOA	GU,MP,MH,PU,UP, GOA.SI	MH.UP.WB

Average Efficiency of Sputum Case Detection for Different States

Efficiency (%)	XC	MC	RC
0	-	PO	HP,KE,TN,AR,PR, GOA,MZ,TR,CH,PO
1-25	HP,J&K,KE,MP,OR, TN,AR,PR,MZ,TR, A&N.CH	AP,AS,HA,A&N, HP,KE,KA, TR,MZ,OR,RA,TN, WB,AR,PR,ME	AP,AS,HA,J&K,KA, MP,OR,RA
26-50	AP,RA,UP,PO	GU,J&K,MP,PU,GOA	GU
51-75	AS,HA,KA	UP	Mil, UP
76-100	PU	MH	
100+	GU,MH,WB,GOA	SI	WB

Note:

KB	-KERALA	CH	-CHANDIGARH	AS	-ASSAM
OR	-ORISSA	HA	-HARYANA	GU	-GUJARAT
RA	-RAJASTHAN	KA	-KARNATAKA	MH	-MAHARASHTRA
AR.PR	-ARUNACIAL PRADESH	PO	-PONDICHERY	PU	-PUNJAB
TR	-TRIPURA	SI	-SIKKIM	ME	-MEGHALAYA
AP	-ANDHRA PRADESH	MZ	-MIZORAM	MP	-MADHYA PRADESH
A&N	--ANDOMAN & NICOBAR ISLANDS	HP	-HIMACIAL PRADESH	UP	-UTTAR PRADESH
WB	-WEST BENGAL	J&K	-JAMMU & KASHMIR		
		TN	-TAMIL NADU		



## A RETROSPECTIVE STUDY OF "NON-COMPLIANT" PATIENTS IN CONTROLLED CLINICAL TRIALS OF SHORT COURSE CHEMOTHERAPY

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(Original received on 16.11.94, Revised version received on 24.1.95, Accepted on 17.4.95)

**Summary:** In a total of 2,332 pulmonary tuberculosis patients admitted to 3 different short-course chemotherapy studies conducted during 1975-1985, there were 60 non-compliant patients who had received less than 75% of the prescribed treatment. A retrospective study was undertaken to find out the reasons for default in these patients since the Tuberculosis Research Centre has very stringent criteria of selection of patients for their studies, an adequate system of motivation of the patients and well organised infrastructure for retrieval of the defaulters.

Unwillingness for treatment was stated as the reason for default by 20 patients and adverse reactions to the drugs by 16 patients. Other major reasons given were pressure of work (14 patients), frequent outstation visits (13) and migration (12).

### Introduction

The problem of drug default has been commonly observed whenever prolonged therapy has to be given. In tuberculosis, non-adherence to prescribed treatment could lead to treatment failure and development of drug resistance while the patient continues to transmit infection.

Treatment non-adherence poses many additional problems for the tuberculosis control programme such as, defaulter actions, retrieval efforts and change of chemotherapeutic schedules,

etc., which have an adverse economic impact due to increase in operational costs.

A retrospective analysis was undertaken of 60 'non-compliant' patients who had received short-course chemotherapy under 3 fully supervised, controlled clinical trials at the Centre during 1975-85<sup>1,3</sup> to find out the reasons for default in spite of the intensive defaulter retrieval procedures of the Centre following a very careful selection of co-operative patients and giving them intensive health education and motivation. Such efforts are not practical under programme conditions.

### Material and Methods

At the Tuberculosis Research Centre, Madras, pulmonary tuberculosis patients who were permanent residents of Madras and were suitable for long-term follow-up and judged to be cooperative were accepted for treatment in the different controlled clinical trials. Suitability of the patients for inclusion in the trials was methodically assessed, initially by a medical officer, a social worker and a health visitor (HV) for 5-7 days. Initial home visits were made by a HV and a social worker to assess domiciliary stability, family set-up, socio-economic background including employment, income, details regarding previous treatment and patients' cooperation with regard to treatment, follow-up and home visits. Apart from these, the close relatives of the patients were also interviewed to ensure cooperation. For every patient started on treatment, a full list of addresses was obtained, namely (i) the patient's home address, (ii) the addresses of relatives and friends and details regarding how

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often he visited them, if employed, the place of work, (iii) if children were at school, their addresses and (iv) the address of his native place<sup>4</sup>.

The anti-tuberculosis chemotherapy in these trials consisted of fully supervised drug regimens containing Rifampicin for a period ranging from 2 to 6 months and the total duration of treatment ranged from 3 to 7 months. The due dates of drug administration were intimated to the patients in advance.

A patient is considered as "non-compliant" if he has received less than 75% of the prescribed chemotherapy during the scheduled treatment period.

A total of 60 (2.6%) non-compliant patients were identified as per the above criterion out of 2,332 patients admitted to 3 short course chemotherapy studies and efforts were made to elucidate the reasons for non-compliance from their case papers.

Various intensive defaulter retrieval procedures had been followed, namely repeated visits by health visitors/social workers/medical officers to the house/work spot/contact address of the patients and even outstation visits, if needed. If a patient failed to attend and if his or her house was found to be locked and the neighbours did not know where the patient (or the family) was, a systematic search was made with the help of various alternative addresses until the patient was traced<sup>4</sup>.

Periodic meetings had also been conducted among the clinic staff to discuss the non-compliance problems and suitable remedial measures had been taken.

## Results

### *Pre-treatment characteristics*

Of the 60 non-compliants, 54 (90%) were males, and 36 (60%) were in the age group of 25-44 years which is the most economically productive period of life. Twenty-eight (47%) patients had received treatment at the clinic of the Tuberculosis Research Centre while the

remaining 32 (53%) had treatment at our sub-centres located at different government hospitals in the city. The duration of stay in the city was more than 5 years for 53 (88%) patients, and 47 (78%) did not change their residence during the treatment period; 77% lived within 5 km of their treatment centre. Eighty two percent were married with families consisting of 5 or less members, 41 (68%) were daily wage earners, such as painters, construction workers, etc., and 13 (22%) belonged to salaried class; 88% of these had monthly income of less than Rs. 300; 27 (46%) were used to taking liquor (14 occasionally and 13 frequently).

### *Pattern of default*

The month of default and the rhythm of treatment are shown in Table 1. Thirty three (55%) patients had defaulted in the first month and another 21 (35%) in the second; thus, 90% of the default had occurred within the first two months. Of these 54 patients, 20 (37%) had defaulted on daily attendance, 17 (32%) on thrice weekly and 17 (32%) on twice weekly attendance. The remaining 6 patients had defaulted during the continuation phase; 5 on twice-weekly and 1 on once-weekly treatment. Thus, it may be observed that there was no association between regularity and frequency of attendance.

During home-visits, it was observed that 50 (83%) of the non-compliants were non-cooperative to the extent of hiding themselves or disappearing from the spot on seeing the Centre's vehicle in spite of motivation, repeated visits, a written compliance agreement (a health contract or "written commitment") and warnings given that they were not being regular in attendance and special efforts made for their retrieval including various monetary benefits such as reimbursement of travel expenses, compensation for loss of wages, diet and family assistance, ambulance and hospital admission provided for 36 (60%) of 60 defaulters.

### *Major reasons for default*

The various reasons for default were obtained from the case records of the 60 non-compliant patients. Some of the patients had given more

**Table 1. Drug collection pattern**

Month of Default	Daily	Frequency of drug collection			Total	
		Once Weekly	Twice Weekly	Thrice Weekly	No.	%
1	13	0	9	11	33	55
2	7	0	8	6	21	35
3	0"	1	4	0	5	8
4	0	0	1	0	1	2
Total default	20	1	22	17	60	100

than one reason for their repeated or continuous default (Table 2). Among these, 'unwillingness for treatment' ranked first, and was given as the reason by 20 (33%) patients. 'Unwillingness for treatment' denotes their general disinterest or indifference and this might be due to their having to attend the clinic daily for the supervised chemotherapy. Adverse reactions to the drugs was given as reason by 16 (27%) patients. Other reasons were pressure of work by 14(23%) and frequent outstation trips by 13 (22%). Temporary absence of patients from the city was mostly because of business, family or social obligations such as vocational commitments, marriages, religious functions, death, etc., Twelve patients (20%) had migrated out of Madras. Alcoholism was found among 7 (12%). Lack of bus fare was given as the reason for default by 5, whereabouts were not known in 4 and fear of injections/blood

**Table 2. Major reasons given for non-compliance**

Reason for non-compliance*	patients	
	NO.	%
Unwillingness for treatment		
Adverse reactions	16	27
Pressure of work	14	23
Frequent outstation trips	13	22
Migration	12	20
Alcoholism	7	12
Lack of bus fare	5	8
Whereabouts not known	4	7
Fear of injections/blood tests	3	5
Taking treatment elsewhere	4	7
Felt well	2	3

\* Multiple reasons were given

was the season tests in 3 cases. Three patients took treatment elsewhere. Only 2 patients discontinued treatment because they felt well.

### Discussion

'Unwillingness for treatment' (33%) was found among the more dissatisfied patients who did not want to adhere to the strict treatment schedule of the controlled clinical trial conditions. Generally, once the symptoms disappear, the standard of regularity also goes down considerably.

Next major reason given was adverse reactions to the drugs (27%). The patients in this group needed a change in treatment schedule in addition to reassurance and motivation by trained health personnel. Next in order came pressure of work (23%) and frequent outstation trips (22%). Out of 60 non-compliers, 41 (68%) were daily wage earners, and 88% of the defaulters had very low monthly income of less than Rs. 300/-. For them to spend a day in the clinic meant loss of wages. We could minimise the extent of their default by administering drugs either at home or at workspot or a more convenient place. For patients who leave home early for work and for those who are out of station often, 'health posts' to provide health care near their homes, at a time convenient to them, may be helpful.

Human nature being what it is, patients who take medicine regularly, voluntarily, without a break are not many<sup>5</sup>. The problem of non-compliance is bound to continue whatever action we might take. However, an understanding of the specific reasons can help to devise specific steps

to reduce the problem, which cannot apparently be eliminated.

#### Acknowledgements

We thank the medical and nursing staff and the social workers of the Centre for their enthusiastic cooperation and are grateful to Dr. R.Prabhakar, Director, Tuberculosis Research Centre for his continued encouragement and to Mrs. Niruparani Charles, Medical Social Worker for her valuable contribution. We thank K. Saroja and Mr. P. Karthigayan for their secretarial help.

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## NIACIN TEST FOR MYCOBACTERIA: A COMPARATIVE STUDY OF TWO METHODS

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(Received on 1.11.94; Accepted on 10.4.95)

**Summary:** The Niacin Test was carried out on 125 strains of mycobacteria by two methods, i.e modified Runyon Method and Paper Strip Test (Difco laboratories). The paper strip method was found easy to perform, safe and showed good correlation (97%) with the routine test.

### Introduction

The Niacin Test is, perhaps, still the most widely used test for differential identification of mycobacteria, particularly in the developing countries where conventional methods of diagnosis of tuberculosis like direct microscopy and culture are used and facilities for rapid diagnosis like BACTEC, gene probe, etc. are not available. Originally described by Konno<sup>1</sup>, the method suggested by Runyon and his colleagues<sup>2</sup> is most frequently used for niacin production. However, certain problems are encountered in this method: aniline may change colour on exposure to light and air, cyanogen bromide when vaporised becomes a 'tear gas' and hydrolysis products of cyanogen bromide, notably hydrocyanic acid, are extremely toxic. For these reasons, paper niacin test strips were compared with modified Runyon Method.

### Material and Methods

The study was carried out in the Department of Microbiology, U.C.M.S. & G.T.B. Hospital, Shalidra, Delhi between March 1990 and March 1994. One hundred strains of *Mycobacterium tuberculosis* and twenty five strains of mycobacteria other than *M. tuberculosis* (MOTT)

were identified on the basis of rate of growth, colony morphology, pigment production and biochemical tests<sup>3</sup>.

All the strains were subcultured in duplicate on Lowenstein Jensen (L.T) slopes. The 3 to 4 weeks old subcultures having approximately 50-100 colonies were used. The slopes were punctured with a sterile inoculation wire to extract niacin from the medium. One ml of sterile distilled water was added to each slope and kept in a horizontal position for 30 minutes and then autoclaved for 15 minutes at 121°C. The autoclaved extracts were used for the Niacin Test by the two methods as follows:

(i) Modified Runyon Method<sup>4</sup> : 0.25ml of autoclaved extract was taken in a test tube and an equal amount of 4% aniline in ethanol and 10% aqueous cyanogen bromide were added to it. Positive results were indicated by the appearance of yellow colour and negative test by no colour.

The *M. tuberculosis* strain H37RV served as a positive control and an uninoculated L.J. slope served as negative control.

(ii) Paper Strip Method<sup>5</sup> (Difco Laboratories)

The Bacto-TB Niacin Test strips are prepared with potassium thiocyanate, chloramine T, citric acid and sodium aminosalicylate. The test control is prepared with nicotinamide. The "disk", when used according to the directions, yields a yellow solution, equivalent to approximately 5 meg niacin.

A 0.6 ml of the autoclaved extract from

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the test strain is put in a special test tube with a stopper: the negative control is 0.6 ml, of distilled water and the positive control is the provided test control. The test strip is dropped in each tube with arrow downwards and stoppered immediately. The tubes are shaken gently but not tilted. After 12-15 minutes, but not later than 30 minutes, the colour of the extract is compared with the controls.

A positive test is indicated by the appearance of yellow colour in the extract tube and positive control and no colour in the negative control.

### Results and Discussion

The comparison between the paper strip method and modified Runyon Method (shown below) is quite good.

	Modified Runyon test		Paper strip method	
	Positive	Negative	Positive	Negative
<i>M. tuberculosis</i> (n=100)	90	10	87	13
MOTT (n=25)	0	25	0	25

Out of 100 *M. tuberculosis* strains tested 90 gave a positive niacin test and 10 were niacin negative by Runyon Method while 87 strains were positive by the strip method and 13 were negative. The 3 strains that failed to give a positive niacin test with the paper strip method can probably be explained by the fact that the modified Runyon test is able to detect 2µg of nicotinic acid per ml as compared to the strip method which detects this compound in the concentration of 5µg per ml. There was full agreement between the two tests in the case of MOTT strains.

Niacin tests have been performed by several workers replacing aniline with either benzidine or O-Tolidine; both give a pink precipitate with a positive test. Aniline which gives a yellow colour with a positive test causes difficulty in the interpretation of the results, particularly with chromogenic mycobacteria<sup>6,7</sup>. Since benzidine was not easily available and results were not very satisfactory with O-Tolidine, the modified Runyon Method was used as the routine niacin test for the identification of mycobacteria<sup>8,9</sup>.

Kilburn and Kubica<sup>10</sup> first used the reagent-impregnated paper strips to detect niacin. The commercially available paper strips have been evaluated by Disalvo and Lindler.<sup>11</sup> We found the paper strip method easy to perform, safe and capable of giving comparable results.

### Acknowledgement

The authors are grateful to H.C. Gupta and (Mrs.) K. Saxena for technical assistance.

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## TUBERCULOUS ENDOMETRITIS IN STERILE FEMALES: A CLINICOPATHOLOGICAL AND BACTERIOLOGICAL STUDY

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(Received on 27.6.94; Accepted on 12.5.95)

**Summary;** Combined histological and bacteriological study of 1,124 endometrial curettings from cases of sterility was done to find out the proportion having tuberculous endometritis. Their ages varied from 18 to 42 years with the peak in 20-30 years age group. On histological examination, 21 (1.87%) had tuberculous endometritis whereas on bacteriological examination 23 specimens (2.05%) were positive for *M. tuberculosis*. The use of the two methods simultaneously yielded a better result.

### Introduction

Tuberculous endometritis is far more common in India compared to the U.S.A. and U.K.<sup>1</sup> The patient usually presents with the problem of sterility. Tuberculous endometritis is due to haematogenous spread of acid fast bacilli, with primary focus somewhere else in the body, and is usually detected on routine examination of the endometrial curettings for some gynaecological or other problems.

The present study was undertaken to evaluate and compare the histological and bacteriological methods of examination in diagnosis of tuberculous endometritis in sterile females (both primary and secondary).

### Material and Methods

A total of 1,124 specimens of endometrial curettings in the Departments of Pathology and

Microbiology, Government Medical College, Amritsar during 6 years i.e. from January 1988 to December, 1993 were taken up for the study. The specimens had been collected in 10% formalin for histopathological examination and in normal saline for bacteriological examination. For histopathology, routine haematoxyline and eosin staining was done after wax impregnation.

For bacteriological study, the specimens were directly examined by Ziehl-Neelsen staining and culture was done on Lowenstein Jensen medium and reported after a period of 4-6 weeks.

The diagnosis of tuberculous endometritis was mainly based on histological findings in which the epitheloid cell granulomas along with Langhans type of giant cells were seen.

### Results

Of the 1,124 cases of sterility, 21 endometrial specimens (1.87%) were histopathologically found to be tuberculous endometritis. However, bacteriologically, 23 cases (2.05%) showed the presence of *Mycobacterium tuberculosis*.

The age of the cases varied from 18 years to 42 years with a peak in the age group 20-30 years (Table 1).

The presenting complaint was infertility: the period of infertility varied from 2 years to 18 years. As many as 62% cases gave a normal menstrual history whereas 26% had menstrual disorders like oligomenorrhoea or menorrhagia and in the remaining 12%, there was history of

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**Table 1. Age distribution of female sterility cases**

Age in years	No. of patients	Percentage
Less than 20	101	8.99
20-30	888	79.00
31-40	112	9.96
41 and above	23	2.05
Total	1124	100.00

amenorrhoea varying from 2 months to 7 months (Table 2).

The histopathological study of endometrium revealed secretory endometrium in 65.91%, proliferative endometrium in 21.36%, hyperplastic endometrium in 9.08% and tuberculous endometritis in 1.87%. In the remaining 20 specimens (1.78%), the curettings were insufficient. In the 21 tuberculous endometritis specimens, the accompanying endometrium was in the proliferative phase in 6 and secretory phase in 4 and in one, only tuberculous granulation tissue was seen.

Bacteriologically, 23 specimens were diagnosed as tuberculous endometritis. The two additions on account of positive bacteriology showed secretory endometrium on histopathological examination (Table 3).

**Table 3. Comparative study of histological and bacteriological results**

Endometrium (histopathology)	No. of patients	Percentage	Bacteriologically positive
Secretory	741	65.91	2
Proliferative	240	21.36	-
Hyperplastic	102	9.08	-
Tuberculous	21	1.87	21
Insufficient material	20	1.78	-
Total	1124	100.00	23

#### Discussion

The proportion of tuberculous endometritis in endometrial curettings varies from 1.5% to 11.8% in various reports<sup>2,3</sup> from India. Our

**Table 2. Distribution of cases according to symptoms**

Symptoms	No. of patients	Percentage
Normal menstruation	697	2.00
Oligomenorrhoea	202	17.97
Menorrhagia	90	8.01
Amenorrhoea	135	2.01
Total	1124	10.00

finding is in agreement with that of Schaffer<sup>1</sup> and Kherdekar et al<sup>4</sup> but much less than that reported by Roy et al<sup>5</sup> (11.8% in cases of sterility).

The simultaneous use of histological and bacteriological methods increased the efficiency of diagnosis. Similar findings have been reported earlier<sup>5</sup>. It may be that the menstrual discharge in some cases yields positive AFB culture but by the shedding off of the endometrium, the diagnosis is missed on histopathological examination. The proportion of tuberculous endometritis was higher in cases which presented with secondary amenorrhoea. Similar findings have been reported by Mukherjee et al<sup>6</sup>.

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## GENERALIZED CUTANEOUS TUBERCULOUS GUMMAS - A CASE REPORT

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(Received on 28.11.94; Accepted on 15.1.95)

**Summary;** A rare case of generalized cutaneous tuberculous gummas with classical morphology is being reported. The diagnosis was based on clinical, histopathological findings and response to short course anti-tuberculosis chemotherapy.

disseminated types of tuberculosis. It will, therefore, be advantageous to be familiar with unusual forms of tuberculosis. Although there are abundant reports of the various types of tuberculosis mentioned above, generalized tuberculous gummas are rarely reported. In the present article an unusual case of generalized cutaneous tuberculous gummas is being reported.

### Introduction

Manifestations of tuberculosis of the skin depend upon the immune status of the host<sup>1</sup>. Tuberculosis chancre is sometimes found in patients who are exposed to *Mycobacterium tuberculosis* for the first time. Tuberculous verrucosa cutis is found in patients who have some degree of immunity and there is direct inoculation. Lupus vulgaris is seen in patients with moderate to high degree of immunity and direct inoculation, direct extension or haematogenous spread. Scrofuloderma and orificial tuberculosis are met with in individuals with poor general health and long standing underlying tuberculosis. Miliary tuberculosis is particularly seen in those who are immunosuppressed and in those with poor natural immunity following post-primary bacillaemia.

During periods of lowered body resistance there is also bacillaemia and haematogenous dissemination from a tuberculous focus which results in tuberculous gummas. These are seen in patients with poor natural immunity.

With the increase in AIDS, we are likely to come across more and more cases of

### Case Report

A forty year old female was admitted to Goa Medical College with multiple cutaneous swellings on the extremities and trunk along with low grade fever, loss of appetite and weight of 7 weeks' duration. The lesions started as deep seated erythematous mildly tender nodules which softened to form ill defined fluctuant abscesses. Some of these went on to form discharging sinuses and ulcers. Prior to admission the patient had received various antibiotics without appreciable improvement.

Physical examination revealed ill defined fluctuant swellings involving the trunk and extremities and ulcers with undermined edges and bluish margins. Cervical lymph nodes were enlarged, firm and matted. Patient was emaciated and anaemic. Apart from harsh vesicular breath sounds with scattered rhonchi, no other abnormalities were noted.

Investigations revealed Hb level of 9 g%, ESR of 65mm/1st hour, the aspirates taken from fluctuating swellings on 3 occasions and examined by smear and culture were negative for AFB as well as fungal elements and anaerobic organisms.

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Mantoux test was negative. The biopsies of lesions revealed necrotizing granulomatous matter suggestive of tuberculosis. X-ray of the chest showed pleural thickening of left apical region. VDRL was non-reactive and ELISA for HIV was negative.

Patient was diagnosed as a case of generalized tuberculous gummas and treated with short course chemotherapy with R, H, E and Z for 2 months followed by R and H for 8 months. Patient showed remarkable recovery with healing of most of the lesions within 3 months of starting therapy and complete healing leaving behind atrophic scars in 5 months.

### Discussion

The emaciated appearance, anaemia and multiple generalized abscesses gave the initial impression of immunodeficiency leading to pyogenic abscesses. However, the detailed clinical scrutiny, non-response to broad spectrum antibiotics, high ESR, a negative ELISA test for HIV and pleural thickening in the left apical region also suggested disseminated tuberculosis. The diagnosis was confirmed histopathologically from the biopsy specimen of an abscess wall. However, we could not demonstrate AFB in smear or culture. The negative tuberculin test suggested the state of anergy leading to dissemination. Finally, the excellent response to anti-tuberculosis therapy clinched the diagnosis.

In the literature, different types of cutaneous

tuberculosis have been reported.<sup>2-6</sup> Among the 142 cases<sup>2,3</sup> reviewed in the Indian literature and 365 reported from abroad<sup>4,5</sup> not a single case of tuberculous gummas was reported. However, a single case<sup>6</sup> of tuberculous gummas has been reported from India showing the rarity of this variant of cutaneous tuberculosis

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## A RARE PRESENTATION OF LUNG CANCER

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(Received on 6.4.95; Accepted on 4.5.95)

**Summary:** A case of central bronchogenic carcinoma resulting in pyopneumothorax is presented due to rarity of pneumothorax occurring in primary lung cancer.

### Introduction

Lung cancer is one of the commonest neoplastic diseases today. Tobacco smoking, atmospheric pollution and certain occupational factors are the major causes of the increasing problem of lung cancer. Most patients in whom carcinoma of the lung is diagnosed are habitual smokers and over forty years of age.

The patients present either with chest complaints or symptoms due to metastatic spread to other organs. Sometimes a chance diagnosis of bronchogenic carcinoma is made in individuals with no respiratory complaints while investigating for some other problem. The common roentgenological findings in these patients are the presence of a hilar prominence, solitary pulmonary nodule, obstructive pneumonitis, mediastinal widening and pleural effusion. We report here a case of central bronchial carcinoma with pyopneumothorax being a very rare complication of primary bronchogenic carcinoma.

### Case Report

O.P., a 50 year old fanner was admitted to Rajan Babu Tuberculosis Hospital in December 93 with the complaints of cough with minimal expectoration, frequent haemoptysis, progressively increasing exertional dyspnoea, anorexia and weight loss for 6 months. He had taken anti-tuberculosis treatment for 3 months with little relief followed by various antibiotics but the

patient continued to deteriorate symptomatically. The patient was a non-smoker, with no past history of tuberculosis or chronic obstructive pulmonary disease.

On general examination, the condition of the patient was unsatisfactory. There was no evidence of clubbing or any significant lymphadenopathy.

Examination of the respiratory system revealed drooping of left shoulder, prominence of the medial border of left scapula and generalised flattening of left chest. Movement of the left hemithorax was diminished as a whole. The trachea was grossly shifted to the left but apex beat could not be localised. Percussion of left hemithorax revealed impaired resonance in infraclavicular and suprascapular areas and stony dullness in other areas. There was no shifting dullness. The breath sounds were absent on left side, but a succussion splash was audible. Thus, a clinical diagnosis of left sided chronic hydropneumothorax was made with suspicion of obstructive collapse of left lung.

Routine investigations revealed Hb:8 g%, TLC: 9700/cumm, DLC: P 62 L 38 cumm and ESR 29 mm in first hour. Blood urea and sugar etc. were normal. Direct smear examination of sputum was negative for acid fast bacilli as well as malignant cells.

Chest X-ray PA view dated 6 months back showed a left hilar enlargement with a bulla in left lower zone but chest X-ray at the time of admission showed marked shift of mediastinum and evidence of hydropneumothorax on the left side. Ultrasound study of thorax revealed thickening of pleura and multiple loculi of air and fluid

within the pleural space on the left side. An ultrasound guided diagnostic tap was done and about 10 ml. of pus was aspirated. The examination of pleural aspirate revealed protein 6 g% and numerous cells, mostly polymorphs. Culture of the fluid showed growth of Klebsiella species.

Fiberoptic bronchoscopy showed a fungating growth just below the carina obstructing the left main bronchus. Biopsy from the growth revealed moderately differentiated squamous cell carcinoma on histopathological examination.

### Discussion

Haemorrhagic pleural effusion with recurrent rapid filling up is a common presenting feature of primary lung cancer. However, occurrence of spontaneous pneumothorax with or without fluid in pleural cavity is seen rarely in lung cancer<sup>1-6</sup>. The presence of malignant neoplasm is around 1.4% in cases of pneumothorax<sup>7</sup>, whereas spontaneous pneumothorax develops in approximately 1 of every 2,000 patients with lung cancer<sup>8</sup>. It is more common to find pneumothorax in patients with metastatic deposits in lung, particularly from osteogenic sarcoma.<sup>7,9,10</sup> This is probably due to the lesser degree of necrosis in peripheral primary bronchogenic tumours as compared to extremely necrotic lesions of metastatic osteogenic sarcoma which on occasion blow out into the pleural space.<sup>5,9</sup> The present case revealed a centrally placed growth in left main bronchus which is unlikely to involve the pleura directly. The possibility of iatrogenic pneumothorax was ruled out as the patient denied history of pleural aspiration before admission to this hospital. Possibly, the valvular obstruction caused by the neoplasm formed an air-cyst which ruptured in to the pleural space leading to occurrence of pneumothorax in this case. Many of the earlier reports<sup>4-6,9</sup> postulated rupture of an obstructive bulla into the pleural cavity as the most likely mechanism of the development of pneumothorax in primary lung cancer.

Although rare, it is necessary to bear in

mind the diagnosis of lung cancer as a cause of pneumothorax especially in persons of more than 40 years of age among whom there is a high frequency of bronchogenic carcinoma.

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200	Title of the Article	A RARE PRESENTATION OF LUNG CANCER
201	Journal Title	The Indian Journal of Tuberculosis
203	Journal Abbreviation	
300	Author	Manoj K
301	Variant Authors	
310	Corporate Author	
315	Author Address	
202	Article Type	
490	Volume	42
491	Issue No.	October, 1995
492	Page No	231
493	Date (dd/mm/yyyy)	
601	Author Abstract	
600	Abstract	
620	Subject Descriptors	
621	Non-MeSH Descriptors	
100	ISSN	0019-5707
040	Language	English
	URL	

## DRUG RESISTANT TUBERCULOSIS IN INDIA - CLINICAL APPROACH

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### Introduction

Availability of powerful antimycobacterial drugs during the 5th and 6th decades of this century had led one to believe that tuberculosis could be effectively controlled. Some of the developed countries of the West had even hoped to eradicate the disease by the turn of the century. But events have taken a turn for the worse in the last few years. There is global concern about the rising incidence of tuberculosis. This has been largely contributed by the emergence of drug resistance and HIV infection. There is a threat of HIV epidemic exploding in India in the near future. This is bound to aggravate the existing grim situation especially that of drug resistant tuberculosis. But drug-resistant/tuberculosis is on the increase in this country even in HIV-negative patients.

The fate of bacillary positive cases under programme conditions in India is a matter for concern. At one year follow up of 406 and 292 cases in 1968 and 1974 respectively, about 10 per cent had died while 27 per cent remained sputum positive<sup>1</sup>. A recent retrospective analysis of 3357 patients (2306 of whom had received short course regimens) followed up for 6 to 36 months, showed that 28 per cent had died and 31 per cent were sputum positive<sup>2</sup>. Sputum conversion, therefore, was achieved in 41 per cent in 1993 compared to 63 per cent in 1968 and 1974<sup>1,2</sup>. Persistent sputum positivity has been attributed to the presence of drug resistance.

### Prevalence of drug resistance in India

There is enough evidence to show that both initial and acquired resistance to anti-tuberculosis drugs have increased. According to the earlier surveys of Indian Council of Medical Research,

initial mycobacterial resistance was 12.5% to S, 14.7% to H and 6.5% to both H and S<sup>3,4</sup>. Resistance to one or more drugs in patients with history of previous treatment was seen in 25% to H, 22.9% to S and 15.8% to both H and S<sup>3</sup>. Some later studies have corroborated the findings and demonstrated significantly higher drug resistance<sup>5-6</sup>. In Gujarat, primary resistance to H and S was shown in 13.9 and 7.4 per cent, while acquired resistance was present in 55.8% and 26.9% respectively<sup>7</sup>. There was no primary resistance to Rifampicin (R) but acquired resistance to R was seen in 37.3% and to both H and R in 33.6 per cent<sup>7</sup>. Primary resistance to R alone or along with other drugs was seen in about 2 to 4 per cent of cultures<sup>8,9,10</sup>.

Although the problem of multi-drug resistance (MDR) is not new, the rising resistance to both H and R is rather ominous: This obviously poses a threat to the National Tuberculosis Programme and institutional treatment of tuberculosis. The major cause of drug resistance is the inadequate and inappropriate treatment received by the patients. Besides the administrative and financial constraints, the problems are due both to the patients and the physicians. The one silver lining is the recent observation on the molecular basis of MDR-tuberculosis, that MDR is not due to a novel mechanism. MDR results from the same chromosomal mutation (or combinations) in strains displaying single or multiple drug resistance in both primary and secondary resistance cases and in patients' with HIV infection<sup>11</sup>.

### Emergence of drug resistance

Susceptible mycobacteria are killed within a few days of exposure to anti-tuberculosis drugs. But the treatment is continued for about 6 months to ensure elimination of different populations of mycobacteria-Survival of these other organisms

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or their ability to multiply in the presence of bactericidal concentrations of the drugs constitutes drug resistance. Resistance can, therefore, be established only by culture and drug susceptibility tests. But there are several clinical criteria which suggest the emergence of resistance in those patients who are given drug treatment. There is little to suggest 'initial' or 'primary' drug resistance in patients who do not give any previous history of drug treatment.

In a patient already on treatment resistance is suspected by the persistence of symptoms and sputum positivity (treatment failure). Although sputum negativity is generally achieved within the first 4-6 weeks of treatment, a period of about 12 weeks is allowed before one considers alteration in chemotherapy. Mycobacterial positivity is important to decide resistance because symptom persistence can occur due to lung destruction, secondary infections and other complications, even after the mycobacteria have been killed. The diagnosis of resistance is supported by the history of inadequate, interrupted and prolonged therapy, poor compliance and extensive disease. Drug susceptibility tests are required for making a definite diagnosis of emergence of resistance.

#### Approach to drug susceptibility testing

Drug susceptibility tests are tedious and costly. It takes several weeks before the results are available. Variable results are common unless technically standardized. It has been the common practice, therefore, to start chemotherapy without the susceptibility tests of initial culture<sup>12-15</sup>. This practice has been strongly discounted by others who believe that this contributes to the increase in the drug resistant strains<sup>6</sup>. While the practice in United States has changed towards initial drug sensitivity testing, it is an enormous task to adopt in India due to the non-availability of facilities, poor standardization, long delays and the cost. Since a large number of patients are seen and treated by clinicians outside the TB Control Programme, it is desirable that drug sensitivity is done in as many cases as possible. But one must never withhold the institution of anti-tuberculosis therapy and clinical guidelines should be used to decide the regimen pending the availability of test reports.

Newer technologies have become available and are being developed further to detect drug sensitivity in shorter periods. With the help of automated BACTEC system the results may be made available in 3 to 4 weeks<sup>17</sup>. High performance liquid chromatography (HPLC), PCR amplification and finger printing and the functional assay utilizing luciferase reporter phages are some of the other techniques<sup>18,20</sup>. It will be quite sometime before the techniques become available for routine clinical use even at the level of referral centres in India.

#### Management policy

Drug resistance in tuberculosis is easier prevented than treated. It is a "man-made" problem and is, thus, amenable to corrective action<sup>21</sup>. Adequate initial chemotherapy is most important in prevention. Fortunately, effective drugs are available for primary treatment of a newly diagnosed case. Treatment with a single drug, insufficient dosages and weaker combinations must be avoided. Treatment requires to be given for prescribed periods. Standard WHO guidelines are now available for national control programmes<sup>22</sup>. If the recommendations are strictly adhered to, the chances of development of resistance are minimal.

In general, the treatment policy is based on two main factors:

- i. Sputum status (positive or negative for acid fast bacilli)
- ii. Previous treatment history

Initial drug resistance in a new case is usually limited to one or two drugs.

I. *Community based approach for new cases*: The standard practice of using three-drug regimen (Rifampicin, Isoniazid and Pyrazinamide) for 2 months, followed by Rifampicin and Isoniazid for 4 months was found inadequate in USA in view of the increasing prevalence of MDR<sup>23,25</sup>. It was, therefore, recommended that patients in communities in which there is even a small risk (> 2 per cent) of single drug resistance, should be treated with 4 drugs until the results of drug-susceptibility testing are available<sup>25,26</sup>.

The WHO guidelines also envisage the initial 4 drugs (RHZE) for 2 months, followed by 2 drugs (RH) for 4 months<sup>22</sup>. Considering the fact that most studies on drug resistance from India reveal a much higher prevalence of resistance to one or more drugs it is prudent to stick to the recommendation.

*II. Treatment of Relapses and Treatment failures:* WHO defines relapse as tuberculosis in a patient declared cured by a physician in the past, while treatment failure is defined as sputum-smear positivity at 5 months or more after the start of chemotherapy<sup>22</sup>. Retreatment is initiated with 5 primary drugs ie. HRZE and S. Streptomycin is administered for the first 2 months while other drugs are continued for 3 months. Sputum is simultaneously sent for culture and susceptibility testing. Based on results of the sensitivity pattern, treatment may be altered in due course of time. Maintenance treatment is continued with RHE for 5 more months.

*III. Treatment of patients with multi drug resistance (chronic tuberculosis):* If a patient remains sputum smear positive at the end of retreatment, one needs to reconsider the choice of drugs. Sputum should be sent for culture and sensitivity testing and treatment altered. Change or addition of new drugs should be done after obtaining a careful history of drug intake. Following principles should be kept in mind:

- i. Never add a single 'new' drug. Add two or more drugs (preferably, one parenterally).
- ii. Add bactericidal drugs, as far as possible.
- iii. If most drugs have been previously used by the patient and no new drug is available, add those drugs which have not been used in the recent past.

In view of the complexities involved in retreatment, it is better decided by the specialists. Most of these patients may require from 4 or more drugs.

In spite of the best available treatment the outcome of MDR-tuberculosis involving resistance to R and H is dismal.

It is difficult to prescribe standard regimens for MDR-tuberculosis cases. The treatment requires to be individually tailored. Addition of newer drugs (e.g. Ofloxacin, Ciprofloxacin, Amikacin) or the other unused second line drugs (Etlionamide, Cycloserine, Aminosalicic acid, Kanamycin etc.) is often required. All these drugs are costlier, more toxic and less efficacious than the first line drugs. The total duration of treatment is often prolonged. Parenteral drugs are continued for 3 to 6 months and the others for upto 24 months or so. But the outcome is discouraging and relapses are frequent. Therefore, a cautious approach and careful monitoring is required. Resectional surgery, as an adjunct to medical therapy, may be considered in patients with localized disease and good cardio-respiratory function<sup>28</sup>.

*Multi drug resistant tuberculosis in HIV positives and AIDS patients:* Treatment of MDR-tuberculosis in immuno-deficiency patients is even more discouraging<sup>29</sup>. The guidelines for initiation and continuation of treatment are similar to those recommended for HIV negative patients<sup>30</sup>.

Drug resistant tuberculosis is an iatrogenic condition due to management failure<sup>31</sup>. There is nothing more revealing than the report from United States on deviation from management practices and established guidelines which might have been associated with the emergence of multi-drug resistance and adverse medical sequelae<sup>32</sup>. Even in that country, there was an average of 3.93 errors per patient. The situation in this country, with innumerable problems of management and an overwhelming prevalence of disease, is even more grim. A multi pronged approach employing new strategies, better management, greatly enhanced budgets and stricter supervision along with educational measures is, therefore, imperative.

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200	Title of the Article	DRUG RESISTANCE TUBERCULOSIS IN INDIA CLINICAL APPROACH
201	Journal Title	<b>The Indian Journal of Tuberculosis</b>
203	Journal Abbreviation	
300	Author	S.K. Jindal
301	Variant Authors	
310	Corporate Author	
315	Author Address	
202	Article Type	
490	Volume	42
491	Issue No.	October, 1995
492	Page No	233
493	Date (dd/mm/yyyy)	
601	Author Abstract	
600	Abstract	
620	Subject Descriptors	
621	Non-MeSH Descriptors	
100	ISSN	0019-5707
040	Language	English
	URL	

### BOVINE IMMUNODEFICIENCY VACCINES

Simian, bovine and feline immunodeficiency viruses have been found to exist in these animals without causing disease in them. However, the human immunodeficiency virus, in contrast, causes a gradual suppression of the immune system, leaving human beings vulnerable to a variety of infections. And eventual death, though not invariably, On the analogy of the BCG vaccine, prepared from a *virus-fixe* strain of a bovine *M. tuberculosis*, used extensively to prevent the occurrence of frank tuberculosis among human beings, some bovine immunodeficiency virus (BIV) vaccines have been prepared in the U.S.A. for possible human AIDS prevention trials. Actually, around 42 likely vaccines are up for such consideration and the BIV Vaccines are just one among them. In the preparation of the BIV vaccines use has been made of non-disease producing clones. To be effective, the vaccine must increase the CD 4 cell (helper cell) counts after receiving signals from the CD 8 cells (suppressor cell) in the blood. Besides these counts, Beta 2 microglobulin, Neopetrin and BCR levels are also measured during the follow up after vaccination.

### TEEN AGE SMOKING

In the western world, especially the U.S.A., the smoking habit had been on a gradual decline because of the sustained anti-smoking campaign waged for over two decades. The mega tobacco companies had, therefore, turned their attention towards developing countries to make up for the loss of cigarette sales - and profits - in the advanced countries. In recent years, rising concern had repeatedly been expressed at the alarming rise in smoking in poor countries, especially in the vast rural areas.

The above noted scenario appears to have changed. A recent federally funded study in the U.S.A. has found out that smoking among teenagers in the U.S.A. has risen to 30 per cent over the past several years. This survey done among 50,000 students found that smoking among 8th graders (13-14 years old) had increased by one

third over a period of 4 years; among the 10th graders, it had risen to 25 per cent from 20 per cent over the same period and nearly 25 per cent of the 10th graders volunteered the information that they had been smoking during the preceding 30 days. Among the 12th graders, 31.2 per cent had smoked within the preceding 30 days, up from 27.8 per cent four years ago.

Apart from that, a very disturbing revelation, got from "leaked" research records of some leading tobacco companies has shown that the highly addictive properties of Nicotine had been known to them for long. Faced with reducing members of adult smokers, these companies had deliberately increased the Nicotine content of their popular brands of cigarettes in order to keep the current smokers "hooked", and then advertised that the tar content of their cigarettes had been reduced to minimize the risk of lung cancer. Simultaneously, an ingeniously devised campaign was started to reach the impressionable teenagers. A multibillion dollar budget was set apart for the purpose. It now appears that their strategy has paid off, at least for the present.

The Clinton Administration has taken some immediate steps in the last few months. It has been proposed that Nicotine use should be regulated as a "categorized" drug by the Food and Drug Administration (FDA) and legislation has been introduced to control cigarette advertisements - especially the subtle ones aimed at teen agers, retailer licensing and vending machine sales. Also on the cards is a further steep tax on cigarettes. Around 90 million dollars that will thus be raised are expected to be spent on health care for the poor (medicare), stepped up anti-smoking education and research on smoking related diseases. Teen age smoking could become another epidemic and health hazard for the developing world, if happenings in the U.S.A. are any guide.

### JOINT HEALTH SERVICES

This journal, time and again, has editorially recommended the need and desirability of enlisting the help and support of the private sector in the gigantic task of setting up an adequate network

of health institutions in the country. The central Ministry of Health and Family Welfare is understood to have recently invited private sector participation in establishing and running a vast health services system in the country, both urban and rural. The number of dispensaries, polyclinics, upgraded block level hospitals and specialized tertiary health institutions in the country is likely to shoot up sharply in the near future, if the plan gets through. Government would be a partner in the endeavour and would be expected to contribute

land, buildings, equipment and even capital while the private sector would take care of providing facilities, running expenses and ensuring high work standards. Since there are serious misgivings, a dialogue has been started between industry, voluntary sector and the Government to work out all the details. Participation of foreign investors, international organisations and NRIs is being anticipated. Besides, it is envisaged that the joint services would provide for both allopathic and the indigenous systems of medicine.

### BOOK REVIEW

**Text Book of Pulmonary Medicine - D. Behera, First Edition 1995.**  
*Jaypee Brothers Medical Publishers (P) Ltd. New Delhi,*  
*ISBN 81-7179-409-2, 34 Chapters with Index, pages 625,*

This is a book which I can unhesitatingly recommend to postgraduate students and specialists in respiratory medicine. It is well written and authentic. The publishers also have done a satisfactory job, apart from some printing lapses.

A text book is perforce dated and recent advances cannot usually be included. A desirable feature of text books is that knowledge is condensed and put in a perspective. This book has brought in the available knowledge appropriately, but the perspective sometimes gets lost or is occasionally found at a place different from where the knowledge has been placed. For example, the chapter on "Normal Respiratory Physiology" mentions the alterations in disease states, but the applications are given in a later chapter entitled "Pulmonary Function Tests". The chapter on "Drugs" fails to include antituberculosis drugs, and even the antimycobacterial properties of Quinolones are not included, thus, watering down a very important aspect of treatment. These days lots of pulmonary patients are being given Quinolones for short periods. When some of them later turn out to be suffering from tuberculosis, the prospect of resistant mycobacteria increases.

There is welcome stress on upper respiratory tract and its diseases but, curiously enough, tuberculosis has not received the space and attention it deserves. In the paras on pathogenesis, the non-inclusion of the fundamental works of Rich, Canetti and others does not give a clear picture and the young clinicians, who will constitute majority of readers may get lost in the micropathology without appreciating macropathology. The paras on bronchiectasis do not even mention parenchymal tuberculosis as a cause, even though most cases of pulmonary tuberculosis treated by chemotherapy will have residual bronchiectasis.

An impression remains that the book is directed more to the research worker, who will no doubt find it very useful and informative. It is hoped that future editions will be oriented a little more to the needs of the clinician.

**S.C. KAPOOR**

## **NEWS & NOTES**

### **NEW TB SEAL**

The Tuberculosis Association of India has selected six motifs of Gwalior Fort, Mysore Palace, Parliament House, Taj Malial, Golden Temple and Golconda Fort as designs for the 46th TB Seal Campaign. It is expected that the Seal will prove popular.

### **State Conferences/Seminars/Workshops**

#### **TB & CHEST DISEASES CONFERENCE, ANDHRA PRADESH**

The 22nd Andhra Pradesh TB & Chest Diseases Conference was held on 8th and 9th July, 1995 at Hyderabad. The Conference was presided over by Dr. K.J.R. Murty, Chairman, Technical Sub-Committee of TB Association of Andhra Pradesh. The Conference was inaugurated by Sri P. Indra Reddy, Hon'ble Minister for Home, Jails and Fire Services, Andhra Pradesh. The theme of the Conference was "Reappraisal of the National TB Programme". About 200 delegates attended the Conference.

#### **KARNATAKA STATE CONFERENCE**

The 10th Karnataka State Conference on Tuberculosis and Chest Diseases was held on 19th August, 1995, at Yavanika Auditorium, Bangalore. The Conference was inaugurated by His Excellency Sri K. J. Ramiah, Governor of Karnataka and was presided over by Sri H.C. Mahadevappa, Hon'ble Minister for Health and Family Welfare, Government of Karnataka.

#### **TUBERCULOSIS WORKERS CONFERENCE, GUJARAT**

The 18th Gujarat State Tuberculosis Workers Conference was held on 24th September, 1995 at the Cama Hall in the Civil Hospital Campus, Ahmedabad. The theme of the Conference was "The cost benefit ratio in management of Tuberculosis".

### **SEMINAR ON TUBERCULOSIS**

The TB Association of Andhra Pradesh, in collaboration with the TB Association of Hyderabad District and the I.M.A., Hyderabad City Branch, organised a Seminar on Tuberculosis on 24th June, 1995 at I.M.A. Hall, Koti, Hyderabad. The Seminar was inaugurated by Dr. T. Babu Rao, Director of Health Services, Andhra Pradesh and Dr. Balbeer Singh Yadav, President of the I.M.A., Hyderabad, presided over the function. About 90 doctors participated in the Seminar.

### **WORKSHOP ON CHEST X-RAY**

The Dist. TB Association, East Godavari and the Dist. TB Centre, organised a "Workshop on Chest X-ray" on 23rd July, 1995 at Kakinada. Dr. Apparao, District Medical and Health Officer was the Chief Guest while Dr. G. Baburao, Prof. & Head of the Dept. of TB & Chest Diseases, Guntur Medical College, Guntur was the Guest of Honour.

#### **ANNUAL GENERAL MEETING, ANDHRA PRADESH**

The 31st Annual General Meeting of the TB Association of Andhra Pradesh was held on 8th July, 1995 at Hyderabad. The meeting was presided over by Dr. I. Ranga Rao, Vice-Chairman of the Association. During the meeting, the Honorary General Secretary of the Andhra Pradesh TB Association requested all the District Tuberculosis Control Officers and Honorary Secretaries of all the District TB Associations to organise health education activities and also increase the sale of TB Seals in their districts. Dr. K.J.R. Murty proposed the Vote of Thanks.

#### **NATIONAL CONGRESS ON RESPIRATORY DISEASES**

The 15th National Congress on Respiratory Diseases, sponsored by the Indian Chest Society, will be held from 1st to 4th December, 1995 at Jamshedpur. For further details kindly contact Dr. R.N. Sharan, Organising Secretary, XVIII N.C.R.D., A.D.M. Hospital, P.O. Baridih, Jamshedpur-831017.

ABSTRACTS

Vol. 42 No. 4

October 1995

Schwartz J. Weiss ST. *The relationship of dietary fish intake to level of pulmonary function in the first National Health and Nutrition Survey (NHANESI). Eur Respir J 1994; 7: 1821.*

Using data from the first National Health and Nutritional Examination Survey (NHANESI) the authors examined the relationship between the effect of chronic dietary fish intake to level of pulmonary function. A detailed subsample of 2526 adults had a medical history questionnaire, that included a 24-hour dietary recall, and performed spirometric examination. Logarithm of forced expiratory volume in one second (FEV<sub>1</sub>) served as a dependent variable in regression analysis which included an adjustment for height, age, cigarette smoking and gender. When added to the regression model including the above variables dietary fish intake showed a protective association with FEV<sub>1</sub>, (OR=0.008-0.004, p=0.028). When smokers were excluded from the analysis, the effect of fish intake on pulmonary function appeared to increase slightly (p = 0.010X ± 0.006, p=0.61). These data suggest that chronic fish dietary intake is associated with higher levels of pulmonary function and is consistent with the hypothesis that eicosapentanoic acid which predominates in marine fish tends to counteract and inhibit the uptake and incorporation of arachidonic acid and membrane phospholipids and dilute arachidonic acid as a potential substrate, for oxidation.

AshwK Shah

Hanna Soini, Erik C. Botgcr and Matti K. Viljanen: *Identification of Mycobacteria by PCR-based sequence determination of 32 - Kilodalton Protein Gene, Journal of Clinical Microbiology 1994, 32, 2944.*

Polymerase chain reaction combined with restriction enzyme analysis is a rapid alternative for identification of mycobacterial species. Recently

it has been seen that the 32-KDa protein gene is specific to mycobacteria and some variation in the nucleotide sequence of this gene has been noticed among mycobacterial species. In this study, a part of the sequence of this gene was studied to ascertain whether this information could be used for PCR-based identification of mycobacterial species. Out of 24 mycobacterial strains representing 10 species, it was found that the sequence of tested members of *M. tuberculosis* complex were identical to each other. Difference was found in the sequence of *M. avium* and *M. intracellulare* species like *M. kansasii*, *M. gastri*, *M. gordonae* and *M. malmoense*, had a unique specie-specific sequence. The authors proposed that the 32-KDa protein gene, having variation in the nucleotide sequence can be used for PCR-based identification of mycobacteria.

V.K. Chalu

Barbara S. Reiser, Alice M. Gatson and Gail L. Woods: *Use of Gene-Probe Accu-probes to identify Mycobacterium avium complex, M. kansasii, and M. gordonae directly from BACTEC TD Broth Cultures. Journal of Clinical Microbiology, 1994, 32, 2995.*

Isolation and identification of mycobacteria have been a very slow process. The radiometric BACTEC System detects growth most rapidly. The utility of Gen-Probe Accu-Probes for identification from BACTEC TB 12B vials containing acid fast bacilli has been evaluated in this study. Culture results for 11,375 clinical specimens were reviewed retrospectively. On repeat testing it was found that additional number of specimens gave positive results for various species of mycobacteria. As such, use of BACTEC TB-Accu-Probe combination has been found to be a simple, reliable method for the rapid identification of mycobacteria most commonly encountered in the laboratory.

V.K. Challu

Fabio O. Sanchez et al: *Immune Responsiveness and Lymphokine production in patients with Tuberculosis and Healthy Controls. Infection & Immunity, 1994, 62, 5673.*

Observations from earlier studies have indicated that patients with tuberculosis frequently have depressed cellular and increased humoral immune responses against mycobacterial antigens. In this study, profile of immune responsiveness that differentiates patients with tuberculosis from healthy tuberculin positive controls was studied. Forty-five patients with newly diagnosed, bacteriologically confirmed pulmonary TB were studied besides sixteen healthy, tuberculin positive adults. None of them were positive for HIV. The results confirmed that patients with TB had altered immune responsiveness to mycobacterial antigen compared with tuberculin positive healthy subjects. The general pattern of response observed in the two groups showed that tuberculin positive healthy controls exhibited a vigorous cell-mediated immune response while the majority of TB patients showed low T-cell reactivity and augmented humoral responses. The different patterns of immune responsiveness is an important contribution to the comprehension of the pathogenesis of TB and future studies could find new possibilities for therapeutic intervention by further exploring the nature of alterations of the immune response in TB patients.

Cegielski J.P. et al: *Tuberculous pericarditis in Tanzanian patients with and without HIV infection. Tubercle & Lung Dis, 1994, 75, 429.*

Clinically severe pericarditis associated with HIV infection is increasingly common in Africa. This study compared the etiology and outcome of pericarditis in HIV infected and non-HIV-infected patients with focus on large pericardial effusions as they tend to be more serious. Out of 62 patients enrolled during 6 months, 28 were confirmed to have pericardial effusion. Pericardial fluid and /or tissue from 22 patients was analysed. Two thirds of these patients were HIV positive. *Mycobacterium tuberculosis* was isolated on culture from pericardial tissue of 12 HIV positive and 8 HIV negative patients. Tuberculosis was found to be the predominant cause of large pericardial effusion in HIV infected patients. The authors are

of the opinion that HIV infected patients with large pericardial effusions may be treated empirically for tuberculosis where microbiological studies are not routinely available and patients are monitored for improvement. However, initial diagnostic evaluation is required for HIV negative patients.

R. Ramachandran

Anglaret, J. et al: *Empiric antituberculosis treatment: benefits for earlier diagnosis and treatment of tuberculosis. Tubercle and Lung Disease, 1994, 78, 334.*

If the classical diagnostic criteria are followed i.e. demonstration of *M. tuberculosis* or a characteristic biopsy appearance, it may take a long time before diagnosis is reached and ATT started. This delay may be critical, especially in HIV infected individuals, with adverse consequences on bacillus transmission and survival/cure. On the other hand, empirical anti-tuberculosis treatment (EATT) with a Rifampicin based regimen may be effective in other conditions, leading to overdiagnosis. In order to test the value of EATT, twenty consecutive suspected patients, pulmonary and non-pulmonary, in whom 3 smears and biopsy of accessible lesions did not give a positive result, were started on EATT. Ten of them were given RHZE, while in the other ten, Rifampicin was not included i.e. they were put on HZE. An important precaution was that cultures were put up from any accessible organ etc., such as bronchial lavage fluid, liver, lymph gland, CSF or bone marrow aspirate etc. It was seen that *M. tuberculosis* grew in culture in ten of the patients, who all responded well to EATT. Another four improved clinically and radiologically on this treatment, while six did not respond and were finally diagnosed as non-tuberculous. The response in all patients who were proven to be tuberculous during the course of treatment was uniform irrespective of the regimen used.

It is concluded that EATT is useful and helps in resolution of the disease and in prevention of bacillary transmission and serious deterioration. HZE is considered better, because of its specific action.

S.C. Kapoor

Trnka L., Dankova, D. and Svandova, E: *Six Year's Experience with the Discontinuation of BCG Vaccination. Tubercle and Lung Disease; 1994, 75, 348.*

In 1986, mass BCG vaccination was discontinued in one area in the Czech Republic with 30,000 annual accretion of infants. Non-vaccinated children from this area were tuberculin tested every two years and those with intensive contact with poultry were also tested with *M. avium intracellulare* complex (MAC) sensitin. 1,90,874 children were tested during 1986-93, of whom 36 were found to be infected with MAC and 27 had developed active MAC disease. As against this, no case of MAC infection occurred among the BCG vaccinated children. The incidence of tuberculosis among vaccinated was 0.9/100,000 pulmonary and 0.2/100,000 lymphadenopathy, while in the non-vaccinated, the rate was 4.8 and 0.7.

It is suggested that prevalence not only of tuberculosis, but also of MOTT should be considered before deciding to discontinue mass BCG, as BCG appears to confer protection against MOTT also.

*S.C. Kapoor*

S. Rajasekaran et al. *Primary Lung Cancer in Non-tuberculosis Upper lobe lesions Ind. JI. Ch. Dis. & All. Sci.; 1994, 36, 55.*

Tuberculosis is the commonest misdiagnosis when upper lobe lesions are seen on X-ray. With the advent of fiberoptic bronchoscopy, it is now possible to elucidate the diagnosis in a large proportion of patients with upper lobe lesions and negative sputa for AFB. For this purpose, one hundred and fifty (150) such patients aged over 30 years and with at least 2 negative reports for AFB on smear microscopy were selected for investigation. Patients with complications like diabetes, renal or cardiac failure, etc. were excluded from the study as were those on AIT, for whatever reasons. The lesion was right sided in 79 and left sided in 71 cases. Lesions seen included consolidations, coin shadows, mass lesions

and cavitation. Lymphadenopathy (paratracheal or hilar) was seen in 59 cases.

Sixty-two patients were found to have primary bronchogenic carcinoma (squamous cell in 42, large cell in 16 and small cell in 3 and adenocarcinoma in one non-smoking female). Twenty-one had intraluminal visible growths on bronchoscopy while blind biopsies in the bronchi of the affected regions yielded diagnosis in 37 patients.

*S.C. Kapoor*

K.A. Qureshi. *Domestic Smoke Pollution and Prevalence of Chronic Bronchitis/Asthma in a rural area of Kashmir, Ind. Ch. Dis. & All. Sci.; 1994, 36, 61.*

Screening of adults in two randomly selected villages in Kashmir valley showed overall prevalence of 7.7% of chronic bronchitis and 1.96% of asthma. Chronic bronchitis was seen to occur in 12.21% of females of the Gujjar community. This high prevalence is attributed to exposure to domestic smoke pollution, poor socio-economic conditions, illiteracy and overcrowding.

*S.C. Kapoor*

J. Whig, B. Bansal and R. Mahajan. *Work Place Challenge: Spirometric Response in Polyurethane (Isocyanate) Plant Workers. Ind. JI. Ch. Dis. & All. Sci.; 1994, 36, 73.*

FEV was studied in 114 workers (of a rail coach factory) who were directly exposed to Isocyanate, before starting the day's work, two hours later and after 6-8 hours of work, 16% showed fall in FEV, (over 20%) at 2 hours and this persisted at 6-8 hours in 6%, while 10% showed a significant (20%) fall after 6-8 hours. This underlines the importance (20%) fall after 6-8 hours. This underlines the importance of Isocyanate as a cause of industrial asthma.

*S.C. Kapoor*