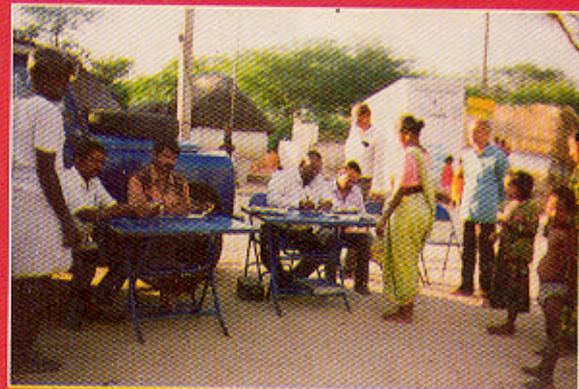
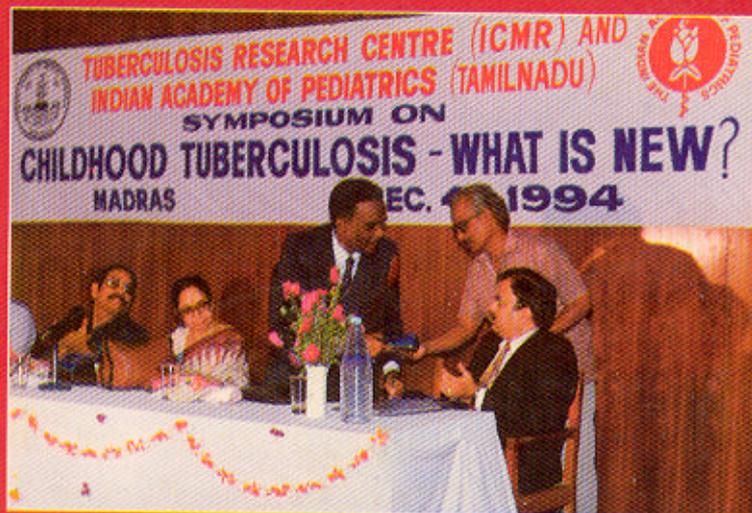


# TUBERCULOSIS RESEARCH CENTRE

CHETPUT, MADRAS - 600 031

## REPORT ON RESEARCH ACTIVITIES DURING 1994



INDIAN COUNCIL OF MEDICAL RESEARCH  
NEW DELHI

**TUBERCULOSIS RESEARCH CENTRE  
CHETPUT MADRAS-600 031**

**REPORT ON RESEARCH ACTIVITIES DURING  
1994**



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**The contents of this report should not be reviewed,  
abstracted or quoted**

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## PREFACE

The Centre is continuing its research activities with a multi-disciplinary approach with an aim to evolve methodologies relevant to the National TB Control Programme. With the resurgence of HIV infection and problem of AIDS among the high risk group in the population, it was felt mandatory for this Centre to evolve methods in operationalising the robust regimens of chemotherapy developed at this Centre to optimise the efficiency of the programme in achieving higher cure rates and better drug compliance. To this end, studies were initiated and are in progress to strengthen the existing drug delivery system and to create greater awareness of the disease among the community. Effective participation of the community in the control programme has been attempted by undertaking studies aimed at sensitizing and creating a demand for health care delivery in respect of tuberculosis. Accordingly, different methodologies are being elucidated to suit the local conditions be it urban, semi urban, rural or tribal areas. Some of the studies completed in this respect have clearly shown that these strategies could be applied in the existing National TB Control Programme, without much deviation from the original protocols and policies for treatment, for their execution. However, these studies need to be extended to more areas in the country to explore their feasibility on a large scale application.

Keeping in line with the original aims and objectives of this Centre, randomised controlled clinical studies are being pursued in pulmonary and extra-pulmonary forms of tuberculosis in order to evolve highly effective and operationally feasible regimens of chemotherapy. Results of studies completed have shown these SCC regimens to be highly effective in the treatment of patients with disease caused by isoniazid resistant strains of tubercle bacilli with an added advantage of drugs being administered orally without recourse to injectable drugs. This could be a major contribution to the programme for application in rural areas where there could be constraints in administering injections and more importantly could avoid transmission of infection with HIV and hepatitis viruses. Preliminary results of the study with split double drug combinations of anti tuberculosis drugs administered on alternative days have been encouraging with a high efficacy and possibility of better drug compliance due to lower rate of adverse reactions and reduced bulk of drugs. Studies are also being continued in respect of management of failures to treatment with short course regimens due to multi-drug resistant strains of tubercle bacilli and relapses among patients who were successfully retreated with short course

chemotherapy. With the paucity of information on quality of life of patients with pulmonary tuberculosis, it has been found necessary to conduct studies with well designed and structured protocols. The results of these studies could throw light on the proper aftercare and rehabilitation of patients with various degrees of involvement of the lungs and severity of the disease, after adequate counselling and proper advice.

Considering the importance of management of pulmonary tuberculosis in children, a study is ongoing to investigate the regimens of shorter duration of 9 and 6 months that could help to formulate uniform policies of treatment by the paediatricians.

The available results of study of brain tuberculosis have revealed that short course chemotherapy could be highly effective and also have thrown light on the diagnostic aspect of the disease without resorting to major surgical intervention by applying non-invasive procedures such as brain scan. Studies on this aspect are being continued to find out the feasibility of adopting minimal invasive procedures such as stereotactic surgery and CT guided biopsies of the brain tissue for evidence of the disease which are done in collaboration with the Institute of Neurology at Government General Hospital, Madras.

Although cutaneous tuberculosis is considered to be a rare clinical entity, a study is in progress to establish the diagnostic criteria. The studies of this nature have relevance to the clinicians for proper management of paucibacillary clinical entity.

A study of multi bacillary leprosy, with multi drug therapy with rifampicin-containing regimens had been conducted and long term follow up of patients has yielded valuable information on the efficacy of the regimens. The study is of clinical significance for the National Leprosy control/eradication programme since there is paucity of information on the efficacy of the multi-drug therapy of lepromatous leprosy. On the analogy of a study on paucibacillary skin lesions in tuberculosis, a study has been initiated to evolve diagnostic criteria in paucibacillary forms of leprosy.

The division of Bacteriology of this Centre is engaged in research with newer anti tuberculosis drugs. **In vitro** and **in vivo** activities of some of these drugs are being studied using the standard strains of **M.tuberculosis** and clinical isolates from patients with pulmonary tuberculosis. A multicentric study with WHO assistance is in progress to study the early bactericidal activity of anti tuberculosis drugs in patients with newly-

diagnosed sputum positive pulmonary tuberculosis. Drugs such as rifampicin and Ofloxacin are being investigated in order to evolve highly effective combinations of these drugs along with other drugs such as isoniazid and pyrazinamide. Studies to evaluate the **in vitro** activities of ofloxacin and ampicillin/sulbactam (a b-lactamase inhibitor) have revealed that the combination could be beneficial in the management of drug resistant tuberculosis and as such, could add to the armamentarium of new drugs in the treatment of multi drug resistant tuberculosis. As a follow up of **in vitro** experiments, **in vivo** action of the combination of ofloxacin and ampicillin/sulbactam in comparison with rifampicin and isoniazid are being carried out using animal models. Rapid methods for drug susceptibility testing of **M.tuberculosis** are being investigated using a simple slide culture technique and a luciferase reporter phage assay. These techniques, if established, have potentials for application under programme conditions for proper management of patients, large scale survey of the prevalence of drug resistance which could help in formulating proper treatment regimens and surveillance of drug resistance which could be a useful parameter for assessing the efficiency of the treatment programme.

Biological characterization of isolates of **MAIS** and **M.fortuitum** complex from clinical specimens and environment from the BCG vaccine trial area in Chingleput district have been made. The results of this study could be of use in the interpretation and significance of the skin sensitivity to mycobactins other than PPD-S observed in the trial area. More information on this aspect is made available through **in vivo** experiments in guinea pigs infected with MAIS complex isolates from soil and clinical samples from the same area. Studies to elucidate the modulations in immune responses in guinea pigs infected with **M.fortuitum** complex isolates of clinical specimens and environment are in progress. Plasmid profile of MAIS isolates is being studied which could be of help to identify markers for strains isolated from different sources.

A study of neopterin levels as a marker of CMI in pleural effusion have been carried out which could help in the understanding of immunopathology of this clinical entity. Simple methods have been developed for estimation of ofloxacin in body fluids which are of non invasive nature using saliva and urine samples.

Bioavailability (Bioequivalence) of anti tuberculosis drugs have gained importance in recent years with the introduction of double- and triple-drug formulations and as such, the combinations available in the market are being investigated.

Biochemical aspects of tubercle bacilli relating to the action of drugs on them and responses of the host mechanisms to the infection are being studied. In particular, biochemical and pharmacological studies relating to the mechanisms of development of drug resistance are being carried out.

Immunological studies were carried out to evaluate the usefulness of Antigen 6 and 38 KDA for diagnosis of infection. Furthermore, purification of antigenic components of tubercle bacilli is being attempted in search of better immuno-diagnostic agents.

With one of the areas of thrust in tuberculosis research being development of immunodiagnosics and molecular biological tools, efforts are being made to develop DNA probes which could be specific for **M.tuberculosis** infection. Another area that is being identified is to initiate research in immunodiagnosics to differentiate infection from disease and recent infection from past infection. Accordingly, efforts are being made from the immunological and molecular biological angles. Family studies using HLA and related molecular biology tools are being carried out among patients and also in a sample of the population. These studies could establish the linkages of immune responses to HLA and the role of HLA class II genes and their products on immunity to tuberculosis.

Immunopathological studies are being carried out in cutaneous tuberculosis to understand the pathogenesis of the disease. Experimental studies using animal models are being carried out to understand the mechanisms of evolution of mycobacterial granulomas and also fibrogenesis in tuberculosis.

Epidemiological studies were carried out to follow up the sputum negative but X-ray positive cases (?suspects) for their symptomatology and bacteriological profile.

A methodology for surveillance of tuberculosis is being carried out which could be adopted on a national level. Surveillance of individuals infected with HIV for development of tuberculosis as a long term follow up study is being continued. Further, periodic anonymous and unlinked screening of patients with pulmonary and extra-pulmonary forms of tuberculosis is carried out to study the trend of HIV infection (point prevalence) among patients with tuberculosis. This is an exercise of importance from the epidemiological point of view and could contribute to the knowledge of dual infection with HIV and TB. Multicentric study to

develop diagnostic criteria in childhood TB is ongoing in centres identified in Madras city.

A community-based study of the socio-economic impact of lymphatic filariasis funded by WHO-TDR unit is in progress. Preliminary work for a community-based study on the effectiveness of DEC-medicated salt in the prevention of Adeno Lymphangitis (ADL) attacks and cutting transmission of the disease is underway. Studies for estimating attack rates of typhoid in the community are also being planned as a preamble to an Indo-US collaborative research project with a new anti-typhoid vaccine.

The Centre conducted CME programme on Childhood TB for the benefit of medical practitioners and postgraduates in medicine.

The Centre has been identified by the National Informatics Centre, Delhi, to establish a national database on tuberculosis. The Library and Information Systems have been upgraded with the availability of a new electronic link provided by ICMR through RENNIC services of NICNET. Speedy literature searches can now be conducted using this medium in addition to the CD-ROM based MEDLINE services already available at this Centre.

In conclusion, I wish to express my sincere gratitude to all my colleagues and members of staff of this Centre and gratefully acknowledge the untiring and unstinted support I have received from them which has enabled the Centre to nurture the research activities considered as of high quality and conforming to the international standards with impeccable and unimpeachable results accepted by the scientific community.

**(Dr.R.Prabhakar)**  
Director

# STAFF MEMBERS

AS ON 31.12.94

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Director,  
Tuberculosis Research Centre,  
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# **ETHICAL COMMITTEE**

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Justice (Retired),  
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## **Members**

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V.H.S. Hospital,  
Madras.

Prof. K.N. George,  
Director,  
Madras School of Social Work,  
Madras.

Dr. (Mrs.) Lalitha Kameswaran,  
Former Vice-Chancellor,  
The Tamilnadu Dr. M.G.R. Medical University,  
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Prof.K.Jagannath	Medicine	Director, Institute of Thoracic Medicine, Madras.
Dr.I.Kandaswamy	Radiology	Professor of Vascular Radiology, Government General Hospital, Madras.
Dr.R.Parthasarathy	Medicine	Former Deputy Director, Tuberculosis Research Centre, Madras.
Dr.S.Radhakrishna	Statistics	Director, Institute for Research in Medical Statistics (Madras Chapter), Madras.
Dr.P.S.Seshadri	Leprosy	Former Assistant Director, Central Leprosy Teaching and Research Institute, Chengalpattu.
Mr.P.R.Somasundaram	Statistics	Former Deputy Director, (Sr.Gr.), Tuberculosis Research Centre, Madras.
Prof.K.V.Thiruvengadam	Medicine	Former Professor of Medicine, Madras Medical College, Madras.
Dr.S.Thyagarajan	Ophthalmology	Former Professor of Ophthalmology, Government Rajaji Hospital, Madurai.
Dr.N.S.Venugopal	Ophthalmology	Former Superintendent, Government Ophthalmic Hospital, Madras.

## **OPERATIONAL RESEARCH STUDIES - COMPLETED**

### **Feasibility of utilisation of village Dais in improving DTP - A pilot study**

(Completed study, 1989-94)

"Dais" are the traditional birth attendants, conducting deliveries at home in the villages. A pilot study was undertaken in Sriperumbudur to explore the feasibility of utilising the services of Dais for the improvement of case finding and drug delivery in the District Tuberculosis Programme (see 1992 annual report). There are 44 villages with a population of 26,413 in Sriperumbudur taluk, Chingleput district, Tamilnadu. A voluntary health organisation ('Prepare') functioning in Sriperumbudur taluk, trains the village Dais to provide primary health care to the village community.

The Dais in these villages were given practical training, by a team consisting of a medical officer, a social worker and a clinic nurse, in identifying chest symptomatics and in collecting sputum specimens from them, for transportation to the Centre. One sputum specimen was collected from each chest symptomatic. The result during the study period of 5 years has shown that it is possible to train even an illiterate person like traditional birth attendant (Dais) for case-finding activity and for drug delivery at the door step of patients. Their service can be utilised in tuberculosis control programme in rural areas.

\*\*\*\*\*

### **Utilisation of NSS volunteers to augment the case-holding component of Madurai City TB programme**

(Completed study, 1993-94)

In an earlier study conducted in Madurai, it was observed that National Service Scheme (NSS) student volunteers can be initiated to various activities of city TB Programme. As a continuation of this, a study was started to utilise male student volunteers for improvising case-holding component of Madurai city TB Programme by (a) distribution of anti-TB drugs to pulmonary TB patients by students through centres closer to patients' home and (b) utilising students for defaulter retrieval.

Male NSS student volunteers from one of the Arts colleges in Madurai were selected for this study. These students were briefed on tuberculosis and various aspects of the TB programme. Field training in house visits and motivation of patients was given in addition. Their willingness to participate in the programme and their ability to communicate with the patient were assessed and found to be satisfactory.

Cases identified and diagnosed based on radiology and/or bacteriology were treated with an 8-month SCC regimen (2EHRZ<sub>7</sub>/6EH<sub>7</sub>). Drugs (pre-packed) were supplied to patients at the centre by student volunteers once a week. Defaulters were visited and motivated by NSS volunteers during the same week and if the patient continues to default, another visit was made by the volunteer in the successive week.

Twenty three patients were admitted to the study and they were due for drug collections on 792 occasions and 80% of these occasions patients collected the drugs on date. Patients were retrieved by students on 65 occasions. In all, 83% of the patients completed more than 80% of their treatment. Thus, it is feasible to utilise students force to improve case holding in the programme.

\*\*\*\*\*

### **Feasibility of involving literate youth for case-finding in tuberculosis in a tribal area in Tamil Nadu**

(Completed study, 1990-94)

In an effort to bring about community participation in a tribal area (Jawadu Hills), a study was undertaken to investigate the feasibility of involving literate youth (LY) volunteers in improving the District Tuberculosis Programme (DTP). The aim of the study was to find out the feasibility of utilising the services of the literate youths from each hamlet for identification of each symptomatic in the community, proper collection of sputum from them, drug distribution to sputum positive patients and documentation of drug supply.

A random sample of 4 health sub-centres (HSC) in Jamnamarathur Primary Health Centre (PHC) area was chosen so that the sample included both interior and roadside hamlets. All the 61 hamlets with about 11000 population in the 4 HSCs were covered. A total of 12 sputum positive pulmonary tuberculosis patients were started on treatment.

## **OPERATIONAL RESEARCH STUDIES - IN PROGRESS**

### **Utilisation of sub-centres for drug delivery and its impact on case-holding**

(Ongoing study 1993-96)

Patients' poor compliance for drug intake under programme conditions is attributed to many reasons and one important factor identified is the inability of the patient to attend PHC due to long distance of PHC from patient's residence and consequent loss of wages. In this study, drug delivery was organised through the sub-centres situated closer to the patient's residence as a measure to improve compliance of patients. The study area selected was West Godhavari district of Andhra Pradesh. Twelve PHCs were randomly selected for the study and six of those were further randomly allocated to the intervention and the other six to non intervention areas. These centres were distributed in tribal, upland and delta areas. As a preliminary measure, training on all aspects of tuberculosis and the programme was given to the PHC staff including pharmacists and MPWs in charge of sub-centres.

In the study centres when a treatment card is opened, for all newly diagnosed cases, the option of collection of drugs is given to the patient; to collect either from the nearest PHCs or the sub-centres. The MPW was asked to issue the drugs to the patients on a weekly basis from the sub-centre and in case of default, MPW will do the defaulter chasing by sending a message or by personal visit. In control centres, the drug supply was through main PHC only.

A comparison among admitted patients will be made between the study and the control centres on treatment completion rate, number of lost cases and number of defaults and action taken, to assess the efficacy of drug distribution through sub-centres. This study is in progress.

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## **Feasibility of involving Non Governmental Organisations (NGOs) in tuberculosis control programme**

(Ongoing study, 1994-95)

The Non-Governmental Organisations (NGOs) have the reputation of successfully implementing various welfare schemes. They are very effective in reaching out to the community and hence it would be worthwhile to attempt to involve these agencies in improving various components of the National Tuberculosis Programme, in view of their role as a link between the provider system and the community.

During 1994, the Centre in collaboration with the Tamilnadu Slum Clearance Board (TNSCB) has interacted with various NGOs, to explore the feasibility of involving the latter in tuberculosis control activities. The major thrust areas of this combined strategy has been the training of grass root level workers of the NGOs in tuberculosis control activities in order to:

- a) disseminate information on tuberculosis to the public through Community awareness campaigns,
- b) equip the animators and grass-root level workers with skills necessary to identify chest symptomatics, and refer them to the Centre for further investigations (case-finding) and
- c) evolve strategies for ensuring treatment compliance for the entire treatment period through measures the NGOs can evolve themselves, such as utilising local leaders, youth, women etc. (case-holding).

A training programme on tuberculosis for animators and grass root level workers of various NGOs was inaugurated on 21-12-94. A module for the training of animators and grass root level workers, developed by the Centre, was released during the function. In addition, three community awareness campaigns were conducted at YMCA (Otteri), Asha Nivas (Abiramapuram) and Gems Foundation (Velachery); forty slum dwellers, 500 domestic maids and 50 slum dwellers, respectively, participated in these camps.

The response of the NGOs with whom the Centre has interacted has been encouraging. They could serve as an effective task force which could be trained to supplement the tuberculosis control activities of the Government. This study is in progress.

## CLINICAL STUDIES - IN PROGRESS

### **Six month regimen for pulmonary tuberculosis with 2 double-drug combinations on alternate days for the first two or three months**

(Ongoing study, 1990-95)

Several highly effective short-course chemotherapy regimens of 6-8 months duration have been evolved for the treatment of pulmonary tuberculosis and in most of these regimens, four drugs, namely, rifampicin, isoniazid, pyrazinamide and streptomycin or ethambutol are given together in a single dose, either daily or intermittently. The number of tablets/capsules to be consumed in a single dose is therefore large and the incidence of adverse reactions such as arthralgia and jaundice is high with daily regimens. The Centre is investigating, both at Madras and its unit at Madurai, a regimen of rifampicin and ethambutol on one day and isoniazid and pyrazinamide on the next day, each combination given thrice a week for the first 2 or 3 months, followed by rifampicin and isoniazid twice a week for the next 4 and 3 months, respectively; so that, the toxicity is expected to be low, while the high level of efficacy is unlikely to be affected. These two regimens are to be compared with a control regimen of rifampicin, isoniazid, pyrazinamide and ethambutol given together in a single dose, thrice a week for the first 2 months, followed by rifampicin and isoniazid twice a week for the next 4 months.

The percentage of culture negativity based on 3 sputum specimens per month for patients with initially drug sensitive organism showed that, the sputum conversion was similar in all the three regimens.

Favourable response at the end of treatment was similar in all the three regimens. Adverse reactions were similar in all the 3 regimens and was not a serious problem.

All patients with favourable response are being followed up for a period of 5 years. Among patients with drug sensitive organisms initially, who have completed 12 months of follow up, bacteriological relapse requiring treatment occurred in 1.7%, 5.6% and 7.4% in the three regimens, respectively. This study is in progress.

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## **Controlled clinical trial of fully oral short course regimens in Madras and Madurai : follow-up phase**

(Ongoing study, 1986-95)

Earlier studies at this Centre have shown that short-course regimens of 5 to 7 months' duration are highly effective in the treatment of sputum-positive pulmonary tuberculosis. All these regimens were fully supervised, included intramuscular streptomycin and were studied in patients who had not received significant previous chemotherapy. These conditions are difficult to apply in the field and hence, a controlled clinical trial is in progress to investigate fully oral regimens of varying duration, rhythm of drug administration, frequency of attendance and supervision of drug administration at the Centre and its unit in Madurai. The regimens investigated include:

1. **2EHRZ<sub>7</sub>(ow)/6EH, (tm):** Fully unsupervised 8 months regimen.
2. **2EHRZ<sub>2</sub>/4EHR<sub>2</sub>(tw/ow):** Fully / partially supervised 6 months regimen.
3. **2HRZ<sub>2</sub>/4HR<sub>2</sub>(tw/ow):** Fully / partially supervised 6 months regimen.

All patients have completed treatment and the results at the end of chemotherapy have been presented in 1991 annual report. Patients with bacteriologically quiescent disease are being followed up for relapse. Among patients completing 40/42 months of follow up, 7%, 12% and 12% of patients with initially drug sensitive organisms and 11%, 26% and 15% of patients with initially drug resistant organisms in the three regimens, respectively, have had a bacteriological relapse requiring treatment. Two thirds of the relapses have occurred during the first 3-6 months after stopping treatment. The follow up is in progress.

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## Treatment regimens for patients who fail or relapse on short course chemotherapy

(Ongoing study, 1987)

Pulmonary tuberculosis patients who have been treated with short course regimens and who (i) show a serious clinical deterioration, (ii) have a persistent radiographic deterioration, (iii) have an unfavourable bacteriological response, or (iv) have a bacteriological relapse requiring retreatment, are prescribed an appropriate regimen depending on the last available drug sensitivity test results.

The chemotherapeutic regimens are as follow

1. 3EmbHRZ<sub>2</sub>/ 6/9RH<sub>2</sub> for patients with organisms sensitive to isoniazid and rifampicin.
- 2(a). 6SREmbZ<sub>2</sub>/6REmbZ<sub>2</sub> for patients with organisms resistant to isoniazid
- (b). 6KREmbZ<sub>2</sub>/6REmbZ<sub>2</sub> for patients with organisms resistant to streptomycin and isoniazid
- 3(a). 3S<sub>3</sub>EmbEthZ<sub>2</sub>/9EmbEthZ<sub>7</sub> for patients with organisms resistant to isoniazid and rifampicin.
- (b). 3K<sub>3</sub>EmbEthZ<sub>2</sub>/9EmbEthZ<sub>2</sub> for patients with organisms resistant to streptomycin, isoniazid and rifampicin.

So far 96 patients have completed treatment in Reg.1,43 in Reg.2(a), 45 in Reg 2(b), 27 in Reg. 3(a) and 41 in Reg.3(b)

Among patients who had received more than 75% of chemotherapy, 92% of patients in Reg.1, 74% of patients in Reg.2(a) and 2(b), 43% of patients in Reg.3(a) and 41 % of patients in Reg.3(b) had a bacteriologically quiescent disease at the end of treatment. Thus, patients with organism resistant to rifampicin along with isoniazid alone, or isoniazid and streptomycin pose a problem in management. This study is in progress.

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## **Quality of life measurements at the end of treatment for patients treated for pulmonary tuberculosis**

(Ongoing study, 1993-95)

Quality of life is a multidimensional concept concerned with the impact of physical symptoms and side effects of treatment on patients' functioning and psychosocial well-being. It is generally assumed that treatment of pulmonary tuberculosis with potent chemotherapeutic agents and making them non-infectious will be accompanied by improved health and well being. However, disturbances in physiological functions persist, even though the precipitating event (bacillus) has been eliminated. Activities that may be disturbed by disturbances in physiological functions are physical, social, emotional, intellectual, economic and spiritual. Impairment is an abnormality of physiologic functions and disability is the effect of impairment on patients' life. Quality of life measurements utilising general health questionnaires such as the Sickness Impact Profile and Quality of Well-being Scale (J chronic Dis 1984,37:85-95) are designed for application to a very wide range of diseases and hence there are limitations regarding their precision and sensitivity. Hence, it has been suggested that disease-specific questionnaire will provide a more precise and sensitive measurement of quality of life than a general index. Two quality of life measures developed for chronic lung diseases are Chronic Respiratory Questionnaire and St.George's Respiratory Questionnaire (Thorax 1987,42:773-78).

### **The objectives of the study are:**

1. to assess quality of life measurements using Disease-specific questionnaire (Chronic Respiratory Questionnaire) in patients who had undergone treatment for pulmonary tuberculosis.

2. to compare the Disease-specific questionnaire (Chronic Respiratory Questionnaire) with 6-minute walking test and pulmonary function tests in patients treated for pulmonary tuberculosis.

A group of 200 pulmonary tuberculosis patients treated with short-course chemotherapy will be included in the study if they had no previous history of any other illness and had not received any anti-tuberculosis treatment at the time of initiation of short course chemotherapy. Initial clinical and respiratory symptoms assessment including chest x-rays are done using "Questionnaire of the European Community For Coal and Steel

on Respiratory Symptoms". Disease-specific quality of life measurement is assessed using chronic respiratory questionnaire.

The following objective measurements of impairment are also undertaken.

1. Pulmonary function tests: Flow-volume loops are recorded in each patient using Morgan Transfer Test Model C. At least 3 acceptable readings are obtained from each patient as per American Thoracic Society recommendations (Am Rev Respir Dis 1987,136:1285-96).

2. Six-minute walking test: This test (JE Cotes, Lung Function, 5th Edition 1993) is carried out in a level corridor. Each patient is instructed to cover as much ground as he could on foot for 6 minutes and to keep going continuously if possible, but not to be concerned if he had to slow down or stop to rest. The patient's aim should be to feel at the end of the test that he could not have covered more ground in the time. An investigator accompanies the patient, acting as time keeper and giving encouragement as and when necessary. The actual distance covered is measured. So far 102 patients have been admitted. The study is in progress.

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### **Short course chemotherapy for pulmonary tuberculosis in children**

(Ongoing study, 1992-96)

Evaluation of various therapeutic regimens for the treatment of pulmonary tuberculosis has been the major point of focus for more than 3 decades. The accent has been on Short Course Chemotherapy (SCC). Though there are many reports available on SCC in adults, information regarding the same for tuberculosis in children is limited. Hence this Centre has started an SCC study in pulmonary tuberculosis in children, in collaboration with the Institute of Child Health & Hospital for Children (ICH), Egmore, Madras (Director: Dr. Merlyn Joseph). In brief, patients aged between 1 and 12 years who had not received more than 2 weeks of previous anti-tuberculosis treatment are admitted to the study. The diagnosis is based on chest radiography.

The patients are randomly allocated to one of the following 2 regimens.

**Regimen I: 9HR:** Rifampicin and isoniazid daily for 9 months.

**Regimen II: 2H<sub>3</sub>R<sub>3</sub>Z<sub>3</sub>/4H<sub>2</sub>R<sub>2</sub>:** Rifampicin, isoniazid and pyrazinamide thrice a week for the first 2 months followed by isoniazid and rifampicin twice a week for the next 4 months.

It is proposed to admit a total of 200 patients (100 in each regimen). So far 90 patients have completed therapy, 45 in the daily regimen and 45 in the intermittent regimen.

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### **Collaborative controlled clinical trial of tuberculous lymphadenitis: follow-up phase**

(Ongoing Study, 1988-98)

The Centre has conducted a controlled clinical trial on treatment of lymphnode tuberculosis, at Madurai, South India, in collaboration with the Paediatric and Adult Surgery Departments of Government Rajaji Hospital (Dr. D. Anantharaj, Dr. M. N. Kamaludeen and Dr. V. Ananthalakshmi). Patients with biopsy confirmed superficial lymphnode tuberculosis were randomised to either of two 6 month regimens of treatment, viz. a) Regimen 1: Daily unsupervised regimen of rifampicin and isoniazid, supplied twice a month for self-administration (6RH<sub>7</sub>), or b) Regimen 2: Twice-weekly supervised regimen of rifampicin, isoniazid and pyrazinamide for two months followed by rifampicin and isoniazid for four months (2RHZ<sub>2</sub>/4RH<sub>2</sub>). The methodology of the study has been described in previous annual reports.

Intake to the study was completed in September 1993. Patients are now being followed up. Two hundred and seventy seven patients (90 children and 187 adults) were admitted to the study. The age and sex distribution, lymphnode culture results and the results at the end of treatment were presented earlier (The annual report 1993). Briefly, after excluding 15 patients from analysis, 116 (87%) of 133 patients in Regimen 1 and 112 (87%) of 129 patients in Regimen 2 had a "Favourable" response at the end of treatment. There was statistically significant difference in the response to treatment between children and adults.

Thirteen (10%) of 133 patients in Regimen 1 and 17 (13%) of 129 patients in Regimen 2 had "Doubtful" response, and 4 (3%) of 133 patients in Regimen 1 (all adults) had an "Unfavourable" response.

Of the 13 patients on Regimen 1 who had "Doubtful" response at the end of treatment, in 11 the nodes had regressed subsequently and the response was reclassified as "Favourable". Of the 17 patients in Regimen 2 who had "Doubtful" response at end of treatment, 15 were subsequently reclassified as "Favourable". All patients have completed nine months of follow-up after treatment. During this period three patients, all adults, have relapsed with recurrence of lymphadenitis (1 in Regimen 1 and 2 in Regimen 2).

In summary, after nine months of follow-up after treatment, 127 (96%) of 133 patients in Regimen 1 and 126 (98%) of 129 patients in Regimen 2 had a favourable outcome. All the seven patients (5 in Regimen 1 and 2 in Regimen 2) who had an unfavourable outcome or relapsed were adults. Follow-up is continuing.

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### **Collaborative study of abdominal tuberculosis : follow-up phase**

(Ongoing study, 1992-2001)

A collaborative controlled clinical study of abdominal tuberculosis was carried out at the Centre. The objectives of the study are as follows:

- (a) to identify the clinical and laboratory profiles of peritoneal, intestinal and mesenteric tuberculosis in South Indian patients, and
- (b) to compare the efficacy of a short-course regimen with that of a standard regimen in the treatment of abdominal tuberculosis.

Patients with 'bacteriological, histopathological or radiological confirmation as well as those with a clinical condition highly suggestive of abdominal tuberculosis, were admitted to the study. Patients were randomly allocated to either of the following regimens.

**2RHZ/4RH (R6 - rifampicin series):** Rifampicin, isoniazid and pyrazinamide daily for 2 months, followed by rifampicin and isoniazid daily for the next 4 months.

**SEH/EH (E12 - non-rifampicin series):** Streptomycin, ethambutol and isoniazid daily for 2 weeks, followed by ethambutol and isoniazid daily for the next 50 weeks.

**Results up to 60 months after admission:** Of the 157 (84 R6,73 E12 series) patients who were symptom free or had clinically improved at the end of treatment,147 (79 R6, 68 E12 series) completed 48/54 months of follow-up. Among them, 7 (3 R6, 4 E12 series) required retreatment, 9 died (1 Tb, 8 non-Tb) and 2 were lost for follow up. None of the remaining 129 (68 R6, 61 E12 series) patients had relapsed of abdominal tuberculosis and are being followed up to 120 months after admission. The follow up is in progress.

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### **Collaborative study of brain tuberculoma: follow-up phase**

(Ongoing study, 1992-96)

A controlled clinical trial to evaluate 2 short course regimens of 9 months duration, one fully intermittent and the second daily, followed by intermittent drug administration, in the management of clinically and CT scan diagnosed brain tuberculoma is in progress at the Centre. The study is undertaken in collaboration with the Government General Hospital and Railway Hospital, Madras.

The main objectives of this study are:

1. to evaluate the efficacy of short course regimens for treating tuberculoma of the brain and
2. to study the CT scan appearance, before, during and at the end of chemotherapy and up to 60 months after the start of treatment.

All patients have completed treatment and are being followed up for a period of 5 years. Among patients who have completed 48 months of follow up, none had a relapse requiring retreatment.

This study has clearly demonstrated that it is possible to treat tuberculoma of the brain with a regimen of 9 months' duration. An intermittent regimen is preferable to a daily regimen since it is associated with fewer adverse reactions while having the same efficacy as a daily regimen. It is also found that clinical recovery was faster than scan clearance. The follow up is in progress.

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### **Collaborative clinical study of cutaneous tuberculosis**

(Ongoing study, 1992-95)

A collaborative clinical study of skin tuberculosis with an aim to evolve diagnostic criteria and to assess a SCC regimen of 9 months' duration is in progress.

Patients diagnosed clinically as having cutaneous tuberculosis by the dermatologist are admitted to the study. All patients aged 12 years or more admitted to the study are treated with rifampicin (450mg) and isoniazid (300mg) daily for 9 months and those aged less than 12 years are treated with weight adjusted dosages. The patients are assessed either at the Centre and also at the collaborating hospitals at monthly intervals during treatment and at 3 monthly intervals up to 24 months. A total of 183 patients were admitted and 153 patients have completed chemotherapy up to December 1994.

Of the 124 patients in the analysis, 50% are lupus vulgaris, 39% are verrucosa cutis, 6% are scrofuloderma, 2% tuberculid and 3% multiple types, 102 (82%) of the patients suffer from single lesion, 16 (13%) are having 2 lesions and 6 (4%) are having multiple lesions.

The diagnosis of cutaneous tuberculosis was confirmed by bacteriology or by histopathology in 98 (85%) of 124 patients. The lesions resolved by the end of the 6th month in 57 (92%) of 62 patients with lupus vulgaris, and by 9 months is 59 (95%). Of the 48 patients with verucossa cutis lesions, 38 (79%) resolved by 6 months and 44 (92%) by 9 months. Thus, in 108 (87%) of 124 patients the lesions resolve at the end of 6 months treatment. In all, 116 (94%) of 124 patients, lesions resolved at the end of 9 months. All patients are being followed up for a period of 3 years. The study is in progress.

## **A controlled clinical study of multi-drug therapy for multi-bacillary leprosy - a 4 year report**

(Ongoing study, 1988-97)

The study was undertaken to find out the feasibility of fixed duration chemotherapy. Treatment was stopped at the end of 24 months irrespective of BI value and the patients were clinically monitored up to 84 months. Chemotherapy was extended for one more year for patients who had reaction and the case reviewed after one year.

Patients were followed up every 6 months till 48 months, and every 3 months till 60 months and once a year up to 84 months. A total of 80 patients were admitted to the study of whom 64 patients have completed 48 months. Fifteen were excluded from the analysis for different reasons (5 died - not due to leprosy, 2 migrated, 1 toxic to Dapsone, 4 non co-operation, 1 taking treatment elsewhere and 2 absent for more than 6 months). Of the remaining 49 patients, 12 had chronic ENL reaction and as they required high doses of steroids treatment was extended beyond 24 months, one patient was negative for BI at 48 months, while 10 patients had gradual fall in BI and the other patient was FTA at 48 months but subsequently he attended at 60th month and his BI was negative. Of the remaining 37 patients who did not have reaction, 5 patients had negative BI while in 32 there was a gradual fall. The study is in progress.

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## **A study to evolve objective criteria for diagnosis and assessing the progress in pauci-bacillary leprosy**

(Ongoing study, 1993-96)

A pilot study was initiated to evolve an objective criteria for assessing the diagnosis and progress in paucibacillary leprosy. A patient was eligible for the study if he/she was aged 5 years or more, disease was classified as BT/TT clinically, skin smear for AFB was negative and has had no previous specific chemotherapy (DDS for more than one month or even a single dose of rifampicin) in the last 6 months. All the patients were prescribed NLEP regimens (rifampicin once a month plus DDS daily for 6 months) and were treated on ambulatory basis.

A total of 60 patients have been admitted and all of them completed 6 months of treatment; 80% were confirmed as leprosy histopathologically, 12% were reported as doubtful and 8% as not leprosy. In addition to histopathological examination, presence of antigen was looked for and in 78% it was found to be positive.

Of the 60 patients who had completed 6 months, seven patients were excluded (3 toxic to DDS and 4 were not available at 6 months for assessment) and the remaining 53 cases were analysed; fifteen were clinically active but there was no histopathological evidence in 7 and 38 were clinically inactive but there was histopathological evidence of leprosy in 13 cases. The study is in progress.

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### **Controlled clinical trial of dapsone as continuation chemotherapy beyond 7 years**

(Ongoing study, 1977-97)

As mentioned in the previous annual reports, the Centre undertook a controlled clinical trial of a rifampicin and a non-rifampicin regimens in the treatment of leprosy at the Govt. Royapettah Hospital, Madras. The findings up to 5 years have already been published (International Journal of Leprosy, 1990, **58**, 273). The 10-year findings were already presented in the 1992 annual report. Interim findings after 10 years are presented here.

In more than 95% of the cases at 120, 132, 144 and 156 months, the BI was less than 0.50 and the patients were clinically inactive. Hence it was decided to stop anti-leprosy drugs for all the patients at 144 months and follow them up once a year till 240 months.

As already reported (see 1993 annual report) 2 patients relapsed both clinically and bacteriologically at 162 and 177 months and they were managed with multi-bacillary NLEP regimen and they responded well. Five patients showed occasional BI positivity but there were no clinical signs suggestive of relapse. They are being monitored clinically and bacteriologically. The study is in progress.

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## LABORATORY STUDIES - COMPLETED

### Evaluation of bactericidal and sterilising action of ofloxacin and sulbactam/ampicillin, alone and in combination with rifampicin and isoniazid, on *M.tuberculosis* in vitro

(Completed study, 1993-94)

The quinolones and combinations of beta-lactam antibiotics with beta-lactamase inhibitors appear to be the most promising among the new drugs with antimycobacterial activity. Of these drugs, ofloxacin and sulbactam/ampicillin, alone and in combination with other anti-TB drugs, have to be evaluated further for their bactericidal action on actively growing (log-phase) and dormant or semi-dormant (stationary-phase) tubercle bacilli.

In this investigation, the bactericidal action of ofloxacin (O) and sulbactam/ampicillin (S/A), alone and in combination with rifampicin (R) and isoniazid (H), was studied first on log and stationary phase. cultures of the standard strain ***M.tuberculosis*** H37Rv as reported earlier (see 1993 annual report). Following this, investigations were carried out on a drug sensitive, pretreatment isolate of ***M.tuberculosis*** (TS51476) **in vitro**.

The colony forming units (cfu)/ml and the reduction per day in the cfu/ml during the six days of incubation in the cultures treated with different drugs and combinations of the drugs were calculated and compared to evaluate the bactericidal action in vitro due to ofloxacin and sulbactam/ampicillin, alone and in combination with R and H, on log-phase and stationary phase cultures of ***M.tuberculosis***.

The results of this **in vitro** study indicate that ofloxacin, when used alone at the higher concentration (5 ug/ml), has bactericidal action slightly higher than that of rifampicin and of isoniazid (1 ug/ml each) on log-phase cultures of ***M.tuberculosis***. The lower concentrations of ofloxacin (1.25 ug/ml) had considerably lesser bactericidal action. On the other hand, both concentrations of sulbactam/ampicillin had moderately high bactericidal action which was only slightly lesser than that of rifampicin and isoniazid.

On the stationary phase cultures, however, even the higher concentrations of ofloxacin and sulbactam/ampicillin had only low or very low activity, with sulbactam/ampicillin having a slightly better activity than

ofloxacin. Rifampicin and isoniazid had moderate activity on stationary phase cultures.

In the 2-drug combinations, the combined effect of ofloxacin on log phase cultures was always additive with rifampicin and with isoniazid. On the other hand, in stationary phase cultures, the combined effect of ofloxacin in the 2-drug combinations with either rifampicin or isoniazid was generally indifferent or only slightly additive. Sulbactam/ampicillin was also additive and sometimes even synergistic in 2-drug combinations with rifampicin or isoniazid on log phase cultures but was indifferent or only slightly additive on stationary phase cultures. In contrast, both on log phase as well as stationary phase cultures, the combined effect of rifampicin with isoniazid was additive.

In the 3-drug combinations, ofloxacin was either additive or synergistic with isoniazid and rifampicin on log phase cultures, but appeared to have a slight antagonistic action on the stationary phase cultures. In the 3-drug combinations, S/A was additive on log phase cultures but was either antagonistic or only slightly additive in the case of stationary phase cultures.

The findings of the present study provide further evidence to support the view that both ofloxacin and sulbactam/ampicillin could be useful in the treatment of tuberculosis, particularly in the initial phase.

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### **In vitro activity of ampicillin/sulbactam on South Indian isolates of *M.tuberculosis***

(Completed study, 1993-94)

Combinations of Beta-lactam antibiotics with Beta-lactamase inhibitors have been suggested as possible chemotherapeutic agents for the treatment of patients with multiple-drug resistance to the commonly used anti-TB drugs.. Recently, Prabhakaran and others (Microbios, **72**, 137, 1992) have reported that ampicillin plus sulbactam inhibited the multiplication of drug-resistant ***M.leprae*** in the mouse footpad. This combination was more active than ampicillin/clavulanic acid against ***M.tuberculosis*** when tested by the radiometric method. A study at this Centre (see 1993 annual report) on the bactericidal activity of this combination on stationary-phase cultures of ***M.tuberculosis*** revealed a

moderate activity in between that of single drugs (isoniazid and rifampicin), tested. Ampicillin by itself revealed no bactericidal activity.

It was therefore proposed to test the **in vitro** activity of ampicillin with sulbactam on strains of **M.tuberculosis** sensitive as well as resistant to SHR/HR.

A total of 64 strains of **M.tuberculosis** comprising of 31 SHR-sensitive and 33 resistant to SHR/HR was tested against a 2:1 combination of ampicillin and sulbactam incorporated in 7H11 agar medium. The concentrations of ampicillin used were 0, 8, 16, 32, 64 and 128 mg/litre. Ten microlitres of a standard suspension of the inoculum was used and the plates incubated at 37°C for 4 weeks at the end of which readings were taken and the MIC determined. The distribution of minimal inhibitory concentrations (MICs) of ampicillin/sulbactam on the strains tested revealed very little difference between the sensitive and resistant strains, the geometric means being 26.8 and 23.8 mg/litre respectively, the overall mean being 25.3 mg/litre. The standard strain **M.tuberculosis** H37Rv tested on 5 occasions yielded a geometric mean of 42.2 mg/litre.

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### **In vitro susceptibility of clinical isolates of M.tuberculosis to trifluoperazine**

(Completed study, 1994)

Trifluoperazine (TFP), an antipsychotic drug, was reported to inhibit the growth of **M.tuberculosis** H37Rv and isoniazid (INH) resistant clinical isolate of **M.tuberculosis** (Ratnakar P and Murthy PS. FEMS Microbiol Lett. 1992, 97, 73). To continue further research work with this drug as an antimycobacterial agent, it is essential to determine the susceptibility pattern of clinical isolates to TFP.

Randomly coded 19 drug sensitive and 15 drug resistant clinical isolates were studied. The standard laboratory reference strain, **M.tuberculosis** H37Rv, was included as control. The broth dilution method was employed to determine the Minimal Inhibitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC). In brief, log phase culture in Middlebrook 7H9 medium, diluted to contain  $10^6$  bacilli/ml, was used. The concentrations of TFP used in the study were 64, 32, 16, and 8 mcg/ml. Viable counts were determined on Lowenstein Jensen (W) slopes and

expressed in  $\text{Log}_{10}\text{cfu/ml}$ . MIC is defined as the lowest concentration of the drug, in mcg/ml, which inhibited more than 99% of the population in the control culture at 7 days. MBC is defined as the lowest concentration of the drug, in mcg/ml; which kills more than 99% of the population in the initial inoculum. The bactericidal activity (BA) is measured as the average reduction in  $\text{log}_{10}\text{cfu/ml/day}$  during the 7-day exposure to the respective concentration of the drug.

The MIC of TFP against 15 of 19 drug sensitive isolates and 13 of 15 drug resistant isolates was  $\leq 16 \mu\text{g/ml}$  and against **M.tuberculosis** H37Rv it was  $\leq 32$  when tested on 4 occasions.

MBC of TFP against 13 of 15 drug resistant isolates was  $\leq 32$  whereas only 4 of 18 drug sensitive clinical isolates had similar value. This difference was statistically significant ( $p < 0.001$ ). The MBC for the reference strain was 64 when tested on all 4 occasions. The MIC:MBC ratio for 10 of 19 drug sensitive isolates was 1:4 whereas 3 of 15 drug resistant isolates exhibited similar value.

The bacterial activity(BA), based on mean viable counts, against the drug resistant isolates was 0.38 and 0.26 when exposed to 32 and 16 mcg/ml, respectively, compared to 0.19 and 0.05 for the drug sensitive strains and the differences were statistically significant ( $P < 0.01$  for 32mcg/ml;  $P < 0.01$  for 16 mcg/ml). These observations show that TFP was more bactericidal to drug resistant isolates than to drug sensitive isolates.

Therefore, further **in vitro** and **in vivo** studies on bactericidal/sterilizing activities against **M.tuberculosis** in mice/guinea pigs need to be carried out to assess the suitability of TFP for human trials.

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### **Characterisation of Mycobacterium Avium Complex (MAC) isolates in clinical and environmental specimens from the BCG trial area - Drug and heavy metal susceptibility patterns of MAC isolates**

(Completed study, 1992-94)

A total of 62 MAC isolates including 14 each from soil and dust, 15 from water and 19 from sputum were tested for their susceptibility to 6 different concentrations each of rifabutin, clofazimine, rifampicin, isoniazid,

streptomycin and ethambutol, and 4 different concentrations of salts of mercury and cadmium, using the agar dilution method. There were 31 strains each of pigmented and non-pigmented type among the strains tested.

The results showed that rifabutin and clofazimine had the highest activity against the strains tested with most of the isolates having low MICs to these drugs (range 1.3-5.0 mg/L). On the other hand, most of the isolates had very high MICs to ethambutol (range 41.3-108.6 mg/L). There was no difference in the pattern of susceptibility between pigmented and non-pigmented strains or between isolates obtained from different sources. Further, the order of activity of drugs for isolates from different sources was similar except in the case of streptomycin and rifampicin. The mean MIC of streptomycin for the non-pigmented strains from water and pigmented strains from soil were significantly higher than that for the non-pigmented and pigmented strains from other sources, and even though the differences were not significant, non-pigmented strains from dust and sputum and pigmented strains from water had lower MICs for rifampicin. In the case of heavy metals, though the non-pigmented strains from dust and the pigmented strains from sputum had the lowest MICs among the different groups, the difference was not significant.

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### **Immune response induced by MAI complex isolates in guinea-pigs**

(Completed study, 1992-94)

The aim and design of the experiment have been already described in detail in the 1993 annual report. Briefly, 40 guinea-pigs were taken and divided into 5 groups. Group 1 was the control group in which the guinea-pigs were not immunised. At 6 weeks, guinea-pigs in groups 2, 3, 4 and 5 were immunised with BCG, the standard strain of **M.intracellulare**, TMC 1403 (MACstd), **Mycobacterium Avium** Complex (MAC) strain from soil (MACenvt) and MAC strain from sputum (MACclin), respectively. In the fifth week after immunisation (i.e., at 11 weeks), all the animals including the controls were skin-tested simultaneously with PPD-RT23 and PPD-B. In the sixth week after immunisation (i.e., at 12 weeks), all the animals were challenged with a South Indian low virulent strain of **M.tuberculosis** (SIV). From each group, 4 animals each were sacrificed at 2 and 6 weeks after challenge. Spleen viable counts were set up at each time point.

The results showed that skin-test response to PPD-RT23 and PPD-8 was negligible in the control group (group 1) animals; significantly higher skin-test response was seen in animals immunised with BCG or different strains of MAC (groups 2, 3, 4 and 5). The Delayed Type Hypersensitivity (DTH) response to PPD-RT23 was maximum in the animals immunised with BCG followed by the response in the animals immunised with MACstd, MACclin, MACenvt and the control animals in the order of decreasing reactivity. The DTH response to PPD-B was maximum in the animals immunised with MACstd followed by the response in MACenvt, MACclin, BCG and the control animals in the order of decreasing reactivity.

The log colony-forming units (cfu) of SIV in spleen was high (>4.0) in the control animals (group 1) at 2 weeks after challenge. Compared to this group, the count was significantly lower in animals immunised with BCG. However, the counts in the animals immunised with the different strains of MAC were not significantly different from that in the control.

At 6 weeks after challenge, SIV organisms could not be detected in the spleen in any of the animals immunised with BCG. In all the other groups, including the controls, there was marked reduction in the counts at 6 weeks after challenge as compared to the counts at 2 weeks except in the animals immunised with MACclin.

These results indicate that immunisation with MAC strains from different sources induce different levels of DTH and protective response in the guinea-pig studied. This was best illustrated in the animals immunised with clinical strain of MAC where the level of DTH response to PPD-B, the homologous antigen, was significantly lower than that in animals immunised with either the standard strain, TMC1403, or MAC from soil. At the same time, persistence of challenge organisms in the spleen at 6 weeks after challenge was also observed only in this group.

## **Methods for the estimation of ofloxacin in plasma, saliva and urine**

(Completed study, 1994)

Ofloxacin is currently given to patients having multi-drug resistant pulmonary tuberculosis at the Centre.

The estimation of ofloxacin by microbiological and fluorometric methods in plasma, saliva and urine has been standardised. The aspects

like precision, sensitivity, recovery, interference of anti-TB and anti-leprosy drugs in the estimation, stability and protein binding have all been studied.

None of the drugs studied interfered with the estimation of ofloxacin by both the methods. Samples containing ofloxacin can be stored up to 8 days before the assay is undertaken. 25% ofloxacin is bound to plasma proteins.

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### **Bioavailability of anti-tuberculosis drugs from triple drug formulation - Rifater 125 SCT**

(Completed study, 1994)

A number of triple drug formulations containing isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA) and double-drug formulations containing isoniazid and rifampicin suitable for daily or intermittent chemotherapy, are now available. No study has so far been carried out to compare the bioavailability of rifampicin, isoniazid and pyrazinamide from a triple drug formulations (Rifater 125 SCT) in Indian subjects. This study was conducted in collaboration with the Pharmacology Unit (Dr.Vijayasekaran) of Madras Medical College, Madras. The study was undertaken in 18 volunteers with normal hepatic and renal function. The results indicate that RIFATER is as good as individual drugs in its bioavailability indices.

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### **Evaluation of antibody level to Antigen 6 and 38 KDa for identification of tuberculous infection**

(Completed study, 1994)

It has been concluded in the annual report 1992 (page 70) that antibody level to PPD has no role in determining the tuberculous infection. PPD is a crude, unfractionated antigen and its limited value in the diagnosis of the disease (not only infection) has been already established in our laboratory. Hence, purified antigens were used in the present study, to evaluate their potential use in identification of tuberculous infection. The 38 KDa antigen used in this study is a purified recombinant antigen, obtained from WHO Bank. Antigen 6 is the 30 KDa antigen of

**M.tuberculosis**, obtained as a gift from Prof. Thomas Daniel, Cleveland.

The present study was carried out in the same fingerprick blood samples collected during the previous study. The study population and the rationale of the investigation have been described in detail in annual report 1992.

It was observed that the sensitivity of detection of infection was 61% with r38 KDa and 75% with Antigen 6. The specificity was 63% with 138 KDa and 72% with Antigen 6.

In the previous annual report (1992) it had been concluded that crude antigens are of limited value in distinguishing between the infected and uninfected population. Now, it is seen that two of the purified antigens i.e., 30 and 38 KDa are also not of much use. However, in view of the fact that serological assays have more practical advantages than skin test, further attempts are needed to develop antigen/antibody detection assays with other purified antigen(s).

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## **Evolution of experimental mycobacterial granuloma**

(Completed study 1993-94)

This study was initiated to follow the course of experimental mycobacterial granuloma vis a vis the presence of Acid Fast Bacilli (AFB) and antigen in the skin of sensitized guinea pigs challenged with-heat-killed **Mycobacterium tuberculosis** (HKMTB). It was found that when sensitized guinea pigs were challenged with  $1 \times 10^7$  HKMTB, the AFB were cleared by day 56, the antigen(s) cleared by the 3rd month and the granuloma itself completely resolved by the 4th month.

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## LABORATORY STUDIES - IN PROGRESS

**Evaluation of bactericidal action of ofloxacin and sulbactam/ampicillin, in comparison with rifampicin and isoniazid, and metronidazole alone, and in combination with rifampicin and isoniazid, on *M.tuberculosis* in the murine model**

(Ongoing study, 1993-95)

Earlier **in vitro** studies at this Centre (1993 and 1994 annual reports) with ofloxacin and sulbactam/ampicillin had led to the conclusion that these drugs may prove valuable for future experimentation against tuberculosis, for example, in the animal models. Recently, it has been shown that metronidazole is bactericidal to dormant cells of ***M.tuberculosis*** under anaerobic conditions **in vitro** and hence it has been suggested that this drug could be of value in preventing the persistence of dormant bacilli and later emergence of active disease **in vivo** (Wayne and Sramek, 1994).

A study has been initiated to investigate the bactericidal and sterilising action of different doses of ofloxacin (O) and sulbactam/ampicillin (S/A) alone, and also metronidazole (M) alone and in combination with rifampicin (R) and isoniazid (H), given six days a week for 3 months on a drug sensitive strain of ***M.tuberculosis in vivo*** using the murine model.

A total number of 200 Balb/C female mice in the 1-2 months age group, will be infected with the ***M.tuberculosis*** strain by tail vein injection. Treatment will be started on the 14th day after infection. Before starting the treatment (14th day), 4 mice will be sacrificed and viable counts (VC) will be set up from spleen and lungs. The remaining mice will be divided into 12 groups and will be treated six days a week for 3 months as set out below.

Group 1 : Control (No treatment)

Group 2 : R

Group 3 : H

Group 4 : O1

Group 5 : O2

Group 6 : S/A1

Group 7 : S/A2

Group 8 : HR

Group 9 : M

Group 10: MR (M only in the 3rd month, R all the 3 months)

Group 11: MH (M only in the 3rd month, H all the 3 months)

Group 12: MHR (M only in the 3rd month, HR all the 3 months)

The bactericidal effect of treatment in the different groups of mice will be estimated by sacrificing 4 mice/group at 4, 8, and 12 weeks after start of treatment and at 3 months after stopping treatment by setting up viable counts for spleen and lungs and by finding out if the organs were positive or negative for tubercle bacilli. The comparison of colony forming units (cfu) in the spleen and lungs, and the positivity of these organs for **M.tuberculosis** in the different groups of mice will be used to evaluate and compare the bactericidal and sterilising action of rifampicin, isoniazid, ofloxacin, sulbactam/ampicillin and metronidazole.

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### **Action of pyrazinamide, alone and in combination with isoniazid and rifampicin, on M.tuberculosis in vitro under different growth conditions**

(Ongoing study, 1994-96)

Pyrazinamide is not bactericidal against tubercle bacilli in macrophages eventhough it is a potent sterilising drug in murine tuberculosis where bacilli are mainly intracellular. Further, pyrazinamide appears to have definite bactericidal activity **in vitro** only at a pH as low as 4.8 - 5.0 and a high proportion of bacilli in human lesions, where they are extracellular in cavity walls, may not be at these very acid pH levels. Even if it is assumed that these pH levels may be possible in the microenvironment of the tubercle bacilli, such conditions should prevail for several weeks if pyrazinamide has to be active. Also, in combination with other anti-tuberculosis drugs, pyrazinamide appears to have antagonism under certain conditions but is effective under other conditions. Hence, further studies are required to understand the conditions under which pyrazinamide is bactericidal in either mouse or human tuberculosis. Based on these data, it has been hypothesised that pyrazinamide is active against persisting, semidormant organisms, where dormancy has been produced by low pH or by the previous activity of drugs.

Recently, it has been shown that metronidazole is bactericidal to dormant cells of **M.tuberculosis** under anaerobic conditions **in vitro** and hence it has been proposed that this drug could be of value in preventing the persistence of dormant bacilli and later emergence of active disease **in vivo** (Wayne and Sramek, 1994).

Hence, a study has been initiated to determine the activity of pyrazinamide (Z), alone and in combination with isoniazid (H) and rifampicin (R), and metronidazole (M) alone on **M.tuberculosis in vitro** under different growth conditions.

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### **WHO-assisted multicentre study of early bactericidal activity**

(Ongoing study, 1994-96)

Several studies of the early bactericidal activity (EBA) of antituberculosis drugs have been carried out. These studies have suggested that the EBA might be a rapid and economical way of measuring the activity of new antituberculosis drugs and of helping to define the correct dose size to use.

All of the EBA studies so far have measured the fall in viable bacilli in the sputum. Earlier studies suggest that there may also be a fall in total visible bacilli during the first few days of chemotherapy, though this fall might occur less rapidly because of the tendency for bacilli to retain acid-fastness despite being killed by chemotherapy. The relationship between total and viable bacilli could be different for isoniazid, which is known to produce loss of acid-fastness as it kills, and rifampicin which does not. Among the new drugs likely to need testing are fluoroquinolones and rifamycins.

Hence, a WHO-assisted multicentric study, of which the Centre will be one of the participants, has been initiated to compare estimates of the EBAs obtained by viable counting with those obtained by total counting, to see whether comparable estimates of the EBAs obtained from colony forming units (cfu) and total counts will be similar in the different centres, and to compare the variation between patients in different centres.

#### **Drugs to be studied**

1. Isoniazid 300 mg daily
2. Isoniazid 18.75.mg daily
3. Rifampicin 600 mg daily on an empty stomach
4. Ofloxacin 800 mg daily
5. No drug

About 20 patients will be admitted to each of these groups by random allocation, making a total of 100 for each centre.

The EBAs of drugs will be estimated by carrying out viable counts on selective 7H11 medium and total counts by microscopy. The estimates of the EBAs obtained by viable counting will be compared with those obtained by total counting.

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### **Immune response and modulation of immune response induced by *M.fortuitum* complex isolates In guinea-pigs**

(Ongoing study, 1994-96)

A total of 24 guinea-pigs were divided into 4 groups of 6 animals each. Group 1 was a control group in which the guinea-pigs were not immunised. At 6 weeks, guinea-pigs in group 2 were sensitised with a soil isolate of ***M.fortuitum*** complex. At 12 weeks, guinea-pigs in groups 2 and 3 were immunised with BCG while the guinea-pigs in group 4 were immunised with the soil isolate of ***M.fortuitum*** complex. In the fifth week after immunisation (i.e., at 17 weeks), all the animals, including the controls, will be skin-tested simultaneously with PPD-RT23 and PPD-B and one week later they will be challenged with a South Indian low virulent strain of ***M.tuberculosis*** (SIV). From each group, 3 animals each will be sacrificed at 2 weeks and 6 weeks after challenge. The immune response will be analysed based on the DTH reaction induced by PPD-RT23 and PPD-B and viable counts in spleen.

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### **Characterisation by plasmid profile of MAIS isolates obtained from various sources in the South Indian BCG trial area**

(Ongoing study, 1994-96)

A total of 61 MAC isolates including 13 each from water and dust, 16 from soil, 18 from sputum from the South Indian BCG trial area, and the standard strain of ***M.intracellulare***, TMC 1403, are being investigated for their plasmid profile. Demonstration of plasmid DNA is being done using agarose gel electrophoresis. Plasmid DNA extraction was performed using Falkinham's modification of Kado and Liu's procedure. Standardisation experiments are being performed using the known plasmid-carrying strain of ***M.avium***, LR25.

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## **Slide culture susceptibility test for M.tuberculosis**

(Ongoing study, 1994-95)

Slide culture susceptibility test is one of the rapid tests by which results are available within a week, enabling clinicians to treat urgent cases of smear positive tuberculosis. Previous studies have shown that slide culture test using acid decontamination gives reliable results for SM, INH and PAS. Further, a simplified test using selective Kirchner's liquid medium, gave better results.

The present study was initiated to standardise the slide culture susceptibility test for **M.tuberculosis**. Sputum smears were prepared on clean, sterile slides cut lengthwise to fit into MacCartney bottles containing plain and drug containing media. After 7 days of incubation, they were washed with 2% gluteraldehyde, air dried, heat fixed and stained with auramine phenol for fluorescent microscopy.

With preliminary standardisation tests, it was found that selective horse blood medium supported good growth of **M.tuberculosis** compared to selective Kirchner's liquid medium and the critical concentrations were 0.2 mg/l for INH and 0.4 mcg/ml for Rifampicin. Smears with single, uniformly distributed bacilli were graded as 1+, single cells with occasional microcolonies as 2+, single cells with many large microcolonies as 3+ and large microcolonies with well developed cords as 4+.

With the test thus standardised, it has been planned to screen at least 100 sputum specimens from known smear positive patients on treatment with various regimens. The study is in progress

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## **Rapid identification of M.tuberculosis and drug sensitivity testing by luciferase reporter phage assay**

(Ongoing study, 1994-96)

Luciferase reporter phage assay is a simple method for assessing drug sensitivity based on efficient production of photons by viable mycobacteria infected with specific reporter phage expressing luciferase gene (Jacobs et al1993). This luciferase reporter phage is the TM4 mycobacteriophage, genetically engineered to express luciferase FF lux gene. This phage

confers the ability to produce luciferase to the viable mycobacterium which it infects. After 3 hours of incubation with the phage of a titre of  $10^{-12}$ , viable mycobacteria liberate photons in the presence of luciferin and sodium citrate which is measured as relative light units (RLU) in the biocounter.

Preliminary experiments have been carried out to standardise this technique. This phage has been found to infect specifically **M.tuberculosis** complex apart from **M.smegmatis** (in which it is propagated) and **M.fortuitum**.

Drug sensitivity testing of primary culture on LJ is possible within 48 hours, but this technique is not sensitive enough to detect the presence of **M.tuberculosis** in smear positive sputum deposits.

It has been planned to screen LJ cultures of **M.tuberculosis** for drug sensitivity using a crude phage of a titre of  $10^{-12}$  approximately. Possibility of purification of the phage will be looked into, in order to increase the sensitivity of this technique.

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### **Neopterin levels as a marker of CMI in pulmonary tuberculosis**

(Ongoing study, 1994-95)

Neopterin a pteridine compound derived from guanosine-tri-phosphate is considered as a marker for cell mediated immunity. In the present study neopterin levels have been determined by HPLC in serum and pleural fluid of patients with pulmonary tuberculosis, tuberculous pleural effusion and healthy controls. The release of neopterin from peripheral blood mononuclear cells stimulated with PPD has also been estimated in the culture supernatant. A total of 25 patients with pleural effusion, 11 patients with pulmonary tuberculosis and 10 controls will be included in this study. Another parameter of CMI, namely lymphocyte proliferation assay is also being performed for comparison. The study is in progress.

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## Studies on the Mechanism of pyrazinamide action

(Ongoing study, 1994-95)

Strains of **Mycobacterium tuberculosis** which are susceptible to pyrazinamide (PZA) have pyrazinamide deamidase that transforms PZA to pyrazinoic acid (PZC). PZA resistant strains of **M.tuberculosis** do not have this enzyme and are not able to convert PZA into PZC. It has been reported that an acidic environment (pH. 5.5) is necessary for the antibacterial activity of PZA, as present inside the macrophage.

An investigation is undertaken to study the possible role of pyrazinamide deamidase in the susceptibility and antimycobacterial activity of PZA and its principal metabolic product PZC, at neutral and acidic pH.

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## Antimycobacterial effect of chloroquine alone or in combination with isoniazid, pyrazinamide or rifampicin in H<sub>37</sub>Rv infection in mice

(Ongoing study, 1994-95)

Chloroquine has been shown to have an antimicrobial effect against several intracellular organisms such as L-pneumophila, H.Capsulatum and **M.tuberculosis** under **in vitro** conditions. This effect is believed to be due to its iron trapping potential. Chloroquine might also interfere with the bactericidal action of pyrazinamide by raising the phagolysosomal pH due to its -NH<sub>2</sub> group. To study these factors, a study has been initiated to ascertain the antimycobacterial effect of chloroquine alone and in combination with pyrazinamide, isoniazid and rifampicin in **Mycobacterium tuberculosis** H37Rv infection in mice.

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## Microsomal mixed function oxidases in experimental tuberculosis

(Ongoing study, 1994-95)

There are several reports on the role of liver and lung mixed function oxidises of mammals in the metabolic transformation of many exogenous and endogenous compounds. But, so far no extensive investigations have been undertaken to study the mixed function oxidases in experimental

tuberculosis and the effect of certain anti-TB drugs on these enzyme systems. The metabolic transformation of many of these drugs may result in detoxification as well as inactivation. The metabolism of foreign compounds by mixed function oxidases involving cytochrome P-450 is altered under abnormal physiological and pathological conditions. The cytochrome P-450 detoxification enzyme system is known to be involved in some drug resistance mechanisms. There are reports that *P.falciparum* and *P.berghei* malarial parasites are known to possess these detoxification enzymes and chloroquine resistant strains had higher levels of cytochrome P-450 than the corresponding sensitive strains. But information is not available on cytochrome P-450 levels in relation to drug resistance in mycobacteria (with reference to anti-TB drugs). Hence the status of some mixed function oxidases which are in general responsible for the metabolism of these drugs is being investigated in a study. This study is in progress.

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### **Characterization and purification of antigenic components of *M.tuberculosis***

(Ongoing study, 1988-95)

It has been reported in the previous years Annual Report (1993, Page 84), that culture filtrate antigens of ***M.tuberculosis*** are being purified by Preparatory electrophoresis.

Rabbits and mice were immunised for production of polyclonal and monoclonal antibodies, respectively. The antigens used for immunisation were H37Rv culture filtrate and 30 KDa antigen. Fusions have been carried out and the results are awaited.

Antigen detection assays will be developed using the polyclonal and monoclonal antibodies.

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## **Development of DNA probes for M.tuberculosis**

(On going study, 1988-95)

The standardization of PCR amplification conditions for the different sets of primers targeting TRC4 fragment in the **M.tuberculosis** genome were described in the 1993 annual report. Subsequently, one set of primers 750/751, was evaluated for its specificity and sensitivity using purified genomic DNA from various strains as well as clinical specimen.

The primers amplified an expected product of 658 bp size from **M.tuberculosis** H37Rv, **M.bovis** and **M.bovis** BCG Madras strain and from multiple strains of **M.tuberculosis** isolated from South Indian patients. No amplification product was detected with human DNA or **E.coli** DNA or in any of the 18 atypical mycobacterial species tested. All the strains of **M.tuberculosis** clinical isolates examined by PCR contained the target of amplification.

Dilutions of genomic DNA, purified from **M.tuberculosis**, were subjected to PCR. The PCR was able to detect 1 pg of genomic DNA. False positivity has been our major problem. Our PCR assays did not show any false positivity for the initial 30 experiments after which false positivity occurred in one of the two negative controls. Subsequently false positivity was observed occasionally and then very often. This high rate of false positivity hindered the clinical diagnosis to a greater extent. Decontamination procedures using dUTP and Uracil N-glycolylase will be evaluated in the subsequent assays with clinical specimens.

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## **Human Leucocyte Antigen (HLA) studies in tuberculosis**

(Ongoing study, 1990-97)

The main objective of this project is to use a combination of serological and DNA probes to analyse the phenotype and the genotype of a number of individuals to find out whether there exists an association between any serological and/or DNA marker and the occurrence of tuberculosis.

HLA-phenotyping and genotyping will be carried out by HLA-antisera and HLA gene probes, respectively.

Further, the role of class-II genes/gene products on immunity to tuberculosis will also be studied in patients with active pulmonary tuberculosis and healthy volunteers.

The progress of the studies is reported under three different sections.

### **I. HLA studies - HLA and immune response: Role of HLA class-II genes/gene products on immunity to tuberculosis**

(Ongoing study, 1990-95)

It has been shown that Human Leucocyte Antigens influence immune functions, especially the class-II antigens. To elucidate the role of HLA class-II genes and their gene products (HLA-DR, -DQ and -DP) on antibody and cell mediated immune responses against **M.tuberculosis** antigens, the present study was undertaken.

Lymphocyte transformation test (LTT) is known as an **in-vitro** correlate of cell mediated immune response. LTT was carried out against **M.tuberculosis** culture filtrate antigen. During the year, 14 healthy volunteers and 25 treated pulmonary tuberculosis patients who remained quiescent even after 5 years of follow-up were HLA typed and lymphocyte response was studied.

The preliminary results on LTT response to varying concentrations of **M.tuberculosis** antigens showed increased response to increased concentration of antigen.

The study on antibody and cell-mediated immune response will be carried out in 50 healthy volunteers, 50 treated pulmonary tuberculosis and 50 active pulmonary tuberculosis patients. The influence of HLA-DR and -DQ antigens on immunity to tuberculosis will be analysed. The study is in progress.

### **II. HLA studies - Investigation in quiescent and relapse cases of pulmonary tuberculosis**

(Ongoing study, 1992-95)

An exploratory study was undertaken to find out whether there is any association between HLA-antigen and/or haplotype and the occurrence of

relapse of tuberculosis in successfully treated pulmonary tuberculosis patients. A total of 100 quiescent patients and 100 relapse patients will be investigated.

During the year, HLA-A, -B, -DR and -DQ serological typing were carried out in 26 quiescent and 26 relapse cases of pulmonary tuberculosis in addition to the 28 quiescent and 28 relapse cases mentioned in previous annual reports. DNA were extracted from the peripheral blood white cells of these patients and stored at -70°C. The work is in progress.

### **III. HLA studies - HLA - Genotyping: DNA typing in pulmonary tuberculosis patients and contacts**

(On going study, 1994-97)

HLA-DR and -DQ genotyping will be carried out in 100 pulmonary tuberculosis patients and 100 contacts.

In addition to serological determination of HLA-A, -B, -DR and -DQ antigens. DNA typing of HLA-DR genes will be carried out using Amplified Fragment Length Polymorphism (AFLP) technique.

For HLA-DQ genotyping, Heteroduplex analysis of HLA-DQ alpha and -DQ beta DNA typing will be carried out. During the year Heteroduplex analysis of HLA-DQ genotyping has been initiated. The study is in progress.

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### **RFLP analysis of M.tuberculosis isolates from South Indian patients**

(On going study, 1993-95)

The detailed objective and methodology of the RFLP analysis of **M. tuberculosis** isolates from South Indian patients with DR probe has been presented in 1993 annual report. The results of the RFLP analysis has been reported as follows:

(1) DR probe was able to finger-print isolates which had only single copy or isolates which had no copy of IS6110.

(2) The RFLP pattern of 69% of true relapse isolates matched the RFLP pattern of the pretreatment isolates indicating that the rate of relapse due to endogenous reactivation exceeds the rate of reinfection.

(3) There are genotypic differences interpreted differently by the 2 probes DR and IS6110. One should use more probes for genotyping the clinical isolates.

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### **Immunopathology of cutaneous tuberculosis**

(Ongoing study, 1992-95)

This project was undertaken to understand the immunopathogenesis of skin tuberculosis and to lay down histologic diagnostic criteria for this form of the disease. It was found that B lymphocytes were seen in considerable proportion in the various forms of skin tuberculosis. In addition, the presence of antigen even in the absence of demonstrable AFB in the sections was noted. The measurement of the Mantoux reaction up to 3 weeks after skin testing indicated that regardless of the type of skin tuberculosis, nearly one third of the patients had a persistent Mantoux reaction (>10 mm). In addition, to delineating the presence of T cells and their subsets, it is proposed to correlate these features of the lesions with those at the end of chemotherapy. Histopathological examination (using conventional and immuno histochemical staining) of the Mantoux reaction on various days up to three weeks also will be undertaken in order to understand the immunopathogenesis of skin tuberculosis better.

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### **Development of an experimental model for fibrosis**

(Ongoing study, 1993-95)

This study was started with the aim of understanding the fibrogenic mechanisms associated with mycobacterial disease. Sensitized guinea pigs were challenged with live **Mycobacterium tuberculosis** and then sacrificed at various time points. In addition to culturing the bacilli, histological examination of the injected site, spleen, liver and lung for the presence of granuloma, organisms and fibrosis was made. Further, the levels of collagen, elastin and hexosamine were also estimated in these organs. It

was found that although culture became negative, the granuloma persisted for up to six months. The levels of collagen and elastin started going up from the twenty second week after infection and remained elevated up to the thirtieth week. Further experiments are in progress where the animals are being observed for a longer time period.

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# EPIDEMIOLOGICAL STUDIES - COMPLETED

## Socio-economic impact of lymphatic filariasis

(Completed study, 1994)

This study was undertaken in three villages of Poondi Panchayat Union, known to be endemic for filariasis as a part of cross-national multicentric study.

**Design of the study:** Initially ethnographic data was collected using focus groups, indepth interview, key informants interview and participant observation. This was followed by census and mapping of the villages and a prevalence study of both chronic and acute forms of filariasis. Subsequently, all individuals were subjected to fortnightly surveillance for the occurrence of adenolymphangitis (ADL). Information on the economic aspects of all cases of ADL and on matched controls was obtained every fortnight.

Using the information from the initial ethnography, semi-structured questionnaires on social impact were prepared and administered to all affected persons. Social impact of filariasis as perceived by unaffected persons was obtained from a sample of unaffected persons in the same village.

**Social impact:** Marriage prospects and marital relationships were the areas perceived to be most affected by the disease. Employment opportunities were perceived to be reduced. Stigma was minimal.

**Economic assessment:** Three types of data have been collected for economic assessments. The first was information on economic status based on assets. The second was an assessment of direct costs in cases and indirect costs incurred because of ADL in case households compared with control households. The third was the 24 hour recall of daily activity for both ADL and chronic cases.

The Economic impacts were more number of consultations in households with ADL as well as with chronic disease as compared to control households. Medical as well as other expenses were higher in case households. This is being looked into further.

## **Symptomatic and bacteriological status of x-ray cases in the community**

(Completed study, 1994)

In the ongoing study for developing a methodology for surveillance of tuberculosis at Tiruvallur, the whole population (.i.e., person aged 10 yrs or more) is screened by MMR, once in three years. Individuals are classified as x-ray cases of tuberculosis if they have:

- a. 'tuberculous' abnormality on a single occasion by two independent readers and are sputum negative or
- b. 'tuberculous' abnormality on two consecutive occasions by at least one reader, and are sputum negative.

The following guidelines (management option) were also adopted for referring these patients for treatment in consultation with the Joint Director for tuberculosis (Directorate of Medical Services).

1. Adequately treated, asymptomatic: leave them alone.
2. Adequately treated, symptomatic (as per District Tuberculosis Programme definition): Collect sputum, give antibiotics and review after 2 weeks. If smear is positive, restart treatment. If negative, collect sputum and review after one month. If, still symptomatic and sputum negative treat as x-ray case.
- 3a. Irregularly treated, or on treatment elsewhere and symptomatic or treatment discontinued within the last 2 months: Continue treatment.
- 3b. Irregularly treated more than two months ago and asymptomatic: Wait for results and treat as in (5) below.
4. Untreated, symptomatic: Initiate treatment after collecting one more specimen of sputum, and adequate motivation. Make provision for patient to continue treatment as nearest centre.
5. Untreated, asymptomatic: Collect sputum and review after 2 weeks. If sputum is positive, or if symptoms develop initiate treatment.

Abacillary cases detected in the survey and satisfying either definitions were visited in their houses and motivated to attend the Passive Case Finding Centre (PCFC) at Tiruvellore, in order that they may be examined

by a Medical Officer, and their clinical status documented before they are referred for treatment. A pilot study was undertaken to document the symptomatic status and the proportion of x-ray cases that were liable to progress to bacillary status within a follow up period of 3 months.

We report here on 306 cases who had been examined by the Medical Officer. One specimen of sputum was collected for examination by smear and culture at the time of clinical examination.

There were 94 symptomatics among the 306 at the time of clinical examination. Twenty-five of the 306 x-ray cases had progressed to bacillary status from abacillary.

A total of 77 cases would have been treated by management option of which 9 were bacillary and only 6 of which had been referred for treatment on clinical grounds. Of these 77 cases, 33 were considered to be normal by the clinician and 18 were diagnosed as having non-Tb lung diseases.

The present definition of x-ray cases followed in the surveys leads to a gross over estimate of the burden of abacillary cases. Empirical management guidelines do not cover even one-third of these cases, and clinical sense requires that only 35 (11 %) of 306 cases need to be treated.

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# EPIDEMIOLOGICAL STUDIES - IN PROGRESS

## Development of surveillance methodology for tuberculosis

(Ongoing study, 1990-2000)

This is a long term epidemiological study undertaken in the BCG Trial area with high non specific sensitivity, with a view to identifying a simple, inexpensive tool for the surveillance of tuberculosis in the community. The following are the parameters being studied:

- 1) Age-specific prevalence of infection and its trend.
- 2) Age-sex- specific rates of disease prevalence, incidence and trend
- 3) The proportion of chronic excretors among prevalence cases and their drug sensitivity status.

The methodology has been described in detail in the annual reports of 1990 & 1991. The planned intake of about 100,000 could not be completed due to lack of x-ray units. So also, the 30th monthly Selective Follow-Up (SFU) could not be taken up. The SFU rounds for 18 months for all villages and 24 months for all but two villages have been completed in Thiruvelangadu panchayat union. The first resurvey has been initiated and one panchayat union (Kadambathur) has been covered during the year.

The coverages obtained for the follow-up rounds and resurvey are found to be maintained at high levels for all examinations like x-ray, sputum examination and tuberculin testing.

In all, 172 sputum positive cases were diagnosed during the year 1994. Of these, 72 were from follow-up rounds and the remaining from resurvey.

More than half of the cases (59%) were positive only on culture. Thirteen percent were positive on smear only and negative by culture.

Of the 135 culture positives for whom drug sensitivity results were available, 22 had a history of previous treatment. Ninety percent of cultures were sensitive. Multidrug resistance was seen in only 3 patients.

**Management of cases:** Sputum positive cases were referred for anti-tuberculous treatment with Short Course Chemotherapy (SCC) at the nearest Primary Health Centre. Information on their symptomatic and drug regularity status was obtained along with two specimens of sputum.

**Passive case finding:** Since it has not been possible to maintain the six-monthly follow up rounds with the available resources, there has been a need to revise the interval between two surveys of the ongoing study for the development of surveillance methodology as 3 years, with selective follow-up at 12 months. So, it has become necessary to improve the passive case finding activity in 8 health facilities in and around the study area by sputum examination for all symptomatics for case detection. A total of 636 symptomatics were registered in all PHCs and sputum collected. Of these, 42 (7.2%) persons became sputum positive cases who were put on treatment with SCC by the Medical Officer of the health facility. The study is in progress.

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### **Association between physical exertion and the occurrence of Adenolymphangitis (ADL)**

(Ongoing study, 1994-96)

Episodes of adenolymphangitis (ADL) are often attributed to physical exertion repeatedly. As an initial step, the perception of the people regarding the degree of exertion associated with the various tasks in each occupation was quantified. This was done by asking 119 randomly selected individuals from the study area to grade the severity of the several components of the different tasks, for e.g., ploughing, digging, sowing, transplanting, weeding, manuring, etc., for farming, digging, load carrying, cement mixing, etc., for construction activities and so on. This grading will later be used to elucidate the role of difficult physical activity in precipitating ADL.

It is seen that carrying head load followed by digging was identified as a very difficult job. Harvesting has been graded as a difficult job. The other jobs are considered to have normal or minimal exertion.

Information on the degree of exertion in the 48 hours preceding the onset of an ADL episode was collected. The study population is those individuals who are prone to get recurrent ADL, as evidenced by having

had two or more episodes in the last 6-month period. A "case" is someone who gets a third or subsequent episode. Those prone to get ADL but have not got an episode at that particular time is the first control and an individual without ADL at all is the second control. Thus, there are two controls per case. So far, information on 70 cases and 140 controls have been collected. The sample size aimed for is 200 cases and 400 controls. This study will be continued along with the proposed study of the efficacy of DEC-medicated salt in preventing ADL episodes in an area with ongoing transmission. The study is in progress.

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### **Surveillance of individuals infected with the Human Immuno-deficiency Virus for the development of tuberculosis**

(Ongoing study, 1989-99)

A longitudinal cohort study was started in July, 1989 with the objective of monitoring the occurrence of tuberculosis among patients with HIV infection.

Patients identified to be positive for HIV infection on ELISA testing from the various surveillance centres (Madras, Vellore and Pondicherry) are included. They are registered in the Centre and followed up at 6-monthly intervals with clinical examination, including sociological assessment and detailed investigations.

The family members including the spouse and other sexual partners are also being registered and followed up to study the pattern of transmission of HIV infection.

The study cohort contains 238 HIV positive patients, of whom 96 had tuberculosis (82 at registration and 14 during follow-up) and were treated with either 2EHRZ<sub>7</sub>/7RH<sub>7</sub> from TRC or routine 8-month short course regimen at the nearest centre. Four of these had multi-drug resistance.

Forty one patients had died over 54 months follow-up, of whom 26 had tuberculosis. Hence, superinfection with tuberculosis appears to increase the risk of mortality at least four times in the HIV infected cases. The various causes of death were ascertained. The study is in progress

## **LIBRARY & INFORMATION SERVICES**

The Library & Documentation Centre is continuing the following services: Tuberculosis ALERT, CD-ROM Medline Searches, E-Mail & Bulletin Board Services, Resource Sharing, Inter-Library Loans, Creation and Maintenance of Bibliographic Databases, Current Contents on Diskette, Online Searches, Development of User-Friendly Softwares, reprint/reports procurements, etc.

The Centre has been linked to the Indian Medlars Centre. Publication of TRC News Bulletin (Quarterly) has been launched (40000 copies). NIC has recognised the Centre as the nodal agency to develop a national bibliographic database on tuberculosis and allied diseases. The Centre got connectivity to RENNIC Services of NIC.

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# APPENDICES

## TRAINING PROGRAMMES

### Trainees

The following underwent training in different departments as follows:

#### **Bacteriology**

Two M.D. (Microbiology) and fourteen M.Sc.(Microbiology) students from Dr.A.L. Mudaliar Post Graduate Institute of Basic Medical Sciences, Taramani, Madras, from 17.1.94 to 21.1.94.

Mrs.R.Shanthi, Laboratory Technologist (Microbiology), Ehrlich Laboratory, Madras, from 15.3.94 to 26.3.94

Seventeen students of Diploma Course in Medical Laboratory Technology, Voluntary Health Services, Adyar, Madras, from 2.5.94 to 14.5.94.

Dr. V.Subramaniam, Research Assistant, Regional Medical Research Centre, Port Blair, Andamans, from 14.5.94 to 28.6.94.

Miss. G.Shakeela, M.Sc. (Microbiology) from A.L, Mudaliar Institute of Basic Medical Sciences, Taramani, Madras, from 23.5.94 to 6.6.94

Two M.D.(Microbiology) students from Madras Medical College, Madras, from 16.6.94 to 30.6.94

Miss Ashwini Nandedkar from Dr. Suresh Amin's Pathology Laboratory, Baroda, from 11.7.94 to 23.7.94

#### **Cardio-Pulmonary Medicine**

Mr. K. Sridhar, II B.E. (Electronics and Communications) student, Sathyabhama Engineering College, Jeppiar Nagar, Madras, Inplant Training, from 9.5.94 to 27.5.94

Mr. C.R.Venkatesh, Technician, Regional Occupational Centre of National Institute of Occupational Health, Bangalore, 26.5.94 to 27.5.94.

Dr. Deepa Chockalingam, Resident, Devaki Hospital, Madras, from 23.12.94 to 30.12.94.

### **Epidemiology**

Dr.A.P. Sugunan, Research Officer, Regional Medical Research Centre, Port Blair, Andamans, from 7.1.1994 to 25.1.1994.

### **Immunology**

Dr. Radha Madhavan and Mr. M. Parthiban Ph.D students from the Department of Rheumatology, Madras Medical College, Madras, from June to August, 1994.

Ms. R. Meera, Department of Biotechnology, Central Leather Research Institute, Adyar, Madras, from September to December, 1994.

Dr. Manonmani, Vector Control Research Centre, Pondicherry, during June, 1994.

Dr. Dhanapal and Dr. Jothilakshmi, Final year M.D.(Microbiology) students, from Madras Medical College, during June, 1994.

Ms.Jothi Rao, JRF, Central Leather Research Institute, Adyar, Madras, from July to September, 1994.

Dr.Sumanlata Lal, Senior Research Officer, RMRIMS, Patna, from 25.07.94 to 04.08.94.

Mrs.Vijayalakshmi Ravi, Centre for Biotechnology, Anna University, Madras, from May, 94 to February, 95.

### **Pathology**

G. Revathy, MSc. (1st year anatomy student), during May-June1994.

Dr. Dhanapal and Dr. Jothilakshmi, Final M.D.(Microbiology), from Madras Medical College, - 1.6.94 to 6.6.94

## **General**

Compulsory Rotating Resident Internee posting students from Sri Ramachandra Medical College, Porur, Madras - for 2-3 weeks.

## **Others**

One- or two-day training programmes were arranged at the Centre for batches of medical students, post-graduates, nursing students and para-medical personnel, as given below:

Three DTCD students from Institute of Thoracic Medicine, Chetpet, Madras.

Twenty Medical Officers, German Leprosy Relief-Association India, Shenoy Nagar, Madras.

Forty five students from Rajiv Gandhi Paramedical Training College, Adyar, Madras.

Inservice training for the MPWs, Lab. Technicians and Health Supervisors in 17 PHC's Chengleput North.

## **SYMPOSIUM ON "CHILDHOOD TUBERCULOSIS - WHAT IS NEW ?"**

A Symposium on Childhood tuberculosis organized by Tuberculosis Research Centre (ICMR) and Indian Academy of Pediatrics (Tamil Nadu Branch), at Madras, on 4th December, 1994 was inaugurated by Dr. G.V. Satyavati, Director General, ICMR. Dr.R. Prabhakar, Director, welcomed the gathering. Dr. Sembon David, DME, Tamil Nadu Govt., presided. Dr. V. Sankara Narayartan, President Elect, IAP, Tamil Nadu Branch, released the souvenir.

There were four sessions addressing different aspects of the subject, namely, epidemiology and diagnosis, radiology and laboratory aspects, clinical aspects and management. Presentations were made by experts in the field followed by a lively discussion. The details are as below:

### **SESSION I - EPIDEMIOLOGY AND DIAGNOSIS**

<b>Subject</b>	<b>Speaker</b>
Epidemiology and natural history of childhood TB	Dr. Manjula Datta
Overview of Mantoux testing	Dr. S.Srinivasan
Role of flexible bronchoscopy, BAL in diagnosis	Dr. Soumya Swaminathan (Organizing Secretary)

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### **SESSION II - RADIOLOGY AND LABORATORY ASPECTS**

<b>Subject</b>	<b>Speaker</b>
Radiographic diagnosis of pulmonary TB in children	Dr. Elizabeth John
Bacteriologic diagnosis	Dr. C.N. Paramasivan
Recent advances in immunology of TB	Dr. P.R. Narayanan

### **SESSION III - CLINICAL ASPECTS**

<b>subject</b>	<b>Speaker</b>
Approach to diagnosis of pediatric TB - State of the Art	Dr. N. Somu
Pitfalls in clinical diagnosis	Dr. Sarala Rajajee
TB meningitis	Dr. Padma Ramachandran
TB of lymphnodes in children	Dr. M. S. Jawahar

### **SESSION IV - MANAGEMENT**

<b>Subject</b>	<b>Speaker</b>
Preventive aspects	Dr. N. Deivanayagam
Chemotherapy of childhood tuberculosis	Dr. M.B. Raghu
TB from the practitioners point of view	Dr. Vasanth Kumar

## STAFF DEVELOPMENT PROGRAMMES

1. Dr. V. Kumaraswami was awarded Ph.D in General Medicine by the University of Madras, during 1994.
2. Dr. Rajeswari Ramachandran, Dr. Rani Balasubramanian and Dr.A.M. Reetha attended a basic course in statistics for doctors' at the Institute for Research in Medical Statistics (Madras Chapter), Madras, from 28.2.94 to 11.3.94.
3. Dr. Alamelu Raja attended training course and workshop on Applications of flow-cytometry in cellular and molecular biology at the Institute of Nuclear Medicine and Allied Sciences, New Delhi, from 14.3.94 to 25.3.94.
4. Mr.M.G.Sreekumar underwent training in Library management & computerisation, at the Anna Institute of Management, Madras, from 21.6.94 to 25.6.94.
5. Mrs. Chandra Immanuel and Mr.K. Jayasankar underwent training programme on HPTLC techniques conducted by Anchrom Companies Ltd., at the Anna University, Madras, during August, 1994.
6. Mr. V.Sundaram underwent training on "computer application for health department", at the Anna Institute of Management, Madras, from 26.12.94 to 30.12.94
7. Dr.M.Kannapiran underwent a 4-month certificate course in personal computer application at the Anna Institute of Management, Madras, from December, 1993.
8. Mrs. Sudha Ganapathy, Ms. Theresa Xavier, Dr. Geetha Ramani Shanmugam, Mrs. Nirupa Charles, Mrs. Beena Thomas, Mrs. Mohanarani Suhadev, Mrs. Meenalochani Dilip and Mr. M. Raja Sakthivel underwent training in HIV/AIDS counselling at the workshop organized by the Aids Research Foundation of India, Madras, during 1994.
9. Mr. M.G. Sreekumar was awarded lecturership in Library and Information Science by U.G.C.

## PAPERS PRESENTED AT SCIENTIFIC CONFERENCES

Name of conference, venue and date	Title of paper	Name of staff member
XIII National Congress on Respiratory Diseases, Madras, 4-6 January, 1994	Bronchoalveolar lavage studies in sputum smear negative pulmonary tuberculosis	Dr.V.K.Vijayan
-do-	Position paper on spirometric norms in India	Dr.V.K.Vijayan (Convenor)
-do-	Pulmonary function tests	Dr.V.K.Vijayan
-do-	Symposium on chronic obstructive pulmonary diseases (pulmonary function changes)	Dr.V.K.Vijayan
-do-	Cardio-pulmonary functional assessment	Dr.V.K.Vijayan (Chairman)
-do-	Management of pulmo- nary tuberculosis patients with bacilli resistant to strepto- mycin, isoniazid and/or rifampicin	Dr.Paulin Joseph
-do-	Use of vancomycin in selective Kirchner's liquid medium for culture of tubercle bacilli	Mrs.Sara Mathew

<b>Name of conference, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
XVIII Biennial Conference of the Indian Association of Leprologists, Madras, 21-22 January, 1994	Controlled clinical trial of 2 MDT regimens in the treatment of bacteriologically positive BULL patients- A 10 year report	Dr.A.Thomas
-do-	-	Dr.V.D.Ramanathan (Co-chair person)
8th Asian Congress of Paediatrics, New Delhi, 6-11 February, 1994	Aerobic capacity and cardio pulmonary response to exercise in healthy south Indian school children	Dr. Soumya Swaminathan
International Conference on Chest Diseases, Apollo Hospitals, Hyderabad, 12-13 February, 1994	Exercise testing in pulmonology	Dr.V.K.Vijayan
-do-	Bhopal gas disaster	Dr.V.K.Vijayan (Chairman)
-do-	Bronchoscopy	Dr.V.K.Vijayan (Chairman)
International Conference on Parasitology and Tropical Medicine, Malaysian Society of Parasitology and Tropical Medicine, Kuala Lumpur, 25-28 August, 1994	The clinical spectrum of filarial disease	Dr.V.Kumaraswami

Name of conference, venue and date	Title of paper	Name of staff member
XII Annual Conference of Indian Society for Medical Statistics on Evaluation Technologies in Medical Education & Health Care Delivery System, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha, 5-7 September, 1994	Acute respiratory infection in children : average number of episodes and its duration	Mr.P.G. Gopi
-do-	X-ray lesions in children with tuberculosis	Mrs.M.P.Radhamani
-do-	Analysis of clinical trial data beyond the analysis of variance	Dr. P. Venkatesan
-do-	Incomplete covariate analysis using Cox's regression	Dr. P. Venkatesan
-do-	Estimation after stop- ping a clinical trial early	Dr. P. Venkatesan
XIV Conference on the Genus Mycobacterium, International Working Group on Mycobacterial Taxonomy, Lisbon, Portugal, 19-24 September, 1994	Characterisation of <b>M.fortuitum</b> complex isolates and MAIS complex isolates obtained from clinical samples and the envi- ronment of the South Indian BCG trial area by susceptibility to drugs and heavy metals	Dr.C.N.Paramasivan

<b>Name of conference, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
49th National Conference on Tuberculosis and Chest Diseases, JIPMER, Pondicherry, 6-9 October, 1994	Comparison of bronchoalveolar lavage and sputum culture examinations in the diagnosis of sputum smear negative pulmonary tuberculosis	Dr.V.K.Vijayan
-do-	An evaluation of split drug regimens for pulmonary tuberculosis- A controlled trial	Dr.A.M.Reetha
-do-	A direct rifampicin susceptibility test for tubercle bacilli	Mrs. Sara Mathew
-do-	Health seeking behaviour and acceptability of available health facilities and awareness on tuberculosis in a tribal area	Mrs.K. Jagga Rajamma
-do- (Meet the Expert Session)	Pulmonary function testing-interpretations. pulmonary function in bronchial asthma	Dr.V.K.Vijayan
-do-	Bioavailability of anti-tuberculosis drugs	Dr. Prema Gurumurthy (Co-chair person)
National Conference on Respiratory Diseases and Environmental Disorders, New Delhi, 22-23 October, 1994	Newer diagnostic modalities in tuberculosis	Dr.C.N.Pammasivan

<b>Name of conference, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
Maths Project Expo X, Consortium of Schools for Maths Experience Programme, Madras, 10-11 November, 1994	-	Dr.P.Venkatesan (Panel-judge)
XVII Medical Congress, Indian Association of Medical Microbiologists, Armed Forces Medical College, Pune, 12-14 November, 1994	Is there any alternative to BCG?	Dr.C.N.Paramasivan
4th International Congress on Cardio-Pulmonary Diseases, International Academy of Chest Physicians and Surgeons (East India Chapter), Calcutta, 25-27 November, 1994	Clinical applications of cardio-pulmonary exercise testing (Guest lecture)	Dr.V.K.Vijayan
6th National Paediatric Pulmonology Conference, Kottayam, 26-27 November, 1994	Pulmonary function tests in children (Guest lecture)	Dr. Sournya Swaminathan
13th Asia Pacific Congress on Diseases of the Chest, Hong Kong, 5-8 December, 1994	Relationship between lung inflammation and changes in pulmonary function in MIC exposed subjects at Bhopal	Dr.V.K. Vijayan
-do-	Role of broncho-alveolar lavage in the diagnosis of sputum smear negative pulmonary tuberculosis	Dr.V.K. Vijayan

<b>Name of conference, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
13th Asia Pacific Congress on Diseases of the Chest, Hong Kong, 5-8 December, 1994	-	Dr.A.M. Reetha
XV Annual Conference of the Indian Society for Probability and Statistics, Manonmaniam Sundaranar University, Tirunelveli, 21-23 December, 1994	Estimation for general patterns of incomplete data	Dr.P. Venkatesan
XXVII Annual Conference of the Indian Pharmacological Society, Seth GS Medical College and KEM Hospital, Parel, Bombay, 21-24 December, 1994	Newer anti-tubercular drugs	Dr.C.N.Pammasivan

**PARTICIPATION BY THE CENTRE'S SCIENTISTS IN  
SYMPOSIA, WORKSHOPS, MEETINGS AND TRAINING  
COURSES HELD AT OTHER INSTITUTIONS**

<b>Name of the event, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
Interface with Comple- xity in Biology, Insti- tute of Mathematical Sciences, Madras, 5 & 27 January, 1994	Networks in immunology Parts I & II	Dr.V.D.Ramanathan
Seminar on Tuberculosis and Respiratory Diseases, Institute of Thoracic Medicine, Madras, 7 January, 1994	Diagnosis and management of interstitial lung diseases	Dr.V.K.Vijayan
ICMR-WHO Workshop on Simulation Modelling in Leprosy, Madras, 4-6 February, 1994	Non-tuberculous mycobacteria and immuno-modulation	Dr.C.N.Paramasivan
Workshop cum Update on Tuberculosis and Respi- ratory Diseases, Insti- tute of Thoracic Medicine, Madras, 7-8 February, 1994	Immunology of tuberculosis	Dr.Alamelu Raja
Meeting of the Fifth CDS/ ISIS (Library Automation Software, UNESCO) Users Group, National Academy of Agricultural Research and Management (NAARM), Hyderabad, 10-13 February, 1994	-	Mr.M.G. Sreekumar

<b>Name of the event, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
Tuberculosis training. programme for medical doctors, German Leprosy Relief Association (India), Madras, 23 February, 1994	Bacteriology of tuberculosis and laboratory investigations of tuberculosis	Dr.C.N.Paramasivan
Tuberculosis training programme for medical doctors, German Leprosy Relief Association (India), Madras, 24 February, 1994	Tuberculosis control in India	Dr.V.K.Vijayan
WHO-Govt. of India Training Course, Institute of Thoracic Medicine, Madras, 28 February - 4 March, 1994	Managing tuberculosis at district level	Dr.V.K.Vijayan (Facilitator)
CME Programme, Gujarat Anti TB Association and IMA (Gujarat), Baroda, 6 March, 1994	Current status of newer anti-TB drugs	Dr.C.N.Paramasivan
International Academy of Chest Physicians & Surgeons of the American College of Chest Physicians, General Hospital, Pondicherry, 6 March, 1994	An update on medicine, cardiovascular pulmonary interactions and oxygen therapy in COPD	Dr.V.K.Vijayan
146th Meeting of the International Medical Sciences Academy (IMSA), Tamil Nadu Chapter, KJ Hospital, Madras, 13 March 1994	Interstitial lung diseases	Dr.V.K.Vijayan

<b>Name of the event, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
Chest Medicine Update ' 1994 American College of Chest Physicians, Association of Physicians of India (Madras Chapter) & Asthma and Bronchitis Association of India (Southern Chapter), Madras, 20 March, 1994	Interstitial lung diseases - current views	Dr.V.K.Vijayan (Chairman)
Public Forum - Know your Asthma - Asthma and Bronchitis Association of India (Southern Chapter), Madras, 20 March, 1994		Dr.V.K.Vijayan
Chest Medicine update 1994, American College of Chest Physicians, Association of Physicians of India (Madras Chapter) and Asthma and Bronchitis Association of India (Southern Chapter), Madras, 20 March, 1994		Dr.A.M. Reetha
CME programme on Respiratory Medicine, Department of Respiratory Medicine, Calicut Medical College and American College of Chest Physicians, Kozhikode, 17 April, 1994 .	Patho-physiology and oxygen therapy in COPD	Dr.V.K.Vijayan

<b>Name of the event, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
CME Programme on Respiratory Medicine, Dept. of Respiratory Medicine, Calicut Medical College and American College of Chest Physicians, Kozhikode, 17 April, 1994	-	Dr.A.M.Reetha
Steering Committee of Therapy for Mycobacterial Diseases and Immunology of Mycobacterial Diseases, WHO, Geneva, 27-30 April, 1994	-	Dr.T.Santha Devi
Bio-Medical Engineering Division, Indian Institute of Technology, Madras, 28 April, 1994	Clinical applications of pulmonary function testing	Dr.V.K.Vijayan
Workshop cum CME Programme on CNS Infections, Dept. of Microbiology and Immunology, Stanley Medical College, Madras, 18 June, 1994	Immunodiagnosis of neurotuberculosis	Dr.Alamelu Raja,
CME programme on Essentials of Immunology, National Academy of Medical Sciences and the Medical Education and Research Trust, St. Martha's Hospital, Bangalore, 26 June, 1994	Immune-mediated lung diseases	Dr.V.K.Vijayan

<b>Name of the event, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
Seminar on Drugless Treatment of Asthma and Chronic Bronchitis, National Academy of Medical Sciences, Indian Medical Association and GSVM Medical College, Kanpur, 16 July, 1994	Exercise for reconditioning and nutritional counselling	Dr.V.K.Vijayan
CME Programme, GSVM Medical College, Kanpur, 17 July, 1994	Current status of lung function tests	Dr.V.K.Vijayan
Symposium on Asthma revisited, Asthma and Bronchitis Association of India (Southern Chapter), Apollo Hospitals, Madras, 7 August, 1994	Pulmonary function tests in bronchial asthma	Dr.V.K.Vijayan
-do-	Childhood asthma - management aspects (Guest lecture)	Dr.Soumya Swaminathan
Indiaclen Meeting, Mahabalipuram, Madras, 8 August, 1994	-	Dr.R.Prabhakar, Dr.Manjula Datta, Mr.P.V.Krishnamurthy
Workshop on Tuberculosis, Estimation of costs of intervention, Administrative Staff College, Hyderabad, 11-13 August, 1994		Dr.R.Prabhakar, Dr.Manjula Datta

<b>Name of the event, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
CME Programme, Department of Cardiology, Stanley Medical College, Madras, 20 August, 1994	Cardio-pulmonary exercise testing	Dr.V.K.Vijayan
Informal Consultation Meeting on the Development of New Strategies for the Control of Lymphatic Filariasis, TDR/WHO Filariasis Field Trials Task Force, Universiti Sains, Penang, Malaysia, 20-28 August,1994	Recent advances in the pathogenesis of lymphatic filariasis	Dr.V.Kumaraswami
CME Programme, Indian Association of Medical Microbiologists (Tamil Nadu & Pondicherry Chapters), Madras, 29 August, 1994	BCG: a multiple vaccine vehicle	Dr. N.Selvakumar
Update on Tuberculosis, Jointly sponsored by the Association of Physicians of India, TB Association of AP & Indian Chest Society (Hyderabad Chapter), Gandhi Medical College, Hyderabad, 11 September, 1994	Disease caused by non-tuberculous mycobacteria	Dr.C.N.Paramasivan

Name of the event, venue and date	Title of paper	Name of staff member
Satellite Symposium of XVI International Union of Biochemistry and Molecular Biology Congress on Collagen-Structure, Biology and Technology, Madras, 15-17 September, 1994	Development of an animal model .for the study of fibrosis induced by tuberculosis	Mr.K.Jayasankar
-do-	-	Dr.Prema Gurumurthy
Meeting of the Filariasis Field Trials Tasks Force, TDR/WHO, Geneva. 19-23 September, 1994	-	Dr.V.Kumaraswami
Workshop on Protocol Development, Operational Research Units, TB Programmes, WHO, Geneva and Foundation for Research in Community Health, Bombay, 27-30 September, 1994	-	Dr.R.Balambal
3rd National Update in Pulmonology, Department of Pulmonology, Sri Ramakrishna Hospital, Coimbatore and the American College of Chest Physicians (South India Chapter), Coimbatore, 2 October, 1994	Pulmonary function tests - a review	Dr.V.K.Vijayan

<b>Name of the event, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
Workshop on Comprehensive Leprosy Care Project of Goa, Panjim, Goa, 9 October, 1994	Microbiology of leprosy bacillus	Dr.C.N.Paramasivan
Social and Economical Impact of Lymphatic Filariasis, Mini-Workshop, VCRC, Pondicherry, 6-9 November, 1994	-	Mrs.M.P.Radhamani, Mr.D.L. Satya narayana Rao
IV International Symposium on Vectors and Vector borne Diseases, Bhubaneswar, 12-15 November, 1994	Recent advances in chemotherapy of lymphatic filariasis	Dr.V.Kumaraswami
Joint ICMR/TDR/WHO 3rd Workshop on Social and Economic Impact of Lymphatic Filariasis, TRC, Madras, 11-14 December, 1994	-	Dr.Manjula Datta, Mr.R.Selvaraj
Tamil Nadu Dr.MGR Medical University, Certificate course on HIV/TB, Madras, 14 December, 1994	Pathogenesis of TB	Dr.V.D.Ramanathan
CME Programme, Child Trust Hospital, Madras, 23 December, 1994	Clinical application of pulmonary function tests in children	Dr.Soumya Swaminathan

<b>Name of the event, venue and date</b>	<b>Title of paper</b>	<b>Name of staff member</b>
Refresher Course in Physiology (Inter- disciplinary) for College Teachers (Zoology), University of Madras, Administrative Staff College, Madras, 28 December, 1994	Gas transport between the lungs and tissues	Dr.V.K.Vijayan
do-	Lung Physiology with special reference to pulmonary diseases	Dr.V.K.Vijayan
Meeting of the Silverplatter CD-ROM Users, Madras, 30 December, 1994	-	Mr.M.G.Sreekumar

## LIST OF PUBLICATIONS

### Papers published

1. Michael Schulzer, Radhamani, M.P., Stefan Gryzbowski, Edwin Mak and Mark Fitzgerald, J. - A mathematical model for the prediction of the impact of HIV infection on tuberculosis. **International Journal of Epidemiology**, 1994, **23**, 400-407.
2. Nirmala Chandrasekaran, Edwin Amalraj, R., Manjula Datta, Krishnamurthy, P.V., Vijayasarithi, Subramaniam, S. and Rajasambandam, P. - Hereditary pattern of cancer. **Indian Journal of Cancer**, 1994, **31**, 86-91.
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24. Padma Ramachandran and Prabhakar, R. Follow-up of patients discharged against medical advice in tuberculous meningitis studies in children. **Indian Journal of Tuberculosis**, 1994, **41**, 143-145.

#### **Papers accepted for publication**

1. Kolappan, C., Selvaraj, R., Abdul Khudoos, Appe Gowda, B.N., Manjula Datta and Prabhakar, R. - Repeatability of nerve thickness assessment in the clinical examination of leprosy. **Leprosy Review**.
2. Rani Balasubramanian, Sadacharam, K., Selvaraj, R., Theresa Xavier, Gopalan, B.N., Prabhakar, R. and Shanmugam, M. Feasibility of involving tribal literate youths for case finding in tuberculosis programme in a tribal area in Tamil Nadu. **Tubercle and Lung Disease**.
3. Mohanarani Suhadev, Sudha Ganapathy, Sivasubramanian, S. and Santha, T. A retrospective analysis of "on-compliant" patients under controlled clinical trials of short course chemotherapy. **Indian Journal of Tuberculosis**.
4. Jagga Rajamma, K., Vijaya Baskar, D., Narayana, A.S.L., Rajeswari Ramachandran and Prabhakar, R. Health seeking behaviour, acceptability of available health facilities and awareness on tuberculosis in a tribal area. **Indian Journal of Tuberculosis**.
5. Soumya Swaminathan, Somu, N., Venkatesan, P., Vijayasekaran, V., Sankaran, K., Prabhakar, R. and Vijayan, V.K. Cellular profile bronchoalveolar lavage fluid in pulmonary tuberculosis. **Archives of Disease in Childhood**.

6. Somu, N., Soumya Swaminathan, Paramasivan, C.N., Vijayan, V.K. and Prabhakar, R. Value of bronchoalveolar lavage and gastric lavage in the diagnosis of pulmonary tuberculosis in children. **Tubercle and Lung Disease.**
7. Vijayan, V.K., Sankaran, K., Sharma, S.K. and Misra, N.P. Chronic lung inflammation in victims of Bhopal tragedy. **Respiratory Medicine.**
8. Vijayan, V.K. Interstitial lung diseases: Mechanisms of lung injury, granuloma formation and fibrosis, cryptogenic fibrosing alveolitis, hypersensitivity pneumonitis, Farmer's lung, histiocytosis X, idiopathic pulmonary haemosiderosis and radiation-induced lung injury. **In: Respiratory Diseases. Ed: Pandey, J.N., Oxford University Press, New Delhi.**
9. Vijayan, V.K. Tropical eosinophilia: aetiology, pathology and pathogenesis. **In: Respiratory Diseases. Ed: Pandey, J.N., Oxford University Press, New Delhi.**
10. Vijayan, V.K. Pulmonary embolism - diagnosis and management. **In: Recent Advances in Clinical Medicine. Ed: Rabbani, M.U., Aligarh Muslim University, Aligarh.**
11. Vijayan, V.K. Hypersensitivity pneumonitis. **In: Clinical immunology (A multi-author book). Ed: Pravash C. Sen Gupta, Calcutta.**
12. Vijayan, V.K. Nitric oxide and the lung. **In: Medicine Update. Ed: Sankar, P.S., Association of Physicians of India, Bombay.**
13. Brahma Jothi, V., Pichappan, R.M., Paramasivan, C.N., Rajaram, K., Sankar Kumar and Prabhakar, R. Immune status and chemotherapy in pulmonary tuberculosis in South India. **Tubercle and Lung Disease.**
14. Paramasivan, C.N., Kamala, T., Daniel Herbert, Venkatesan, P., Alugu Palli, S., Larsson, L. and Prabhakar, R. Heterogeneity within mycobacteria belonging to **M.avium** complex and **M.fortuitum** complex isolated from environmental and clinical samples of South Indian BCG trial area. **Microbiology.**

15. Kamala, T., Paramasivan, C.N., Daniel Herbert, Venkatesan, P. and Prabhakar, R. Immune response and modulation of immune response induced in the guinea pigs by **Mycobacterium avium** complex (MAC) isolates from soil and sputum samples from the South Indian BCG trial area. **Indian Journal of Medical Research.**
16. Daniel Herbert, Paramasivan, C.N., Manjula Datta, Vallishayee, R.S. and Prabhakar, R. IgG antibodies against antigens of various mycobacterial species in children and in pre- and post-BCG young adults. **Indian Journal of Tuberculosis.**
17. Sara Mathew, Paramasivan, C.N., Balambal, R., Rajaram, K., Fathima Rehman and Prabhakar, R. A direct rifampicin sensitivity test for tubercle bacilli. **Indian Journal of Medical Research.**
18. Sara Mathew, Manjula Datta, Paramasivan, C.N. and Prabhakar, R. Vancomycin for controlling contamination in selective Kirchner's liquid medium for tubercle bacilli. **Indian Journal of Medical Research.**
20. Selvakumar, N., Vanajakumar, Gopi, P.G., Venkataramu, K.V., Manjula Datta, Paramasivan, C.N. and Prabhakar, R. Isolation of tubercle bacilli from sputum samples of patients in the field studies by the Cetylpyridinium Chloride-Sodium Chloride (CPC-NaCl) and Sodium Hydroxide (NaOH) methods. **Indian Journal of Medical Research.**
21. Alamelu Raja, Narayanan, P.R., Rema Mathew and Prabhakar, R. Characterization of mycobacterial antigens and antibodies in circulating immune complexes from pulmonary tuberculosis. **Journal of Laboratory and Clinical Medicine.**
22. Raghu, B., Sarma, G.R. and Venkatesan, P. Effect of anti-tuberculosis drugs on the iron-sequestration mechanism. **Indian Journal of Pathology and Microbiology.**
23. Rajeswari, R., Sivasubramanian, S., Balambal, R., Parthasarathy, R., Ranjani, R., Santha, T., Somasundaram, P.R., Ganapathy, S., Sudarsana, K., Zaheer Ahamed Sayed, Kalyanaraman, S. and Prabhakar, R. A controlled trial of short-course chemotherapy for tuberculoma of the brain. **Tubercle and Lung Disease.**

## **JOURNAL CLUB**

Journal Club meetings were held each week, at which published scientific articles covering different areas of research were reviewed by staff members of various departments in turn. A synopsis of the paper(s) to be presented and the reference details were circulated in advance, to facilitate better participation by the audience in the discussion that followed the presentation. In all, 40 such meetings were conducted during the year.

In addition, a quiz programme on tuberculosis and related diseases was conducted.

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## **LECTURES BY VISITING SCIENTISTS**

<b>Subject</b>	<b>Speaker</b>
Regulation of antigen responsiveness by cytokines in filariasis	Dr. Siddharth Mahanty, Senior Staff Fellow, Laboratory for Parasitic Diseases, National Institute of Allergy & Infectious Diseases, National Institutes of Health, USA.
Tuberculosis/diagnosis	Dr. F. Howard Schneider, Senior Vice President, Dynagen Inc., Boston, USA.
Interaction of HIV and tuberculosis	Dr. Richard Hayes, London School of Hygiene, and Tropical Medicine, UK..

## **DISTINGUISHED VISITORS**

1. Mr.Richard Hayes, Epidemiologist, The London School of Hygiene and Tropical Medicine, London, U.K.
2. Mr.P.K.Morgan, P.K. Morgan Ltd., Chatham, Kent, U.K.
3. Prof.V.Gnanaprakasam, Vice-Chancellor, Tamilnadu Veterinary and Animal Sciences University, Madras.
- 4.. Phily M. Grimlang, F. Edward Hebert Medical School, USUHS.
5. Dr.Lennart Larssou, University of Lund, Sweden.
6. Dr.Jerry Porteous, Centre for Clinical Epidemiology and Biostatistics, Faculty of Medicine, University of Newcastle, Australia.

## STAFF MEMBERS ON ADVISORY COMMITTEES OF OTHER INSTITUTIONS

Staff member	Name of committee
Dr.R.Prabhakar	Indo-UK ODA Programmes on Tuberculosis, U.K.
-do-	Editorial Board, Ceylon Medical Journal, Colombo, Sri Lanka.
-do-	Project Review Committee, Indo-US Science and Technology Initiative, Department of Science and Technology, Government of India, New Delhi.
-do-	Standing Technical Committee, Tuberculosis Association of India, New Delhi.
-do-	Executive committee, ICMR, New Delhi.
-do-	Project Review Committee for Tuberculosis, ICMR, New Delhi.
-do-	Editorial Board, Indian Journal of Tuberculosis, New Delhi.
-do-	Scientific Advisory Committee, Regional Medical Research Centre, ICMR, Port Blair, Andamans.
-do-	Scientific Advisory Committee, RMRIMS, Patna.
-do-	Scientific Advisory Committee, JALMA, Agra.

Staff member	Name of committee
Dr.R.Prabhakar (continued)	Joint Scientific Advisory Committee , RMRC, Bhubaneswar.
-do-	Research Advisory Panel, Schieffelin Leprosy Research and Training Centre, Karigiri.
-do-	Planning Board, The Tamilnadu Dr. M.G.R. University of Medical Sciences, Madras.
do-	Senate, The Tamilnadu Dr.M.G.R. University of Medical Sciences, Madras.
-do-	Board of Management, Vision Research Foundation, Shankar Netralaya, Madras.
-do-	Research Sub-Committee, Vision Research Foundation, Shankar Netralaya, Madras.
Dr.C.N.Paramasivan	Task Group, International Working Group on Mycobacterial Taxonomy "Selection of methods and Strategies for use in the clinical mycobacte- riology laboratcry", USA.
-do-	Editorial Board, <b>Indian Journal of Tuberculosis</b> , New Delhi.
-do-	Editorial Board, <b>Indian Journal of Medical Microbiology</b> , Madras.
-do-	Board of studies in Microbiology, University of Madras, Madras.

Staff member	Name of committee
Dr.T.Santha Devi	Steering Committee of Therapy for Mycobacterial Diseases and Joint Steering Committe for Mycobacterial Diseases and Immunology of Mycobacterial Diseases, WHO, Geneva.
Dr. V.K.Vijayan	International Governor, International Academy of Chest Physicians and Surgeons of the American College of Chest Physicians, USA.
-do-	Expert Member, Central Crisis Group (CCG) for Chemical Disasters, Ministry of Environment and Forests, Government of India, New Delhi.
-do-	Editorial Board, <b>Indian Journal of Chest Diseases and Allied Sciences</b> , V.P.Chest Institute, New Delhi.
-do-	Core Committee, Technical Report on clinical studies, Bhopal Gas Disaster Research Centre, Bhopal.
-do-	Convenor, Position paper on "Spirometric Norms in India", Indian Chest Society, Bombay.
-do-	National Advisory Committee, World Conference on Cardio-Pulmonary Diseases and Critical Care Medicine, December, 1995, American College of Chest Physicians (Western India Chapter), Bombay.

Staff member	Name of committee
Dr.V.K.Vijayan (continued)	Respiratory Medicine Panel, Institute of Integral Health Studies, Madras.
-do-	Expert Member, Crisis Management Group for Chemical Road Transportation Emergency, Tamilnadu Pollution Control Board, Government of Tamil Nadu.
-do-	Assistant Editor, <b>Lung India</b> , Madras.
-do-	Advisory Board, Lung Sounds Asthma and Bronchitis Association of India (South India Chapter), Madras.
Dr.Padma Ramachandran	State Resource Facility, Continuing Medical Foundation in Paediatric Update, Indian Academy of Paediatrics, Tamil Nadu State Branch, Madras.
Dr.Manjula Datta	Scientific Advisory Committee, Regional Medical Research Centre for Tribals, Jabalpur.
-do-	Curriculum Development committee for Clinical Epidemiology, The Tamilnadu Dr.M.G.R. University of Medical Sciences, Madras.
-do-	Steering Committee, Advanced Centre for Clinical Epidemiological Research and Training, Madras.

Staff member	Name of committee
Dr. V. Kumaraswami	Expert, WHO Panel on Parasitic Diseases (Filariasis), WHO, Geneva.
-do-	Filariasis Field Trials Task Force, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), Geneva.
-do-	Steering Committee (Filariasis), TDR/WHO, Geneva.
Dr. Soumya Swaminathan	Editorial Committee, IAP, <b>Journal of Practical Paediatrics</b> , Madras.
Dr.K.V. Kuppu Rao	Executive Council, Indian Association of Biomedical Scientists, Madras.
Dr. V.D. Ramanathan	Consultant for Histopathology, Central Leprosy Training and Research Institute, Chingleput and CJIL Field Unit, Avadi, Madras.
Dr. P. Venkatesan	Editorial Board, <b>Biomedicine</b> , Madras.

## **PRIZES AND AWARDS RECEIVED BY STAFF MEMBERS**

1. Dr. V.K. Vijayan was awarded the "Calicut Medical College Alumni Oration Award", Calicut for the year 1994.
2. Mrs. Sara Mathew was awarded gold medal for the best paper presented at the 13th National Congress on Respiratory Diseases held at Madras, during 1994, entitled "Use of vancomycin in selective Kirchner's liquid medium for culture of tubercle bacilli".
3. Dr. P. Venkatesan was awarded the "Dr.R.N. Srivastav Award" for the best paper presented by a Scientist <45 years of age at the 12th Conference of the Indian Society for Medical Statistics held at Wardha in September, 1994, entitled "Analysis of clinical trial data beyond the analysis of variance".