1.6 Pharmacology and Biochemistry

1.6.1. Metabolic disposition of anti-leprosy drugs and related studies

Background and work done
Ofloxacin is being tried as a part of modified MDT regimens for leprosy. At this juncture adequate knowledge of the transport of these chemotherapeutic agents will be of help in the development of new agents. Both norfloxacin and dapsone are very hydrophilic with appreciable partition coefficients for n-octanol-phosphate buffer (pH 7.22). A preliminary study has been conducted at this Institute on the accumulation of these two agents using modified fluorescence methods. By employing exogenous norfloxacin concentration of 10 ug/ml, a steady state concentration (SSC) of 100 ng of norfloxacin/mg cells, by dry weight was obtained for M. smegmatis. The accumulation kinetics of dapsone was slower compared to those of norfloxacin and the transport mechanism was found to be energy independent as evidenced by the lack of any significant effect of dinitrophenol and CCCP on the intracellular accumulation of both the drugs. The accumulation of norfloxacin was found to be linear over the external concentration range of 10-50 g/ml.

In order to study the mode of transport, the effect of ethambutol and isoniazid on norfloxacin accumulation was studied during the year. The drugs were added to the growing M. smegmatis culture in Sauton’s medium 24/48 h prior to cell harvesting and was also added 10 minutes prior to addition of the norfloxacin to ensure the presence of both drugs through out the penetration experiment. The results showed that norfloxacin accumulation was not affected by subinhibitory concentrations (0.5-1.0 g/ml) of ethambutol (Fig15.) although the results with isoniazid were varying.

Conclusion
Accumulation and permeation kinetics of dapsone, based on fluorescence method, was slower in M. smegmatis compared to those of norfloxacin. The findings suggest that the mycobacterial cell wall does not act as a barrier to norfloxacin accumulation and that norfloxacin enters M. smegmatis strain used in our study by an energy-independent, non-saturable porin pathway.

Duration : 1998-2003
Future Programme:

Further studies on mycobacterial accumulation of other antimicrobials like ofloxacin in drug sensitive as well as drug resistant strains are being pursued as part of new project.

1.6.2. Studies on mycobacterial cell wall lipids

Scientists: K. Venkatesan, Nirmala Deo and V.M. Katoch

Duration: 1998-2003

Background and work done

Dimyccerosates of glycosylphenolphthiocerols (Phenolic glycolipids) have been shown to be present in standard strains of *M. kansasi*, *M. bovis*, *M. africanum*, *M. gastri*, *M. marinum*, *M. microti*, *M. leprae* and *M. tuberculosis* Canetti strain. These lipids which are mostly located at cell surface have been implicated in mycobacterial pathogenesis and they have been of use in the immunodiagnosis of mycobacterial infections. Simple and rapid lipid extraction procedures and thin layer chromatographic systems for detection of lipids based on polarity developed by Minnikin and coworkers and efficient column chromatographic systems standardised at our Institute have enabled us to isolate and purify these antigenic
lipids from a few selective mycobacterial strains. The yield of PGL was found to be ranging from 1.2-2.0 mg/100 mg lyophilised cells of *M. bovis* AN5, *M. bovis* BCG and *M. kansasii*. During the year under report, the uptake and incorporation of radioactivity from 1-14C-palmitic acid into various cell wall lipids of *M. bovis* BCG and *M. kansasii* were evaluated. The findings indicate incorporation of radioactivity to the tune of 0.35 % in PGL, 0.55 % in wax esters (phthiocerol dimycocerosates) and 1.0 % in mycolic acids of the organisms incubated with 1-14C palmitic acid (Sp. Activity 20.06 Ci/mol) (Fig. 16). Extended studies using 14C acetate and 14C-propionate showed that the incorporation of these labeled substrates into cell wall lipid fractions was more compared to palmitic acid.

**Conclusion**

Two phenolic intermediates have been identified in the biosynthesis of PGL by *M. bovis*. 14C-labelled acetate, propionate, valerate and palmitic acid have been found to be incorporated significantly in cell wall lipids which can be used in the studies on biosynthesis of mycobacterial lipids.

**Future programme**

Further studies are underway, as part of a new project, to isolate labelled intermediates of the PGL biosynthetic pathway and use them for mycobacterial uptake studies. The studies will also be pursued using other radiolabelled substances like valerate.
1.6.3. Intracellular expression of proteins with mycobacteria - A proteomic analysis (DST funded project)

Scientists: Deepa Bisht, Nirmala Deo and K. Venkatesan
Duration: 2001-2005

Background

A formidable worldwide resurgence of tuberculosis is being witnessed in the wake of AIDS and leprosy, although on the decline, persists as a major health problem in developing countries. Dismal performances of BCG in some populations, as well as of other candidate integral vaccines have underlined the need for molecular characterization of immunopathologically important mycobacterial constituents in the quest for better drugs, diagnostics and vaccines. The mechanisms by which mycobacteria survive the potentially hostile environment of the macrophages are fundamental to our understanding of their virulence and pathogenicity. The genes/proteins involved in their survival strategies within macrophages have not yet been defined. Elucidation of proteomics may provide new targets for antimicrobial drug/vaccine development.

Work done

As already reported, an in vitro model system has been developed to study the intracellularly expressed proteins. During the year, experiments were carried out to standardize and analyze the protein profile of mycobacterial cell lysate under infected and non-infected conditions. Cell lysate was prepared by sonication and centrifugation. To study the infected condition, murine peritoneal macrophages were infected with Mycobacterium bovis BCG. At the end of fifth day infected cells were collected and lysate was prepared. Macrophage lysate was also analyzed to serve as control. Expression of proteins under infected condition was analyzed by SDS-polyacrylamide gel electrophoresis (PAGE). Initial findings show overexpression of proteins around 65-70 KDa (Fig. 17&18).

Future programme

The two-dimensional gel electrophoresis technique will be standardised using IPG (immobilised pH gradient) strips of different pH range. Over-expressed proteins will be analysed by 2D-PAGE for its homogeneity.
1.6.4. Biochemical markers in leprosy reactions

**Scientists**: K. Venkatesan, K. Katoch, Nirmala Deo and Deepa Bisht  
**Duration**: 2001-2003

**Background and work done**

There is a dire need of biochemical and other markers for having an idea about the onset of leprosy reactions and also to monitor the course of reactions. Studies conducted so far suggest the usefulness of lysosomal enzyme beta glucuronidase in the case of ENL reactions with circulating immune complexes. The study was extended to cases with reversal reactions. The order of increase found in ENL cases was not seen in these cases. Another marker tried was cholesterol in blood. The serum cholesterol levels were very low in the case of ENL reactions but patients with reversal reactions also showed slight decrease in serum cholesterol levels.

**Conclusion**

Selective release of beta glucuronidase from leucocytes incubated with ENL sera and the serum levels of beta glucuronidase and cholesterol been found to be useful markers for predicting the onset of ENL reactions and monitoring the course of such reactions.
1.7 Therapeutic Trials

1.7.1. Pyrazinamide as a part of combination therapy for BL/LL group of patients

Scientists: Kiran Katoch, V.M. Katoch, Mohan Natrajan, V.D. Sharma and D.S. Chauhan
Paramedical and technical Staff: N. Crispin, S. Shinge, Kalicharan, S.K. Bhan, Noel S. Singh, Shri Ram and A. Robi
Duration: 1990-2004

Background and work done

This study was initiated in 1990 to see the effect of Pyrazinamide on persisters in leprosy. The addition of Pyrazinamide to the anti-tubercular regimen had a very beneficial effect in the elimination of persisters and relapses, and this also helped in the shortening of the duration of treatment. At that time the treatment of leprosy was given with the standard MDT which was continued till smear negativity. It took approximately 3 to 5 years of MDT to achieve smear negativity in highly bacillated BL and LL cases. In TB the beneficial effects of Pyrazinamide were seen when it was added to the regimen in the intensive phase. This intensive phase lasts for 2 months out of the total duration of treatment. Likewise in leprosy also Pyrazinamide was added to the MDT regimen in the initial 1 year of the 3 to 5 years treatment period. As was prevalent at that time, the patients were treated till smear negativity and were followed up on placebo after completion of the treatment. Thirty highly bacillated BL/LL patients with an average initial BI of 4 to 5+ were included in the study. Nineteen of these patients could be followed up and have now completed a follow-up of 8 to 10 years after stoppage of therapy. No relapse has been observed during this period.

Fig. 19. Progress of patients on MDT and MDT + PYZ
Conclusions

The regimen was well tolerated and accepted by the patients.
Clinical response to the treatment was good.
No persister was detected in the tissue biopsies of patients, both by mouse foot pad inoculation (MFP) and estimation of ATP after 1 year of therapy (Fig. 19).
By 4 years of therapy 94% of the patients became smear negative and all the patients became smear negative by 4.5 years of therapy and treatment was stopped (Fig. 19).
No relapse has occurred in the post-treatment follow-up of 8 to 10 years.

Since the introduction of this regimen, the profile of diseases and treatment regimens have changed considerably. Such highly bacillated cases are seen much less commonly now and continuous treatment regimens have given way to fixed duration therapy (FDT) of one year duration. It, therefore, appears that this regimen has no place in the present anti-leprosy treatment regimens. However, this study has shown that Pyrazinamide did help in reducing persisters and relapses in this group of patients. This regimen may be useful in treating patients who suffer from both leprosy and tuberculosis.

1.7.2. Chemotherapy trials in MB leprosy using conventional and newer drugs - ofloxacin and minocycline

Duration : 1993-2005

Background and work done

As reported earlier this trial was undertaken in consultation with NLEP to see if the addition of these newer drugs ofloxacin and minocycline to the standard MDT is effective in the treatment of leprosy. This study was undertaken with the following objectives:

(i) To investigate the therapeutic efficacy of newer drugs in monthly administration.
(ii) To study the treatment failure and/or relapse in MB patients. This is to be compared with standard treatment failure of 10% and cumulative relapse rate of 5%.
(iii) To measure the side effects of the newer drugs.
(iv) To measure the effect on complications such as reactions (reversal reactions, ENL, neuritis).
(v) To assess the relationship between the detection of persisting viable bacteria and relapses, if any.

(vi) To enable the National Leprosy Eradication Programme and patients to have the opportunity to choose alternate regimens according to the needs of the programme and/or individual patients.

These patients were treated with the regimen (designed in consultation with ICMR and NLEP) comprising of rifampicin 600 mg once a month supervised, minocycline 100 mg once a month supervised, ofloxacin 400 mg once a month supervised, combined with dapsone 100 mg and clofazimine 50 mg daily unsupervised. Treatment was continued for 12 months followed by placebo daily. Intake of the patients was completed 6 years back. The progress is being monitored by clinical, histological and bacteriological and other relevant parameters (BI, mouse foot pad, ATP and molecular probes).

The details of the clinical progress, the results of viability testing and molecular markers have already been described in the earlier Annual Reports.

In the post treatment follow-up of about 6 years, 3 patients (3%) have relapsed. However, none of the patients with a pre-treatment BI of ≤ 2+ has relapsed during this period. Two patients with pre-treatment BI between to 2+ to 2.9+ and one with pretreatment BI between 3+ to 3.9+ have relapsed.

Follow-up of the cases continued during 2003. There were no relapse during this period.

**Future programme**

All the patients will be monitored during the follow-up.

### 1.7.3. Relapses in MB leprosy following 2 years MDT

**Scientists** : B.K. Girdhar, Anita Girdhar, J.K. Chakma and Anil Kumar

**Paramedical and technical staff** : H.R. Dwivedi, Dalveer Singh, Sukhas Ram and Kalicharan

**Duration** : 1996-2006

**Background and summary of the work done**

Since the introduction of MDT, at the global level, there has been a marked and significant decline in the active case load of leprosy with several of the parameters showing a positive change. All this has been attributed to the marked efficacy of the MDT across the leprosy spectrum. The early results from clinical laboratories and the field studies with its use in MB patients showed that practically there were no relapses when given till the point of smear.
negativity or till the end of 2 years, which ever was later. This had led to the concept and testing of fixed duration therapy (FDT) for MB patients. A two-year treatment, as opposed to therapy till smear negativity (TSN), was thus recommended for all MB cases irrespective of bacterial load or classification. With FDT too, the short term results were found to be satisfactory. In all the reports on the efficacy, limited follow-up was the common factor.

Our result of a study conducted on the same lines, using WHO recommended three drug combination given for 2 years to 222 MB (BT /BB/BL/LL) patients followed-up for 5 years, had shown a relapse rate of 6.3 % per 100 patient years (14 relapses in 930.55 patient year) follow-up, significantly more than what the field workers had reported.

The follow-up of the cohort has been continued. Of them, 32 patients have completed almost 10 years follow-up, with a mean of 9.84 years. During this period, apart from earlier 5 relapses in these 32 patients, 3 additional patients have relapsed and these relapses have occurred at the end of 7.5 years, 10.25 years, and 9 years of follow-up indicating that a fourth of all the available patients (8 of 32) relapse over 10 year after stoppage of therapy. Two of the 3 patients, who relapsed late, had LL and had initial BI of 5.5+ and 3.75+ (arithmetic mean of BI of 4 sites). In both of them, the smears became positive again. Relapse in the third patient, who initially had been diagnosed as BT, was with appearance of new lesions appearing insidiously at the end of 9 years follow-up. Patients responded to re-treatment with same drugs indicating that the relapses were on account of reactivation and multiplication of persister organisms that were drug sensitive.

Further 2 other patients had acute onset of inflammation in the earlier skin lesions. Both of them responded well to corticosteroids and hence were labeled as reversal reaction and not relapse. Though this is unusual, long persistence of dead mycobacteria and / or their skeletons / antigens is well known as also is the regain of some degree of specific hypersensitivity by the lepromatous patients long after smear negativity.

Occurrence of 2 of the 3 relapses, among initial high BI patients, re-enforces that with limited therapy, this group is at a higher risk of having problems of relapse.

1.7.4. Long-term follow-up of lepromatous patients given therapy till smear negativity

**Scientists**: B.K. Girdhar and Anita Girdhar, J.K. Chakma and Anil Kumar

**Paramedical and technical staff**: H.R. Dwivedi, Dalveer Singh, Sukhas Ram and Kalicharan

**Duration**: 1996-2006
Background and work done

In this Institute, during the early years of MDT, all lepromatous patients were being given three drug combinations for the entire length of therapy—till they became skin smear negative. Of the 301 lepromatous patients followed-up in this group, initially for a mean duration of 3.6 years, 12 patients had shown bacteriological and/or clinical relapse over a follow-up period of 1085.46 patient years, giving a relapse rate of 1.11/100 pt. yrs. Like in the other study, about half the cases showed bacterial worsening only.

This relapse rate is lower than that seen among the patients given the same drug combination but for 2 years fixed duration only. The difference was particularly marked and statistically significant when comparison was made of high BI patients in the two groups (1.27 vs. 4.29 per 100 patient years).

As in the earlier study of long term follow-up in FDT treated patients, patients are being continuously monitored in this group as well. Twenty one patients have had more than 10 years follow-up post treatment. Among them one has shown smear positivity again. This patient was initially 5+ and had LL type of disease. Detailed comparison of the outcome in the two schedules is given in the table 9.

### Table 9. Comparison of results of follow-up of lepromatous cases treated with two-years FDT versus others treated till smear negativity

<table>
<thead>
<tr>
<th>(TSN)</th>
<th>2 yrs. MDT (FDT) treated group</th>
<th>MDT given till smear negativity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients</td>
<td>222</td>
<td>301</td>
</tr>
<tr>
<td>Follow-up (years) Mean</td>
<td>4.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Patient years</td>
<td>930.55</td>
<td>1085.46</td>
</tr>
<tr>
<td>Relapses Number</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>% of total patients</td>
<td>6.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Per 100 pt. Years</td>
<td>1.43</td>
<td>1.10</td>
</tr>
<tr>
<td><strong>Long Term Results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with (10 yr. follow-up)</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>Follow-up (years) Mean</td>
<td>9.84</td>
<td>10.34</td>
</tr>
<tr>
<td>Patient years</td>
<td>315</td>
<td>218</td>
</tr>
<tr>
<td>Relapses Number</td>
<td>3 (+5)*</td>
<td>1 (+!)*</td>
</tr>
<tr>
<td>% of total relapsed patients</td>
<td>9.37</td>
<td>4.76</td>
</tr>
<tr>
<td>Relapses per 100 pt. Years</td>
<td>0.95</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Number of relapses during the first 3-4 years follow-up
From the early results shown in the table, and also observed from survival analysis, it is evident that the risk of relapse is significantly higher in the MB patients given treatment for only 2 years. The long term follow-up does show that the outcome of the MB patients treated till smear negativity is significantly better as compared to those given 2 years FDT. This is despite the fact that the former group consisted of patients from BT to LL type, had low mean BI with many being smear negative right from the beginning. In contrast, the later group had only BL/LL (majority LL) patients, who were all skin smear positive and had initially a large bacterial load.

The relapses observed in both the groups were similar as about 40% patients in both the studies had only a bacteriological relapse and all the relapsed patients responded to retreatment with same drugs and became skin smear negative in 12 to 24 months. This indicates that the relapses in MB patients following MDT are due to re-activation of drug sensitive persister organisms that escape the bactericidal effect of 3 drug combination.

1.7.5. A comparative study of high dose vs low dose oral corticosteroid therapy in RR and its effect on recent nerve function impairment in leprosy

**Scientists**: Anita Girdhar, J.K. Chakma, A. Ravindiran, S. Husain, Anil Kumar, G.N. Malaviya and B.K. Girdhar

**Duration**: 2002-2006

**Background and Work done**

The symptomatic course of leprosy in some patients is complicated by the occurrence of reactions that are mostly responsible for disability, deformity and destitution. While in lepromatous (LL and BL) patients, this occurs due to deposition of immunocomplexes (ENL or type II reactions), in borderline cases it is the result of changes, more often increase in cellular hypersensitivity (RR or type I reactions). Where as several drugs are effective in the therapy of former, corticosteroids are the main stay in the treatment of type I reactions in leprosy.

It has been observed that in RR, the outcome with steroid administration is better when steroids are started early and when given for fairly long duration and in adequate doses. However, what is adequate dose and duration is not settled. In this study we have tried to look at both immediate and long term response to two dosage (high and low) schedules of steroids in patients of leprosy with borderline reactions and nerve damage.

Randomized controlled trial has been undertaken with independent assessment of nerve function in borderline tuberculoid (BT) leprosy patients with type I reactions.
Patients of the age group 15-60 years of both sexes having recent problems of reactions and/or nerve function impairment (NFI) of 3 months or less, were taken for the study. Pregnant/lactating females, individuals with diabetes/hypertension and those unwilling to come monthly for follow-up were excluded.

**Regimens**

**Low Dose Regimen:** 30 mg daily for 3 months followed by 20 mg daily for 2 weeks and there after reduced by 5 mg every 2 weeks. Total = 5 months.

**High Dose Regimen:** 60 mg daily for 2 months, there after reduced by 10 mg every 2 weeks till a dose of 10 mg is reached, thereafter reduced by 5 mg every 2 weeks. Total = 5 months

Patients were seen every month. Formal periodic assessment for clinical response and any drug related side effects was done during and after steroid therapy.

Sensory assessment was done using common pin and graded nylon monofilaments for touch sensation, moving two point discrimination using U clip and the vibration sense was assessed using tuning fork. Motor power was graded on scale 0-5.

Forty patients were included in the study and randomly allocated to the two regimens. Fifteen and 13 patients are available in the groups who completed the 5 month trial period and are being followed-up and have completed 10-12 months of surveillance. Skin lesions became flat with regression of erythema in 3.4±1.9 (range 1 to 9) months in those who received higher dose of corticosteroids as compared to 4.92±1.77 (2 to 12) months in the other group of patients given 30 mg, the difference being significant (p < .05: student t-test).

Both lesional and peripheral sensations were assessed. Some degree of sensory recovery was found in both the groups but there was no marked difference. In contrast, better motor function was seen in the former group. There were 2 patients in each group in whom no improvement or deterioration was seen in the 5 months' steroid trial period.

The study was started in early 2002. The detailed result of patients who have had 10-12 months follow-up following the 5 months trial period are given in table 10. It is seen that the patients who were administered higher dose of corticosteroid did better in terms of non recurrence of RR and nerve function recovery or loss.
Table : 10. Long term effect of steroid administration.

<table>
<thead>
<tr>
<th>Group</th>
<th>Follow-up Mean ± SD</th>
<th>Range (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg Group</td>
<td>9.67±1.47</td>
<td>2-16</td>
<td>No recurrence of skin reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No nerve pain or tenderness Of the 2 patients, who had deterioration in motor function during steroid therapy, one improved</td>
</tr>
<tr>
<td>30 mg Group</td>
<td>10.46±2.18</td>
<td>0-17</td>
<td>Recurrence of reactions in 2, with nerve pain and tenderness in 1 New NFI in 1 ulnar palsy</td>
</tr>
</tbody>
</table>

A total of 16 minor problems were seen in those given 60 mg corticosteroids as against 9 in the other group. Details are given in the table 11 below. These problems regressed soon after (1-3 months) of the stoppage of steroids on completion of 5 months.

Table : 11. Minor steroid related problems

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>60 mg group</th>
<th>30 mg group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Striae atrophicae</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mooning of face</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Epigastric burning</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Weight gain</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>1(minor bleeding)</td>
<td>1 (head ache)</td>
</tr>
</tbody>
</table>

In both the groups, none of the patients had increase in blood sugar or rise in blood pressure. However, in the higher steroid group, one patient had to be excluded from the study, in the second month, on account of psychosis. Another case in this group developed herpes zoster while on high dose of corticosteroids. The follow-up is being continued.
1.7.6. **Evaluation of the effect of addition of immunotherapy with \textit{Mw} vaccine to standard chemotherapy in borderline leprosy**

**Scientists** : Raj Kamal, Kiran Katoch, Mohan Natrajan and M. Arora.  
**Para medical and technical staff** : Noel Crispin, Shyam Shinge, Kalicharan, R.F. Lal, Kumereshan, Ved Mitra, Sam Deepak Lal, S.N. Masih and Pritpal Kaur  
**Duration** : 2001-2006

**Background**

This trial has been initiated to assess the additive effect of immunotherapy with \textit{Mycobacterium w} with standard MDT in borderline leprosy cases (PB and MB).

**Work done**

As reported in the annual report last year, the cases of the borderline spectrum (BT, BB, BL) are being included in this study. Detailed clinical examination, charting, smear examination of all untreated borderline cases was done, biopsies were taken from the active lesions of all cases at start of therapy and every six month thereafter till the completion of therapy.

- Standard MDT was given to all the patient according to the type of disease.  
- \textit{Mw} 0.1ml (0.5x10^7 bacilli) was injected intra-dermally at the start of therapy and every six months in addition to chemotherapy.  
- Follow-up is being done with respect to the following  
  - Local reaction to \textit{Mw} vaccine  
  - Incidence of reactions  
  - Clinical progress of the lesions  
  - Histopathology for bacillary and granuloma clearance.

During the year under report more cases have been included. A total of 128 cases (BT= 53, BB=44, BL= 31) in the trial limbs plus 20 as control (BT=10, BB=4, BL=6) have been included in the study. The follow up of the patients has continued.

The clinical progress of the patients at one year is as shown in the following table 12.
Table: 12. The clinical progress of BB/BL patients at 1 year (3 doses of Mw vaccine plus MDT).

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Progress of patients</th>
<th>BB (in %)</th>
<th>BL (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of lesions</td>
<td>decreased</td>
<td>78</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>same</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Erythema</td>
<td>decreased</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>same</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Infiltration</td>
<td>decreased</td>
<td>95</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>same</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Sensation</td>
<td>improved</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>same</td>
<td>50</td>
<td>65</td>
</tr>
</tbody>
</table>

The BT patients were followed up after completion of 6 doses of MDT and 2 vaccinations on placebo. In them also more patients improved. Erythema and infiltration regressed completely in all the patients and there was an improvement of sensations in the lesion in 75% of the cases.

Histological findings with MDT and Mw

The histological findings in both the categories of cases (i.e. BT and BB/BL) are summarized in tables 13 & 14. Cases of both the categories wherein the histopathology was nonspecific or the infiltration fraction (IF) was less than 20%, were not included in the study.

Table: 13. Fall in Granuloma Fraction (GF) in BT patients

<table>
<thead>
<tr>
<th>N</th>
<th>Initial</th>
<th>After first dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>N_{high GF}</td>
<td>8</td>
<td>70%</td>
</tr>
<tr>
<td>N_{GF moderate}</td>
<td>10</td>
<td>40%</td>
</tr>
<tr>
<td>N_{GF &lt; 10}</td>
<td>7*</td>
<td></td>
</tr>
</tbody>
</table>

*excluded

Table: 14. Fall in Granuloma Fraction (GF) in BB/BL patients

<table>
<thead>
<tr>
<th>N</th>
<th>Initial</th>
<th>After first dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>N_{high GF}</td>
<td>13</td>
<td>68%</td>
</tr>
<tr>
<td>N_{GF moderate}</td>
<td>12</td>
<td>30%</td>
</tr>
<tr>
<td>N_{GF &lt; 20%}</td>
<td>5*</td>
<td></td>
</tr>
</tbody>
</table>

*excluded
Dramatic decrease in granuloma fraction has been observed especially in some of the BT cases following Mw vaccination + MDT as shown in the fig. 20.

Future programme

The study will continue to include the required number of cases and their follow-up as per the approved plan.

1.7.7. Uniform MDT (U-MDT) regimen for all leprosy patients (A WHO funded multicentric study)

**Scientists** : K. Katoch, Pawan Sachan, Chief Co-ordinator - M.D. Gupte (NIE, Chennai)

**Field and Laboratory Staff** : Raghvendra Singh, Shailendra Singh and Rajendra Kumar

**Duration** : 2003-2008

**Background**

This project was presented, discussed and approved by the SAC held in November 2003. Briefly if the same regimen is given to all types of leprosy patients it is operationally much more easy to treat them. Majority of cases which are detected under field conditions are early cases i.e. PB and smear negative MB cases. The use of Clofazimine in the PB regimen for 6 months has been tried by us earlier and was reported to substantially decrease the incidence of persisting activity, reactions and with no relapses in the post treatment follow up of 5 years. Therefore all the PB cases getting this treatment will be gainfully treated. For smear negative MB cases the bacterial load is low and theoretically, for most of
these cases the duration of the present day MDT regimen can be reduced to 3 to 6 months based on the data obtained from animal experiments. This study is a field based study and the patients will be followed up for 5 years after stoppage of therapy and failures if any detected during the follow-up will be put on standard MDT. This study is a multi-centric study funded by WHO and we are one of the four participating centres in India.

**Work done**

Forty-six leprosy patients have already been included in the study from the Patara block of the Ghatampur field unit. These include 31 males and 15 females. Nineteen patients were of the age group of 15 years and below, 23 were between 16 and 45 years of age and the rest 4 patients were above the age of 45 years. There were 19 PB cases and 27 MB cases. Two patients were smear positive and the rest were skin smear negative.

**Future programme**

The trial will continue to include more cases as per approved plan.
1.8 Reconstructive Surgery

1.8.1. Posterior tibial neurovascular decompression in patients with plantar ulceration

**Scientists**: S. Husain and G.N. Malaviya  
**Duration**: 1993-2003

**Background and work done**

Plantar ulcer is a secondary problem due to anesthesia of the sole. Recurrent injuries to the feet give the ulcer. Heeling of ulcer is poor due to vascular ischemia and recurrence is common due to anesthesia. To improve the sensation and the vascularity posterior tibial neurovascular decompression is planned in foot.

This procedure is done as a routine for patients who come with the history of early ulcer, blisters and loss of sensation in the sole. The protective foot wears are given to all operated patients. Long term followup of those posterior tibial neurovascular decompression show improvement in sensation upto 60-70% in all early cases while the healing of ulcer was also seen due to increase of blood flow in the sole.

This project has been completed and posterior tibial neurovascular decompression is being done as a routine procedure for early case of sole anesthesia and ulceration.

1.8.2. Closure of heel ulcers by skin stretching: A follow-up study

**Scientist**: G.N. Malaviya  
**Duration**: 2000-2005

**Background and work done**

Plantar ulcer is a secondary problem in leprosy due to anesthesia of the plantar skin. Posterior tibial nerve damage is common in leprosy and is second to the ulnar nerve in frequency. This result in plantar anesthesia which if neglected can result in ulcers which at times refuse to heal because of recurrent trauma in day to day activities. Heel ulcers are quite common among leprosy affected persons. Wide variety of methods for treatment is available to manage these ulcers but those are far away from being ideal.

Heel has a special padding of adipose tissue enclosed in small compartments made of fibrous septae. An ulcer over heel destroys these tissues and when it heals what is left is a brittle fibrous plug which breaks down frequently. An ideal method of treatment should provide-a full thickness skin cover, good padding almost like natural heel pad and sensations.
While interrogating patients with heel ulcers, it was observed that many of these ulcers begin as fissures on the posterio-medial aspect of heel; during winter months. With the arrival of summer and sweating, the proximal part (vertical part) of these fissures heals leaving the distal part (over heel pad) as ulcers. This lower part fails to heal probably because of continued trauma due to walking for day to day activities. Radiographs of these patients revealed that the depth of these ulcers was only up to the dermis or at best the fat pad in its superficial part. Since the padding was intact only an appropriate skin closure can heal these ulcers. Since the skin was adherent to deeper tissues by fibrous septae, stretching of skin was planned so as to mobilise it for a tension free closure.

17 feet in 11 patients, 10 males and one female, were operated and followed-up. Their age varied from 12 to 54 years (mean 25 years). 6 Cases had ulcer on both sides. The sole was completely anesthetic in all of them. Posterior tibial artery pulsations were normal in all. Clinical diabetes mellitus was ruled out while selecting the cases for surgery. The problem started as fissure at 14 sites and as blister leading to sinus formation in other 3. All cases had ulcer for one year or longer. The follow-up data is presented in table-15.

### TABLE : 15. Follow-up Data and Ulcer Recurrence after Closure of Ulcers

<table>
<thead>
<tr>
<th>Follow-up Period</th>
<th>Upto 1 Month</th>
<th>&gt;1-3 Months</th>
<th>&gt;3-6 Months</th>
<th>&gt;6-12 Months</th>
<th>&gt;12-18 Months</th>
<th>&gt;18-24 Months</th>
<th>&gt;24-36 Months</th>
<th>&gt;36-48 Months</th>
<th>&gt;48 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Feet Re-examined in patients who came for follow-ups</td>
<td>15</td>
<td>09</td>
<td>12</td>
<td>11</td>
<td>12</td>
<td>08</td>
<td>11</td>
<td>06</td>
<td>02</td>
</tr>
<tr>
<td>Ulcer Free Feet</td>
<td>11</td>
<td>06</td>
<td>07</td>
<td>07</td>
<td>09</td>
<td>05</td>
<td>08</td>
<td>06</td>
<td>02</td>
</tr>
<tr>
<td>Minor Recurrences</td>
<td>04</td>
<td>02</td>
<td>04</td>
<td>02</td>
<td>01</td>
<td>03</td>
<td>03</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Major Recurrences</td>
<td>00</td>
<td>01</td>
<td>01</td>
<td>02</td>
<td>02</td>
<td>00</td>
<td>00</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

**Note:**
1. Two cases having major recurrences were on oral steroids for neuritis.
2. Two cases had sensory recovery (one after 6 and another in between 18-24 months after closure of heel ulcer.

Of the 17 feet 8 could be re-examined after 36 months or more. It was encouraging to note that all were ulcer free. Most of the minor recurrences were usually seen in the first 6 months after surgery. Major recurrences were seen in 2 cases who were on steroid therapy.
for neuritis and in them ulcer persisted even after 18 months post-operatively. Sensory recovery was seen in two cases - in one after 6 months and another between 18 and 24 months after ulcer surgery. The callosities and the suture line did not show hyper-keratosis and the scar merged well into the surrounding skin after one year.

The available data suggests that it is worth separating the cases in which the ulcer is not extending deep in the fat pad and calcaneum by radiography of the foot. The simple ulcers can be made to heal with a good scar by a simple surgical procedure like skin stretching and suture. Ulcer recurrences, if any, are of minor nature and most of them occur within 6 months after surgery.

Attempts will be made to retrieve the cases to complete the follow-up before concluding the study in 2005.

1.8.3. Early diagnosis of nerve damage in leprosy: Neurophysiological studies on peripheral nerves

- **Scientists**: S. Husain and G.N. Malaviya
- **Duration**: 1995 - 2005

**Background**

Peripheral nerve involvement is common problem in leprosy. This results in sensory and motor loss in limbs; the end result is clawing of hand, foot drop and wrist drop, and ulcer formation in hand and foot. At present, there is no clinical/laboratory tool available which can detect early nerve damage.

The studies published in literature on the electrophysiology of peripheral nerves have shown that both motor and sensory nerve conductions are diminished in leprosy. Keeping this in mind, a study on nerve conduction was started in leprosy patients who are not having neurological complaint.

This pilot study revealed that 15% of total new cases at OPD of CJIL & OMD, who are not having any neurological complaint, are having diminished motor & sensory nerve conduction velocity and decrease in amplitude while the latency was found to be increased. In some cases only latency was increased while the nerve conduction velocity and amplitude was normal. When all these cases were regularly followed up, about 30% of these cases developed the nerve problems and defined nerve damage.

So far 210 cases without any clinical neurological symptoms were undertaken for electrophysiological investigation where 41 patients showed abnormal electrophysiological findings. Out of 41 cases, 19 developed the neurological deficit. All these cases are under regular follow up for any further nerve problem.
Work done

Forty cases of established leprosy have been included in the study during this period. The observation show that the latency increases as compared to normal, while the nerve conduction velocity and the amplitude decreases in cases where neurological involvement is established. In cases where no neurological deficit is present, these parameters remain close to normal values. In 17 cases however, latency increased by 25% with very minimal changes in nerve conduction. These cases are being followed up to find out whether they are at higher risk to develop neurological deficit. Six developed neurological deficit and were treated with doses of steroids (30mg/day) along with nerve decompression. These cases are under follow-up.

1.8.4. JALMA Flap for restoration of volume of first web space in muscle atrophy associated with ulnar palsy in leprosy

**Scientists** : S. Husain and G.N. Malviya

**Duration** : 1997-2006

Background and work done

Ulnar nerve palsy is common in leprosy and results in clawing of fingers and hollowing of the first web space due to atrophy of adductor pollicis and first dorsal interosseous. Correcting of finger clawing makes the hollowing deformity more obvious when the patient opens the hand fully or greets someone. This makes the patient more conscious about his web space hollowing.

In the past, surgeons have tried silicon gel injection, autologous fat graft, and dermo fat graft to fill this depression. But the success was very short and limited as most of the time the graft was absorbed or rejected due to foreign body reaction. Keeping all these problems in mind a viable adipocutaneous flap based on the cephalic vein and the major tributary of the radial artery from the lower forearm was taken and transferred to the depression of the first web space.

This procedure has been named as 'JALMA Flap'. Sixteen cases have been operated by this procedure; 13 cases showed improvement, 1 case had partial absorption of the flap while other 2 cases had total absorption of the flap and recurrence of the hollowing. The scar over the radial side of the fore arm is a big cosmetic problem. To minimize this scar a two hole procedure to harvesting the graft is planned.
1.8.5. Prevention of deformities in leprosy: Decompression of peripheral nerve trunks

**Scientists**: S. Husain and G.N. Malaviya  
**Duration**: 1997 - 2007

**Background and work done**

Nerve damage in leprosy is a serious problem and results in the patient becoming deformed. Our experience shows that decompression of the affected nerve in early stages can arrest deformity formation in a fair number of cases.

A long-term study of the decompression of peripheral nerves (ulnar and median, posterior tibial) was undertaken. All cases with history of nerve pain and paraesthesiae were undertaken for decompression and postoperatively followed up for any improvement or deterioration. In the study of the median nerve in 26 patients prevention of functional deformity was achieved in 14 patients.

In a parallel study of the ulnar nerve in 238 patients, 108 showed improvement, 104 had retained useful power and 26 cases deteriorated.

This study was continued during this period. Thirty different nerves have been operated for prevention of deformities. Good results in cases of ulnar and median nerves have been observed whereas lateral popliteal nerve does not show much improvement.

1.8.6. Three-tail Tibialis Posterior transfer in Drop foot correction

**Scientist**: S. Husain  
**Duration**: 2002-2007

**Background and work done**

Drop foot is a common deformity due to involvement of Lateral Popliteal nerve in leprosy. For correction of drop foot the Tibialis Posterior muscle is taken as a motor unit and is divided in two slips and sutured with Tibialis Anterior or Extensor Hallucis Longus and Extensor Digitorus Longus slips as a routine procedure as per the complete or incomplete drop foot. It has been observed that the two-tail procedure is not giving the required lift of dorsum of foot and some times not able to present the rotation of foot. Keeping this in mind, we have started three-tail transfer in all drop foot cases. Here, tendon of the Tibialis Posterior muscle is split in three tails and sutured at Tibialis Anterior tendon, Extensor Hallucis Longus and Extensor Digitorus Longus slips at equal tensions.

So far eight cases have been operated and these cases are under follow up.