14th INTERNATIONAL LEPROSY CONGRESS ABSTRACTS

CHEMOTHERAPY

CH1

TREATMENT OF PAUCIBACILLARY PATIENTS WITH MDT CONTAINING RIFAMPICIN, DAPSONE AND PROTHIONAMIDE

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With the introduction of MDT, there has been improved patient compliance and the duration of treatment has been greatly reduced. However with WHO recommended MDT for 6 months, the incidence of persisting activity in lesions, late reations/relapses have varied considerably and has been quite high in many of the reports. The present study was undertaken to see whether the addition of one more bactericidal drug i.e. Prothionamide could help in reducing these limitations of currently used MDT.

112 untreated paucibacillary patients belonging to Indeterminate(I), Tuberculoid(TT) and Borderline Tuberculoid (BT) types and with BI of less than 2 on the Ridley scale were treated with Rifampicin (600mg once a month), Dapsone (100mg daily) and Prothionamide (250mg daily). Treatment was stopped at the end of 6 months. The patients tolerated the drugs fairly well. 6% of the patients had early reaction which subsided with additional steroid therapy. The inactivity rate was 60% at 6 months which improved to 96% at 12 months. None of the cases had late reaction and there was one relapse in about 2 years of post treatment follow-up. The comparison of these results with those of WHO regimen and extended 12 months regimen shows that addition of Prothionamide appears to have a significant effect on clinical improvement as well as in the reduction of the late reactions.

CH2

MULTIDRUG THERAPY FOR TREATMENT OF LEPROSY PATIENTS IN NEW CALEDONIA AND FRENCH POLYNESIA. RESULTS AFTER 10 YEARS.

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Multidrug therapy (MDT), including daily administration of rifampicin, has been implemented in 1982 in French Polynesia, and in 1983 in New Caledonia, for treatment of leprosy cases. Since 1983, 100% of newly detected patients are given MDT. Until 1991, a thioamide was given in addition during the first two months for multibacillary (MB) patients in French Polynesia.

From 1982 to 1992, 365 patients were given MDT: 170 MB and 195 paucibacillary (PB). To date, 32 patients are still under MDT (20 MB and 12 PB). Of the 365 cases, 321 (88%) were compliant to the treatment. Resolution of cutaneous lesions and improvement in the local nerve damage was observed in all of the treated patients. Even in case of reaction, no residual disability of grade > 1 was notified. Among the 62 patients treated with a thioamide, 9 (15%) experienced hepatitis. No relapse has been detected in patients treated with MDT, as compared with a 30% cumulative relapse rate in MB patients treated with dapsone monotherapy in French Polynesia, before implementation of MDT.

CH3

7-YEAR SURVEILLANCE OF 657 CURED MB PATIENTS RE-TREATED WITH MDT

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Since 1983, 657 MB patients clinically cured with DDS monotherapy together with BI of 2 or more at any site smeared previously were re-treated with DDS,RFP and B663 in combination. Four hundred and eighty seven of them were males and 170 were females, their age ranged from 17 to 70 years and their disease duration ranged from 1 month to 39 years. Cured patients not re-treated were used as controls for this trail.

All patients were administered RFP and B663 1200mg each once monthly with supervision and DDS 100mg daily self-administered. This treatment was continued for 12 months and was completed within a period of 15 months. Six hundred and twenty cases (94.27%) of them completed regularly the prescribed course but 37 did not due to the occurrence of side effects or complications. Exclusive of 2 who died of non-leprosy cause and 1 migrated out of Shanghai after completion of re-treatment, the remaining 654 were followed for a period of 4-7 years (534 cases for more than 7 years), no relapsed case was identified. But there were 17 cases detected as relapses among the 137 control patients, giving an overall relapse rate of 12.41% and a mean annual relapse rate of 1.55%. Type I lepra reaction was seen in 7 cases during and after the re-treatment and was successfully controlled with steroids preparations. The authors suggest that although this study has already shown a satisfactory recent effect of re-treatment with MDT, but it is still in need of further observation.

CH4

EFFECT AND SURVEILLANCE OF 1,076 LEPROSY PATIENTS TREATED WITH MDT IN SHANDONG PROVINCE OF CHINA

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One thousand and seventy six active leprosy patients were detected in Shandong province from 1982 to 1991.Of these patients, 619 cases were MB and 457 were PB; 927 were new cases never treated before and 149 were relapsed cases after DDS monotherapy. All cases were treated with MDT until clinically inactive and skin smear negative and then received additional treatment with DDS+RFP for another 12 months. Afterwards, the patient was clinically and bacteriologically monitored annually.The results showed that the BI of skin smears was decreased by 0.7+ each year in the first 3 years. By the end of 1991, 762 of 1,076 cases reached the criteria of cure clinically and bacteriologically. The average treatment duration for cure was 53.1 months in LL, 45.5 months in BL, 42.3 months in BB,37 months in BT, 33.2 months in TT and 32.1 months in indeterminate cases.As regards the five year cured rate, there was no significant difference between the newly diagnosed and relapsed cases. the 762 cases above mentioned have already been monitored after release from treatment for a total of 2284.5 person-years. The longest period monitored was 9 years in PB and 6 years in MB. Only one BT patient relapsed. No leprosy reaction was found after stopping therapy, except neuritis with severe neuralgia occurred in one BB case.

CH5

BACTERIOLOGICAL RESPONSE OF BL/LL PATIENTS TO MDT FOR VARIED DURATION: A RETROSPECTIVE FIVE YEAR FOLLOW UP

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The analysis of five year bacteriological reports available in the hospital records of 678 LL and 180 BL patients who received WHO MDT regimen for varied duration, showed that there was a progressive reduction in the respective average Bacteriological Index(BI) by 0.75 and 0.9 index per year, irrespective of the period of therapy.

At an 18 month average duration of therapy the average BI of LL patients was 1.9+(with 36% negative patients) and that of the BL patients was 1+(with 63% negative patients). The difference observed in BI response of LL and BL patients with comparable initial BI (i.e. 3.9+ and 3.4+ respectively) was statistically significant, indicating that a proper classification is needed for any controlled drug trial.

Progressive reduction in the average BI with increasing percentage of negative patients was observed even after discontinuation of therapy in all the patients with varied ranges of duration of therapy.

In 243 LL patients, there was reduction in BI from initial 3.7+ to 1.4+(with 46% negative patients) at the end of 2 years fixed duration MDT. The subsequent follow up showed further reduction in the average BI up to 0.1+ (with 93% negative patients) at the end of third year of surveillance.

CH6

FIXED DURATION MULTIDRUG THERAPY (FDT) FOR MULTIBACILLARY (MB) LEPROSY IN INDIAN RURAL PROGRAMMES

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On the basis of the available evidence of bacteriological decline after FDT (WHO regimen) for 24 months in MB patients, the National Leprosy Eradication Programme of India has adopted this procedure as a national policy. Field level experience on operational aspects of successful practice of FDT is still lacking. In 1989 NLEP gave permission to us to study FDT in Bulsar (Gujarat) and Chittoor (Andhra Pradesh) districts. We present the methodology adopted to re-train staff in respect of newer principles of chemotherapy, field follow-up after termination of treatment, selection of sties for skin smears, ensuring reliability of smear examination and reporting systems etc.

Observations on bacteriological decline over 2½ to 3 years given below are in conformity with results reported earlier (Ganapati et al 1992).

BI at RFT*	No. of Pts	BI at First Year 4 to 5	3-4	2-3	1-2	0-1	Rendered -ve No.	%
4 - 5	1	-	-	-	-	-	-	-
3 - 4	6	1	2	-	-	-	3	50
2 - 3	11	1	-	-	3	2	5	45
1 - 2	21	-	-	1	-	10	10	48
0.1-1	59	-	-	-	-	30	29	49
Total	98	3 (3%)	2 (2%)	1 (1%)	3 (3%)	42 (43%)	47	48

*RFT : Release from Treatment

At 2nd year of surveillance 37 (88%) out of 42 cases were rendered negative and 3 (16%) were stationary and at 3rd year of surveillance 19 (95%) out of 20 patients were negative and in one patient BI was stationary.

CH7

FACTORS ASSOCIATED WITH RATE OF HEALING IN PAUCIBACILLARY LEPROSY TREATED WITH MDT

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This study was carried out in the Leprosy Control Unit, of CHAD Hospital, CMC, Vellore. 2129 Paucibacillary Leprosy Patients who were released from treatment after 6 months of WHO MDT Regimen were studied.

The effect of factors like 1)age 2) sex 3)Type 4) No. of Patches and 5) Prior treatment with Dapsone on the rate of healing of disease were analysed using Survival Analysis.

74% of the cases healed by the end of 1 year and 95% by the 2nd year. Almost all had healed by the end of 3rd year.

Age, sex and type of leprosy did not affect the rate of healing. The rate of healing was quicker among those with single lesions as compared to those with more than 5 lesions ($P < 0.05$). Interestingly those who had prior dapsone monotherapy showed a singificantly quicker rate of healing ($P < 0.001$).

Persistance of patches after 6 months of MDT does not warrant continuation of treatment.

CH8

LOW RISK OF RELAPSE AFTER PAUCIBACILLARY TREATMENT AMONG CHILDHOOD LEPROSY PATIENTS

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This study deals with the risk of Relapse in children who have undergone Paucibacillary Treatment. This study was conducted in The Leprosy Mission Hosipital, Vizianagaram of Coastal Andhra Pradesh in South India.

248 children who had completed Paucibacillary Treatment in 1985 and were followed upto 1992 were included in the study. Of the 248 children 157 were male and 91 were female. 6(2.4%) were less than 5 years of age, 89(35.9%) 5-9 years of age and 153 (61.7%) were 10-14 years. 204 were classified as TT, 33 as BT and 11 as indeterminate. 200 of them had only one patch and 48 of them had 2 patches or more.

The risk of relapse was computed after 2 years and 7 years of follow up. The two year risk of relapse was 2.016/1000 person years of risk and the seven year risk was 1.2/1000 person years of risk. This study shows that the risk of Relapse among childhood patient after Paucibacillary Therapy is very low or even negligible as compared to Adult patients after Paucibacillary Treatment.

CH9

FIXED DURATION THERAPY (FDT) IN MB LEPROSY

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The conventional WHO-recommended MDT regimen for MB leprosy requires that it be administered for a minimum period of 2 years or till the patient attains bacteriological negativity, which ever is later.

Considering the efficacy of the Combination of Rifampicin, Clofazimine and DDS, it was hypothesised that this combination administered for a period of TWO YEARS ONLY may be adequate to effect killing of M. lepra population in an infected individual and that the bacterial clearance can continue to be done by the immune system of the individual. Therefore, a trial was instituted where the WHO-recommended MDT Regimen for MB leprosy was administered for two years, and its efficacy assessed in terms of "relapse". 261 previously untreated bacteriologically positive MB leprosy patients were included.

All patients continue to have bacteriological clearance during surveillance. The rate of bacteriological clearance is similar to that of patients continued treatment till attainment of bacteriological negativity. None of these patients have relapsed as yet, during 539 person-years of follow-up.

This study is supported by UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES.

CH10

PRELIMINARY RESULTS OF THE EVALUATION OF A SURVEILLANCE SYSTEM OF SIDE EFFECTS OF MDT

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MDT leprosy treatment started as a routine in the State of São Paulo, Brazil, on July, 1991. All the newly diagnosed cases should be included and patients already under single drug treatment should be evaluated. Cases of serious adverse reactions (even death) have been reported after the implementation of the new treatment. In order to develop a better knowledge about the relationship between unexpected clinical events and MDT, a special surveillance system has been set up on May 20, 1992.

This study covers the period of time from that date to December, 1992. Cases wich have been reported and investigated were classified, following clinical, laboratory and epidemiological criteria, as confirmed, probale or discarded.

The system received 159 notifications, 84 of them (51.6%) have been considered confirmed, 55 (35%) probable and 21 (13.4%) discarded. From the confirmed cases, 43.7% were males, 43.7% in the 30 to 50 years old age group and 32.5% from 50 to 70 years old. Some 40.3% of the patients had to be admited to hospitals. The most frequent diagnoses were: 27(32.5%) cases of Influenza-like syndrome, 8 (8.6%) cases of Acute Renal Failure, 5 (7.2%) cases of Toxic Hepatitis, 11 (15.8%) association of the two diagnoses above. Out of the 83 confirmed cases, 70 (86.4%) were old patients who were switched to MDT.

The present study aims to evaluate operational difficulties on MDT implementation and also to evaluate the special surveillance system itself.

CH11

EFFETS SECONDAIRES DES MEDICAMENTS. OBSERVATIONS FAITES CHEZ DES PATIENTS HAITIENS.

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Etude retrospective de 720 dossiers de patients hanseniens suivis de 1984 a 1992, de l'Institut Cardinal Leger contre la lepre d'Haiti.

Au cours de cette communication on mettra en evidence les differents effets secondaires aux medicaments anti-hanseniens (disulone, rifampicine, Lamprene) observes chez ces patients.

CH12

" DISABILITY GRADING " OF PATIENTS IN A MDT PROGRAM - COMPARISON WITH A SIMILAR GROUP TREATED WITH DAPSONE ALONE AND FIVE YEAR FOLLOW-UP

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We reviewed the "Disability Grading" (WHO 1988), the number and severity of Reactions, Neuritis, Treatment required (use of Steroids and Thalidomide) and the prevalence of foot and stasis ulcers in about 1.000 patients that completed MDT and have been followed for 5 or more years. The RI-ISOPRODIAN regime was used in most patients (RIFAMPIN - DAPSONE - ISONIAZIDE - PROTHIONAMIDE). The same evaluations were done in a similar group of patients treated with Dapsone monotherapy. Results will be presented and discussed.

CH13

PROFILE OF RELAPSE CASES IN FIELD TRIAL OF COMBINED THERAPHY IN MULTIBACILLARY LEPROSY

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Profile of five relapase cases following two different regimens of Combined Therapy-Regimen A and Regimen B - in 1174 BL and LL cases, most of them previously Dapsone treated and skin smear negative at intake in a field based trial supported by UNDP/World Bank/WHO Special Programme for TDR at Hemerijckx Leprosy Centre, Polambakkam, South India is presented. The duration of treatment was 2 years of Combined Theraphy or till skin smear negativity whichever is later followed by 8-10 years of follow up. Out of the five relapses, one was MB type and the four being PB type relapses. Their past history, course during Combined Therapy, and Relapse profile including clinical picture, Histopathology and Mouse foot pad inoculation particulars are presented and discussed.

CH14

M.LEPRAE VIABILITY IN SKIN AND NERVE AFTER MDT AND THEIR SENSITIVITY TO ANTI-LEPROSY DRUGS

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Multi-Drug Therapy has not eliminated the problem of 'persisters' in leprosy. The THELEP trials report presence of 'persisters' in 9% of the MB cases treated with MDT.

However in a recent Bombay-based pilot study we recorded a higher incidence of viable M.leprae (30%) in peripheral nerves of treated MB cases. This study was continued to include more cases as well as to establish the sensitivity of the persisting organisms to the drugs in use.

Skin and nerve biopsies were simultaneously obtained from 20 MB cases who had completed a minimum two years of WHO recommended MDT. these were primarily tested for viable bacterial load in footpads of T200x5R (TR) mice. Inocula obtained from these footpads were repassaged into normal mice where confirmation of the growth as well as tests for sensitivity to DDS and Rifampicin were carried out.

The results obtained are discussed in light of 2-3 years follow-up of these patients.

CH15

CONTROLLED CLINICAL TRIAL OF 2 MULTIDRUG REGIMENS WITH AND WITHOUT RIFAMPIN IN HIGHLY BACILLIFEROUS BL/LL SOUTH INDIAN PATIENTS A 10 YEAR REPORT

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A controlled clinical trial of 2 multidrug regimens in lepromatous and near lepromatous cases with BI 2.5 or more on Ridley's scale was conducted. Patients were randomly allocated to the following:

a) On admission: either a 2 drug regimen of Dapsone plus clofazimine daily for 60 months or a similar regimen with rifampin and isoniazid in addition for the first 3 months followed by clofazimine and dapsone for the next 57 months.

b) At 60 months: either a 2 drug regimen of clofazimine and dapsone or dapsone alone daily.

c) At 84 months: either daily dapsone or placebo if their BI was 1.00. Those patients who had BI 1.00 continued to get the treatment allocated at 60 months.

A total of 210 patients were admitted to the study of whom 148(74%;excluding 9 deaths)were available for assessment at the end of 10 years. Clinical examination by an Independent assessor and bacteriological assessments were done periodically. All the patients showed excellent clinical and bacteriological improvement upto 10 years except one who was retreated due to reactivation.

CH16

FOLLOW UP STUDY OF 81 LEPROSY CASES TREATED BY SHORT TERM MDT IN TURKEY

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Between early 1982 and early 1984, 74 patients were taken into the short term course RMP+ETH+DDS regimen and 51 patients were taken into the short term course RMP+CLO+ETH regimen.Treatment term was 28 weeks. In first two weeks daily treatment of 600 mg. RMP was applied and then all patients received 600 mg. RMP weekly.

After completing MDT, during the last 6 years these patients followed up in the hospital or in field work. In the first group, we were able to examine 49 patients (64 %). In this group, only 3 patients had more than BI=2 on skin smears. In the second group 32 patients (63 %) were examined.In this group, only one patient had BI=5 on skin smears. Other patients who completed the trial had no m.leprae in skin smears and had no evidence of clinical activation or sign of relaps.

In this study, we discuss the effectiveness of short term MDT after a long period with bacteriological and clinical results.

CH17

TWENTY YEARS AFTER STARTING THE ERADICATION PROJECT IN MALTA

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Since the Malta Leprosy Eradication Programme was inaugurated in June 1972, 257 paients have been treated with Isoprodian-RMP. The duration of treatment was not fixed, but was determined for each patient. The medication was safe and well tolerated. To date only one patient has relapsed, 17 years after completion of MDT. Apart from the importance of leprosy eradication for Malta itself, this result is of far-reaching significance:

1. Final, relapse-free cure of leprosy can be obtained within a short time without any particular organisational procedure through the use of proper doses of antimycobacterial substances made up as fixed combinations.
2. By treating all patients with the same combination (no difference is made between pauci- and multibacillary cases) but for a varying period of time, epidemiologic eradication of leprosy is rapidly and safely obtained through the use of chemotherapy.
3. Through selection of appropriate drugs, low-cost combinations can be made up (5 - 10 US $ monthly per case).

CH18

EIGHT YEARS FOLLOW UP OF MULTIBACILLARY LEPROSY AFTER 24-27 MONTHS OF MULTIDRUG THERAPY

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During 1983, 80 untreated MB patients from Shandong and Yunan Provinces were treated with 24-27 months of MDT. These patients were examined, treated and followed annually by independent leprosy control teams of these two provinces. At the fifth year of follow-up, 100% (33/33) of patients from Shangdong and 95.3% (41/43) of patients from Yunnan have converted to smear negative. The data of clinical, bacteriological and histopathological examinations will be compared with that of MB patients treated till smear negative elsewhere in China Results at the eighth year of follow up plus their level of PGL antibody will be presented

CH19

RECAIDAS EN HANSENIANOS MULTIBACILARES TRATADOS CON MONOTERAPIA SULFONICA.

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Se estudian entre 352 enfermos multibacilares (LL) tratados con monoterapia sulfonica el número de recaidas despues de conseguirse la negativización.

Se observan un total de 33 recaidas entre 7 a 39 años despues de inactividad bacteriológica.

La recaida en 8 de los enfermos fue de la forma Dimorfa (BL y BB). Todos los casos fueron tratados con Multiterapia.

CH20

RELAPSES IN 20,091 CURED LEPROSY CASES IN SHANDONG PROVINCE OF CHINA

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A retrospective analysis on 20091 cured leprosy cases in Shandong Province of China from 1955 to 1990 is presented. Analysed with life-table method, the relapse rates for MB and PB cases were 6.48‰ person years and 4.29‰ person years respectively. The levels of the relapse rates were closely related to the therapeutic drugs used in the past. In MB patients treated with DDS and DDS+RFP, the relapse rates were 7.92%(446/5,628) and 1.07%(15/1,405) respectively. The former rate is significantly higher than the later one. In PB patients treated with thiacetazone, DDS and WHO-PB regimen the relapse rates were 12.6%(96/763), 5.4%(589/10,903)and 0.18%(2/1,101)respectively. The relapse rate in the WHO-PB regimen treated group was significantly ower than those in other two groups (U=7.70 and 11.8, P<0.001). No relapse was found neither in MB(256) nor in PB (35) cases treated with WHO-MB regimen. 96.3% of relapses in MB and 90.1% relapses in PB occurred within 15 years after cure and most of them were cured again with DDS monotherapy.

According to the analysis mentioned above, we suggest that the follow-up period for the patients cured with DDS monotherapy should be for a minimum of 15 years after release from treatment and an additional short term MDT should be considered for those who are younger than 60 years of age in order to prevent them from relapse.

CH21

SINGLE DOSE RIFAMPIN CANNOT PREVENT RELAPSE IN SKIN-SMEAR NEGATIVE MULTIBACILLARY LEPROSY PATIENTS AFTER DAPSONE MONOTHERAPY

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Between 1982 and 1985, a single dose of RMP 1500mg was administratered by 136 multibacillary leprosy patients who had become clinical and skin-smear negative after various duration of dapsone monotherapy, and then anti-leprosy chemotheray was totaly stopped. By the end of June 1992, 15 relapses were detected among the patients. The relapse rate per 100 patients-year was 2.12%, the cumulative risk of relapse at the 7th year of follow-up was 8.8% at least the same as in other studies where patients received only monotherapy. Therefore, the administration of a single large dose of RMP to multibacillary patients who had already become clinical and skin-smear negative after dapsone monotherapy could not prevent the relapse.

CH22

MULTI-DRUG RESISTANCE IN LEPROSY

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Since its introduction in 1982, Multi-Drug Therapy (MDT) is heralded as one of the most important and stimulating contributions to leprosy control. Data from routine programmes also indicate a high degree of efficacy of WHO/MDT after about 8 years of follow-up. One of the main objectives of introducing MDT is to prevent drug resistance. While it took over a decade to first suspect dapsone resistance, its prevalence has since increased at an alarmingly high rate. In a much shorter period thereafter, secondary resistance has been reported with rifampicin, clofazimine, ethionamide and prothionamide. To date however M.leprae resistance to MDT has not been observed. while 58% of currently registered patients and an estimated 2.5 million undiagnosed patients of leprosy yet remain unexposed to MDT, we report here 2 cases of lepromatous leprosy--fully treated with regular WHO/MDT who exhibited resistance with both dapsone and rifampicin in the mouse footpad. The paper discusses implications of emergence of multidrug resistance in leprosy. The need for continued surveillance and accumulation of data on multi-drug resistance in leprosy is stressed, to be certain about the prevalence and to devise strategies to effectively prevent or decelerate its spread.

CH23

PRIMARY DAPSONE RESISTANCE IN CEBU, PHILIPPINES: RECENT FINDINGS

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The use of Dapsone as monotherapy in leprosy in developing countries has resulted in the occurrence of secondary DDS resistance in patients. Exposure of the community to these individuals has brought about the emergence of primary dapsone resistance in endemic areas.

Tissue specimens taken from active lesions of 38 untreated LL-BL patients sequentially admitted to various studies were inoculated into inbred, locally-produced CBA/J mice. Dapsone sensitivity was determined by feeding the inoculated mice varying concentrations of the drug in the diet. Our results demonstrate primary dapsone resistance in 52.6% of the 38 patients tested. This is a significant increase over earlier surveys in Cebu in which 8.1% [Cellona et al, 1989] and 3.6% [Guinto et al, 1983] of patients had primary dapsone resistant leprosy. This finding stresses the importance of vigorous implementation of MDT to check the resurgence of primary drug resistant cases. Details comparing the results of the present study with those of earlier studies in the Philippines will be presented and discussed.

CH24

STUDY OF RELAPSE IN PAUCIBACILLARY LEPROSY PATIENTS IN MULTIDRUG THERAPY PROJECT IN BHARUCH DISTRICT, GUJARAT, INDIA.

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The prospective study of relapse includes paucibacillary cases of leprosy belonging to non-lepromatous group consisting of tuberculoid, neuritic and indeterminate.
6018 patients paucibacillary leprosy(till Dec.92 who had completed the prescribed period of treatment and now under surveilliance for varying periods are evaluated for evidence of clinical relapse of their disease. Paucibacillary regimen being according to WHO was rifampicin 600 mg. supervised once a month for six months and dapsone unsupervised 100mg daily for six months. The criteria applied for diagnosis of relapse

after excluding Type I reaction, were extension of existing skin lesions, appearance of new skin lesions, paresis, paralysis of previously unaffected muscles and presence of acid-fast bacilli in skin smears.
The relapse rates in these 6018 patients will be compared with relapse rates in PB patients who had received dapsone monotherapy for a minimum period of 2 years in Bharuch district using following parameters.:
a) Age, b) Sex, c) Type, d) Duration of treatment e) Prior treatment.
The findings indicate that short course chemotherapy [1]. The drugs are well tolerated and side effects are minimal. The results of the study and factors associated with occurrence of relapse, time interval and period of follow-up will be presented.

[1] using rifampicin is superior to dapsone monotherapy per se.

CH25

TREATMENT OF HIGHLY BACILLATED BL/LL CASES WITH A PYRAZINAMIDE CONTAINING REGIMEN

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Pyrazinamide has been shown to have a marked sterlizing effect in tuberculosis. A pilot trial earlier showed that it has some beneficial effect in leprosy also. We have initiated a trial in which highly bacillated untreated BL/LL cases were given Rifampicin 600mg once a month, Clofazimine 50mg daily and Dapsone 100mg daily, till the attainment of smear negativity combined with Pyrazinamide 1500mg daily in divided doses for 1 year. The progress was monitored periodically by clinical, bacteriological, BI, mouse foot pad, bacillary ATP measurements and histopathological parameters. Smears from the same sites and biopsies were repeated yearly. 25 patients on this regimen have completed the follow-up of three years after start of therapy. The patients tolerated the drugs fairly well. These patients have been compared with similar cases on same MDT without Pyrazinamide. The incidence and magnitude of reactions and nerve damage was comparable and was easily controllable with routine anti-reaction treatment. There was no growth in the mouse foot pad in Pyrazinamide and non-Pyrazinamide groups at 2 years and beyond. While about 16% of patients at 2 years and 5% cases at 3 years had detectable bacillary ATP levels in non-Pyrazinamide group, no bacillary ATP was detected in biopsies from patients on Pyrazinamide containing regimens at these time periods. By 3 years, 32% of patients of Pyrazinamide group became smear negative and mean BI fell from initial 4.6 to 0.7 whereas in non-Pyrazinamide group 6% patients became smear negative and mean BI fell from initial 4.2 to 1.3. Pyrazinamide containing regimen appears to have some role in achieving improved sterlizing effect in multibacillary leprosy.

CH26

CLINICAL TRIALS OF MINOCYCLINE IN LEPROMATOUS LEPROSY

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In our first clinical trial of minocycline 100 mg once daily for 3 months, the 8 lepromatous leprosy patients responded exceedingly rapidly both clinically and bacteriologically. After 1 week of therapy 6 of the patients had noticeable improvement observed in either skin erythema or induration, 2 showing improvement in both. After 3 months of minocycline all the patients had noticeable improvement in their skin lesions, 6 patients having complete resolution of all erythema and induration. One patient had mild transient vertigo 1 month into the trial which resolved spontaneously without the need to discontinue treatment. No other adverse reaction or laboratory abnormality was noted in the treated patients. Of considerable importance and possible significance, no patient had a lepra reaction during the trial period. Serum minocycline levels in the studied patients were as expected from the literature: 1.84 ± 0.48 μg/ml (range 1.07-2.66 μg/ml) and trough 0.43 ± 0.11 μg/ml (range 0.33-0.58 μg/ml). At 1 month 3 patients had lost viable *M. leprae* (as determined by mouse inoculation), 6 by 2 months, and all by 3 months. Because minocycline has been utilized without significant toxicity for long periods of time and for over 2 decades, the rapid clinical response and clearance of viable *M. leprae* found in this study lend strong support for its use in the therapy of leprosy.

Currently being completed is a second clinical trial of minocycline administered first as a single 200 mg dose and followed 1 week later with 100 mg twice daily for 3 months. In this trial patients on clinical grounds also improved rapidly and similarly lost viable *M. leprae* from the skin as in our first clinical trial. Results will be presented quantitating the killing of *M. leprae* by the initial single 200 mg dose and, also, after 1 week of twice daily therapy.

CH27

SHORT TERM RIFAMPICIN CONTAINING REGIMENS FOR MB LEPROSY YIELD TO HIGH RISK OF RELAPSE

L. Blanc, P. Jamet, O. Faye, S. Sow, P. Bobin

Between 1977 and 1986, 435 MB leprosy patients entered 12 different MDT rifampicin containing regimens in Institut MARCHOUX. Among this cohort, 100 relapses occured during follow-up time from end of treatment to January 1993. Relapses were diagnosed on clinical, bacteriological and histological criteria, to date 66 were confirmed by the presence of viable M. leprae in skin biopsy specimen and 21 results pending ; all the isolated strains remained susceptible to RMP. Relapse rate ranged from 2.29 (0-4.5) to 7.3 (4.8-9.8) per 100 patients year, risk of relapse at year 5 ranged from 0% for regimens of one year duration to 14% (11-17) for regimens of 4 weeks duration. Average risk of relapse at year 5 was high for the 3 regimens that duration were three months or less (8.4%), compared to the ones of one or two years duration (1.7% and 5.2% respectively). For these last regimens, risk of relapse at year 10 ranged from 7.7% (4-13) to 43% (27-57) but there was no evidence that the duration of therapy (one year versus two years) changed the risk of relapse. Time distribution of relapses for regimens having at least 10 years follow-up showed pikes at year 7 and 9. The risk of relapse was not totaly explained by the therapy. Other possible risk factors for relapse would be interesting to be analysed (Bacteriologic Index, HIV infection, Steroid therapy for reactions...).

Acknowledgment : This investigation received partial financial support from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

CH28

BRODIMOPRIM/DDS AND BRODIMOPRIM/DDS/RIFAMPICIN - *IN VITRO* AND *IN VIVO* RESULTS FOR A NEWLY DEVELOPED EFFETIVE MDT AGAINST LEPROSY -

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A new combination consisting of Dapsone (DDS) and the dihydrofolate reductase inhibitor Brodimoprim (BDP) has been developed for the treatment of leprosy. The combination of these two drugs shows strong synergistic inhibitory activity. This is demonstrated on *Mycobacterium lufu* as a model strain as well as on *M.leprae in vitro*. The *in vitro* efficacy has been

convincingly confirmed in mouse foot pad experiments. The combination shows a perfect fit in its pharmacokinetic properties resulting in parallel serum concentrations (~ 1:1 ratio) with a half life of ~ 24 hr. On the basis of these results, trials on previously untreated patients (=100) have been performed in Alert/Ethiopia and Asuncion/Paraguay with the following regimens: Alert, A: 200 mg BDP daily, B: 200 mg BDP + 25 mg DDS daily and in Asuncion, C: 200 mg BDP + 100 mg DDS + 600 mg Rifampicin daily. Regimens A and B were stopped after 3 months of treatment and treatment was continued with WHO MDT in accordance with the initial protocol. Regimen B shows convincing clinical and laboratory efficacy after 3 months. Treatment with regimen C was - in contrast to the initial protocol - completely stopped because of the excellent clinical results. Patients are now under relapse control. Tolerance of all 3 regimens was generally good.

CH29

PROGRESS IN CHEMOTHERAPY RESEARCH OF LEPROSY

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Since the last Congress in 1988, we have demonstrated that clarithromycin (CLARI) and minocycline (MINO) alone showing promising bactericidal activities against *M.leprae* in mice; pefloxacin (PEFLO),ofloxacin (OFLO), CLARI and MINO alone displayed very powerful bacericidal activities in lepromatous patients, with rare and mild side effects. In mice, additive effects were shown with the combinations of CLARI+ MINO and CLARI+MINO+ rifampicin (RMP); and single dose of CLARI+ MINO or CLARI+MINO+OFLO displayed definite bactericidal activity against *M.leprae*, only slightly inferior or comparable to that of single dose of RMP. The results of these studies clearly indicate that three new classes of bactericidal agents are added to the short list of antileprosy drugs. Combining these drugs with RMP may permit significant shortening of the duration of multidrug therapy (MDT) and develop a fully supervised, monthly administered MDT regimens; in addition, the these new drugs, probably in combination with clofazimine, may play an important role for the treatment of RMP-resistant leprosy.

At present, we are testing the bactericidal activities of various combinations of new antileprosy drugs in *M.leprae*-infected nude mice; evaluating the bactericidal activities of the single dose of various combinations CLARI+MINO and CLARI+MINO+OFLO in lepromatous patients; participating the multicenter field trial of one-month treatment with the combination RMP+OFLO for both MB and PB leprosy; measuring the minimal effective dosages and minimal inhibitory concentrations of OFLO and sparfloxacin against *M.leprae* in mice; and assessing the specificity and sensitivity of the PCR technique in monitoring the therapeutic effect. The methodologies and preliminary results of the studies will be discussed.

CH30

MINOCYCLINE AND RIFAMPICIN IN LEPROSY

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Twenty (20) biopsy proven, previously untreated leprosy patients were entered into the study using a 28 day course of daily minocycline (100 mgs.) and rifampicin (600 mgs.). These patients were otherwise in good health between the ages of 15 and 65, non-pregnant and non-lactating. There were 12 TT, 4 BT, 1 BB, 1 BL, 2 LL patients enrolled. The results showed clinical improvement in all patients, earlier for those in the TT and BT types and within the year for the more serious forms of the disease. The drug combination was well tolerated with no disturbance of baseline laboratory functions. Patients are still being followed-up every three (3) months for the last 2 years with no clinical evidence of relapse.

CH31

COLCHICINE IN TYPE II LEPRA REACTION AND ITS COMPARISON WITH CORTICOSTEROIDS.

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Leprosy is a scourge of the mankind which makes the individual afflicted by it not only suffer but also undergo the odium of an outcaste. Various drugs are being used in the management of the Type II lepra reaction like CLF, Steriods, Thalidomide, Levamisole etc. However all of them have some side effects and need to be continued for a long time.

We have undertaken a comparative study to assess the efficacy of colchicine and steriods in type II lepra reaction. Group A consists of 30 patients treated with colchicine and Group B consists of 30 patients treated with steriods.

Colchicine was effective in controlling mild to moderate degrees of Type II Lepra reactions within a short span of time. It also reduced patients stay in the hospital. Colchicine was more effective in controlling neuritis & arthritis as compared to steriods. Colchicine is a safe drug except GIT symptoms. Colchicine allowed continued administration of antileprosy treatment without the risk of reaction. Colchicine was not effective in controlling severe degrees of lepra reaction specially in those who were getting recurrent episodes, those who had received steriods or steriods + CLF as an anti reactional treatment in the past. In our opinion Colchicine should be tried before starting steriods in Type II lepra reaction.

CH32

OFLOXACIN-RIFAMPICIN TRIALS IN MULTIBACILLARY LEPROSY - PRELIMINARY OBSERVATIONS ON REACTIVE EPISODES

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With the object of reducing the duration of treatment in leprosy, WHO has instituted multicentre double blind controlled trials with ofloxacin and rifampicin. In this presentation we submit our preliminary observations on 58 untreated multibacillary leprosy patients with BI more than 2.0(47 had BI $\geq$ 3.0) in an "open" clinical trial. 28 patients receiving 400 mg ofloxacin and 600 mg rifampicin daily for 28 days are compared with a group of 30 patients who were administered WHO MDT for 12 months. While the object of this on-going investigation is to make long term clinical and epidemiological observations, we report here a special feature observed so far, namely the occurrence of reactive episodes over a period of 6 months to 2 years.

14 (50%) out of 28 patients have undergone reactions in the ofloxacin group as opposed to 7 (23%) out of 30 patients in the WHO MDT group. One female patient in the ofloxacin group aged 16 who underwent erythema necroticans associated with severe neuritis had to be admitted for monitored administration of high doses of steroids and clofazimine. Rest of the reactions were mild and easily controllable with steroids. 12 out of 14 and 4 out of 7 reactions were encountered in the first 6 months in the ofloxacin and control groups respectively. Mean BI in 8 patients declined from 4.5 to 2.5 in 1 year.

We conclude that:- (1) Reactive episodes may be a feature of ofloxacin-rifampicin regimen, (2) Trial designs should include precise neurological assessments in view of the possible effect of reactions on the nerves and (3) A trial group with anti-inflammatory components like clofazimine is indicated.

CH33

OFLOXACIN CONTAINING COMBINED DRUG REGIMENS IN THE TREATMENT OF LEPROMATOUS LEPROSY

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Adult untreated 23 Lepromatous leprosy and 3 Borderline lepromatous leprosy patients with a Bacteriological Index of 4+ or more were admitted into the hospital of Central Leprosy Teaching and Research Institute, Chengalpattu,

India between 1989-1991. After prescribed investigations, the patients were randomly allocated in blocks of 3 to three regimens containing Clofazimine, Dapsone and Ofloxacin with Clofazimine and Dapsone common to all. The drugs were administered orally in doses of 300 mg. once in 4 weeks and 50 mg. daily of Clofazimine, 100mg. daily of Dapsone and 400mg./800mg. daily of Ofloxacin for 56 days under supervision. Sequential biopsy results for proportion of viable M.Leprae calculated through the analysis of median infectious dose (ID50) in mouse foot-pad revealed no growth by 56th day from all patients treated with regimens containing Ofloxacin and by 28th day in regimen containing 800mg. of Ofloxacin. Moderate to marked clinical improvement has been observed in significantly higher proportion of patients treated with Ofloxacin containing regimens. No serious complications or side effects were noticed with any of the regimens requiring suspension of treatment or administration of steroids.

This study received assistance from UNDP/WORLD BANK/WHO special programme for research and training in tropical diseases (T.D.R.).

CH34

MINOCYCLINE IN LEPROMATOUS LEPROSY

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Minocycline, a tetracycline derivative, has recently been found to have bactericidal effects on M. leprae in the mouse footpads. In the chemotherapy of leprosy there is a need for new bactericidal drugs. Resistance to individual drugs in the current Multidrug Therapy(MDT) for leprosy has been reported. Furthermore, of the 3 drugs used in MDT only Rifampicin is bactericidal. The use of combined bactericidal drugs should reduce the frequency of relapses, minimize the effects of lapses in therapy as well as shorten the duration of treatment.

The present study assesses Minocycline given for 6 months to patients with lepromatous leprosy. Minocycline was given at two dose levels, and intermittently during the 1st month, followed by 100mg daily for 5 more months. Fourteen lepromatous (LL/BL) patients were admitted to the trial: 10 were new untreated, and 4 were relapsed lepromatous. Minocycline efficacy was measured in terms of clinical changes, changes in the bacterial index and histology. Determination of the levels of PGL-1 antigen was also done. Studies for viability of M. leprae by mouse footpad inoculation, and radiorespirometry were also performed. Results thus far indicate that Minocycline is very effective and the absence of significant side effects suggest it can be safely used in the treatment of leprosy.

Detailed results will be presented and discussed.

CH35

FIVE YEARS EXPERIENCE OF MDT IN AMRITSAR(PUNJAB)

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A clinicopathological evaluation of 510 new leprosy patients registered between 1982 to 1987 revealed:
1. 23.53% (120) infectious cases (Dharmendra's operational classification, 1986),
2. Majority of males (3:1), in their prime age group (21-40 years) and housewives or involved in manual labour,
3. 29.21% compliance rate of treatment [Modified W.H.O regimens with additional six months (minimum) 100mg dapsone daily for PB cases and initial intensive 2 weeks therapy with 600 mg Rifampicin and 100 mg Dapsone daily alongwith 100 mg Clofazimine EOD for MB cases],
4. 36.91%(117; 96 PB and 21 MB) clinicopathological correlation,
5. Complete clinical cure in 23.6% (26; 16 PB and 10 MB) with clinical inactivity in 74.55% (82; 73 PB and 9 MB). Two PB cases active even after 19 and 14 months therapy,
6. Untoward side effects in 13 MBMDT cases in the form of ENL in 2(6.9%), ichthyosiform lesions and/or reddish brown pigmentation of face, conjunctivae or of lesions in 11(37.93%) cases,
7. No relapse, and
8. Histological cure complementing clinical cure only in 15% (3; 2 PB and 1 MB) cases.

Strategies of leprosy eradication by 2000 AD need revision in the light of above observations, in our view.

CH36

AN OBSERVATION ON THE EFFECT OF MDT IN THE TREATMENT OF 1,095 LEPROSY PATIENTS IN SHAANXI PROVINCE, CHINA

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One thousand and ninety five cases of leprosy were treated with MDT regimen, recommended by WHO in Shaanxi province from 1987 to 1990. Eighty hundred and seventy nine cases of them (80.27%), including 695 MB cases and 184 PB patients, were clinically cured. Out of these cured cases, 103(9.41%)(MB 90, PB13) were markedly improved, 101 (9.22%) (MB 86, PB 15) were improved, and 12 MB cases (1.1%) remained unchanged. The total clinically effective rate was 98.9%, showing an obvious effect within a relative short time. In 883 MB cases treated with MDT for 24 months, the annual average decrease of BI of out patients and hospitalized cases were 0.94 and 0.91, giving a declining rate of 94.44% and 88.11% respectively. In 553 hospitalized MB cases treated with MDT, after the completion of the prescribed doses, their HI (histological index)decreased from 1.34 to 0.11, with an annual average decline of 0.62 and a decrease rate of 91.79%. BI decreased in parallel with the decline of HI. The proportion of the occurrence of type II leprosy reaction in 325 previously untreated MB cases on MDT was 24.3%, similar to that (22.58%) of 558 cases with DDS monotherapy. In the above said 558 cases 26.34% of type II leprosy reaction were seen when they were retreated with MDT. No significant difference of the frequency of typer II lepra reaction was found between pre-MDT patients and post-MDT cases, suggesting the limited effect of the routine dosage of B663 in the control of the reaction.No type I leprosy reaction was seen during the periods of treatment and surveillance. The side and toxic effects of MDT were acceptable and did not interfere the carrying out of the MDT programme.Six hundred and forty five MB and 184 PB cases were cured clinically and were followed up for 1-3 years, no relapse was detected.

CH37

THE OBSERVATION OF 328 MB CASES TREATED WITH MDT AND FOLLOW UP STUDY

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Three hundred and twenty eight MB patients were observed during the treatment with MDT (WHO regimen, 1982) for 36 months and monitored for 24 months after the end of their drug treatment. One hundred and fifty of them were previously untreated (group 1), 161 were previously treated by DDS+RFP (group 2) and the remaining 17 were relapses after cure with DDS monotherapy (group 3).

All cases were examined clinically, bacteriologically and histopathologically before, during and after MDT regularly. The observation indicated that there were satisfactory clinical improvements in all cases, macules disappearedy in 3-6 months, and nodules flattened in 3-15 months. And there was a steady fall in BI value before and even after the discontinuation of the treatment. Skin smears became negative in 110 cases 24 months after stopping the drugs. Five-year histopathological observation in 30 cases showed that all BIG(bacterial index of the granuloma), GF (granuloma fraction) and HI(histopathological index) decreased steadily. The side effects of MDT were acceptable. The authors stressed the effectiveness of MDT in reducing and controlling the frequency and severity of lepra reactions and deformities.

CH38

THE EFFECT OF MDT FOR 27 MONTHS AND POST-TREATMENT SURVEILLANCE FOR 72 MONTHS IN MB CASES

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Forty seven cases of active MB leprosy patients were regularly treated with RFP, B663 and DDS for 27 months with satisfactory clinical, bacteriological and histopathological improvements. The side effects were mild. MDT was also effective in controlling Type I leprosy reaction. After stopping MDT, there were both steady clinical improvement and steady decrease of the BI also decreased steadily approaching zero in the sixth year after stopping the medications. Histopathologically inflammatory infiltration also gradually subsided. In the period of Six years' surveillance, except 4 cases who died of non-leprosy cause, the remaining 43 cases were all cured and no relapse was detected, indicating that MDT short-term regimen was very effective in the treatment of MB leprosy patients. The authors stress the importance of implementation of MDT short-term regimen on a wider scale in order to reach the goal of basic elimination of leprosy in China by the end of the year of 2000.

CH39

OBSERVATION OF 607 PATIENTS OF MULTIBACILLARY LEPROSY UNDER SURVEILLANCE OF THREE YEARS AFTER COMPLETION OF MULTIDRUG THERAPY

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From 1984 through 1991, 607 patients of multibacillary leprosy with positive smears in 20 counties of Liangshan and Panzhihua prefectures of Sichuan province had completed MDT courses, recommended by WHO in 1982, and were under surveillance for three years. Marked steady clinical and bacteriological improvements were observed. Forty five of them were previously untreated cases with active skin lesions and BI value of 1.00 to 4.60 at the start of MDT. Their skin lesions subsided after 12 months of MDT and the annual average decline of BI in the period of five years was 0.58 and that of the first three years was 0.83. BI of 36 patients of them became negative and that of the other 9 remained positive in the third year of surveillance. A half of another 562 cases, DDS treated previously and with BI value of 0.16 to 4.66 before MDT, also had active skin lesions at the start. Their skin lesions also subsided after 12 months of MDT, and the annual average decline of BI in the period of five years was 0.31, and was 0.49 in the first three years. In the third year of surveillance, BI of 519 cases of them decreased to zero but the smears remained positive in 43 cases.

In the period of suruveillance, lepra reactions, mostly only skin reactions, were seen in 9 patients (ENL 2, neuritis 2, type I reaction 5). They were successfully controlled by steroids and did not cause new deformity.

CH40

RESULTS OF SKIN SMEARS FROM EIGHTY FOUR MULTIBACILLARY PATIENTS ON MDT MB REGIMEN RECOMMENDED BY WHO

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Eighty four multibacillary (MB) patients whose skin smears were positive were treated 24 months with the regimen of multidrug therapy (MDT) for MB patient recommended by WHO (1982) since 1987. At the end of the first 12 months of MDT there 15 (17.9%) cases whose skin smears became negative and 54 cases (64.3%) whose skin smears became negative after the 24 months of MDT completed. After that MDT was stopped and the patients were supervised once or twice a year under the doctors and technicians with physical exam and skin smears for the exam of bacilli. At the end of the first year of supervision the number of patients whose skin smears became negative increased to 63 cases (75.0%) and at the end of the second year of supervision the number of patients whose skin smears become negative increased to 78 cases(92.8%) continuously. The results observed above like some authors who introduced MDT MB regimen to MB patients until the skin smears becoming negative. That is to say that the 24 months of MDT for MB patients recommended by WHO (1982) is enough for the most of the MB patients. But the real and final efficiency of MDT for MB patients recommended by WHO will be confirmed by relapse in the future.

CH41

THE ANALYSES OF TREATMENT TIME FOR LEPROSY CASES CURED WITH DDS AND MDT IN YANGZHOU PREFECTURE, CHINA

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In the paper the data to be analysed are based on Yangzhou, China, in order to reveal the features on time distribution of the cure and to propose the appropriate time to cure leprosy patients with MDT. The leprosy cases are divided into Old PB and Old MB(treated with DDS before), New PB and New MB (never treated before). The treatment regimens include WHO MDT and Mod MDT (Modify MDT: local MDT). The method of moment is used to test for normality for the time distribution of cure. The results indicate that most of data are skewness distribution, therefore we use the median (year) of cured time to compare them. By end of the year 1990, total 14723 cases are cured by DDS with median of 11.46 years, 83 Old PB cases by WHO MDT with median of 2.09 years, 110 New PB cases by WHO MDT with median of 2.62 years, 367 Old MB cases by WHO MDT with median of 3.47 years, 58 New MB cases by WHO MDT with median of 4.43 year, 168 MB by modify MDT with median of 2.49 years. The cured median of all PB cases with WHO MDT is 2.48 years, the median of all MB cases with WHO MDT is 3.60 years. The results indicate that the optimal time to treat leprosy cases until cure: PB cases with MDT need 1.5-2.5 years, MB cases with MDT need 3.5-4.5 years. The differences between males and females in DDS and Mod MDT have high significance ($p<0.01$). It is interesting to show that the MB cases with Mod MDT need shorter time to cure than WHO MDT regimen ($p<0.01$).

CH42

A STUDY OF 315 MULTIBACILLARY CASES OF LEPROSY UNDER MDT AT JNRMH, TALA, RIZAL PHILIPPINES.

Roland C. Samson, MD, Jimmy Dayanghirang, MD.

Multidrug treatment, following the WHO regimen, was introduced at Dr. Jose N. Rodriguez Memorial Hospital, Tala, Rizal, Philippines in 1981. The main objectives were: 1. to treat all active cases admitted in the hospital, irrespective of their previous treatments; and 2. to supervise the daily intake of the MDT drugs. Since then 315 patients have finished MDT, completed the surveillance period and were released from control in January 1993.

No major problems with the use of multidrug regimen were encountered, except for the initial apprehension of patients in taking the new drugs, which was readily overcome.

This study was failed to detect any significant side-effects associated with the use of multidrug regimen. Few cases of

leprosy reaction's during the treatment have been observed. There were few complaints about dofazimine - induced pigmentation, that gradually disappeared during the surveillance period.

We are of the opinion therefore that multidrug therapy has proved successful; the drugs are acceptable to the patients and the use of MDT in leprosy control was a wise decision.

CH43

FACTOR INFLUENCING PATIENT'S COMPLIANCE TO MDT/ OMS IN RIO DE JANEIRO.

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Default from treatment for Hansen's Disease is probably one the most important reasons of the endemic status in Rio de Janeiro State, Brasil. Annual defauters rate in the last five years are around forty-five per cent.

Four hundred and eighty six defaulters were interviewed, in order to detect the most common causes of now-attendance to the supervised monthly dose in several cases leading to default before healing. Among others, profissional factors and "forgetting" the right day were frequently found. The results will be presented, analysed and discussed by the outhors in this intervention.

CH44

USE OF PGL-1 IN THE FOLLOW-UP OF MULTIBACILLARY LEPROSY PATIENTS UNDER SURVEILLANCE AFTER RELEASE FROM TREATMENT(RFT).

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Detection of IGG and IGM antibodies to phenolicglicolipid-1 by ELISA method has been used, to evaluate its usefulness in the serum diagnosis and monitoration of treatment.

A group of thirty-six multibacillary patients was followed after RFT with PGL-1 titrations by the ELISA method, on a 3 month basis. The objetive of the study was to evaluate the viability of this test in the early diagnosis of relapse. Patients were into two groups according to bacteriological positivity or negativity at the end of treatment.

It was observed that the two groups showed the expected results, already described by other authors:

Higher titrations in the BI positive group and a slow decline along the time in the two groups.

However, considerable individual variations were observed, becoming a limitation to the use of this method in early diagnosis of relapse.

CH45

TEN-YEAR COHORT ANALYSIS OF PAUCIBACILLARY LEPROSY PATIENTS WHO RECEIVED MULTIDRUG THERAPY

Thirunavakarasu S, Narayanan R, Matheus M, Lobo D, Thomas C.J.

Our institution GREMALTES based in Madras is a pioneer in URBAN Leprosy Control. We initiated MULTIDRUG TREATMENT (MDT) in 1983.

Between 1983 and 1992 - 13,250 patients received MDT, of which 11,552 are PAUCIBACILLAY (PB).

A cohort analysis of all the PB cases over the ten-year period is presented, using the following parameters:

- Treatment Regularity/Compliance
- Proportion of Drop-outs
- Proportion of Mono-lesions
- Cure rate
- Relapse rate
- Proportion of cases with complications like Neuritis/Reactions

The significance of the results, their relevance to the impact of MDT and for planning and implementation of Leprosy Control Programmes specially for URBAN areas is discussed.

CH46

FIXED DURATION COMBINED CHEMOTHERAPY IN MULTIBACILLARY LEPROSY

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The principal objective of this study is to measure relapse rates in multibacillary leprosy patients who have completed 24 doses of the combined drug regimen recommended by the **WHO** study group of 1981.

From November 1987 to January 1992, 424 new leprosy cases were included in the trial. None had previously done any antileprosy treatment and all were skin smear positive with BI of 2+ or greater. They have been receiving the treatment recommended by the **WHO** 1981 Study Group. After 24 supervised monthly doses within up to 36 months their treatment was ceased regardless of skin smear status. 240 patients have already completed the 24 doses. 96 patients have completed 2 or 3 years of followup. There have been no relapses. The followup will continue for 5 years.

This trial received financial support from **UNDP/WORLD BANK/WHO/TDR**

CH47

MDT IN MANAUS: READMISSION AFTER RELEASE FROM TREATMENT

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Between December 1982 and December 1990, 6,198 leprosy patients from the municipality of Manaus were treated with the **WHO**/1981 multidrug regimen. 32 of these patients (0.52%) needed to be readmitted to treatment.

The clinical findings that necessitated readmission to treatment are presented, and concepts of relapse and reaction are discussed.

CH48

MULTIDRUG THERAPY OF MULTIBACILLARY LEPROSY PATIENTS - A TEN YEAR FOLLOW-UP STUDY

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In 1980, 79 untreated multibacillary patients with a bacterial index ranging from 2.5 to 3.4 were chosen for the study. Of these 25 patients were dropped out for various reasons which include 8 patients who were found to be dapsone resistant. They were divided into 3 groups. One group (A 14) received daily dapsone 100mgs alone, a second group (B 19) rifampicin 600mgs and dapsone 100mgs daily and a third group (C 21) rifampicin 600mgs, dapsone 100mgs, INAH 175mgs, and prothionamide 175mgs daily.

All patients were assessed clinically for the severity of the disease and for disability. Skin smears, skin biopsies, foot-pad inoculation studies for viability of the bacilli, hemogram, liver and kidney function studies were also conducted in the beginning of the study and at every 6 months. Reaction episodes were carefully recorded. At the end of 3 years the drugs were completely stopped and the patients were carefully followed. Now, 10 years after discontinuation of therapy 1 was dead, and 20 migrated and were lost to follow up. Thirty three patients, 10 from group A, 10 from group B, and 13 from group C are available for follow up. Skin smears, skin biopsies, clinical evaluation of the disease and of the disability, were done on all the 33 patients.

The results will be presented and discussed.

CH49

FIXED-DURATION MDT IN MULTIBACILLARY PATIENTS. TWO YEARS OF SURVEILLANCE. Nery JAC, Gallo MEM, Malta AM, Viana SM, Almeida SM, Borges E, Sarno EN. Leprosy Department, Oswaldo Cruz Foundation, Av. Brasil, 4365 - Manguinhos, 21.045-900 - Rio de Janeiro - RJ - Brazil.

MDT, according to the WHO recommendation, was introduced in the FIOCRUZ Out-patient Unit. 115 had completed regularly the treatment and are now under surveillance. At the completion of MDT, all patients showed no active leprosy lesions, involution of dermal infiltrate (AFB + in the skin 55.9%) except for 11% of patients with type II reactions aspects. The BI was negative in 20% and the MI in 97,4%. When the final BIs were compared with BI of the intake, it was observed a decrease in 82,2%, increase 1.6% and no change in 16%. The neurological exam demonstrated improvement in 24.5% of the patients, worsening in 7.6% and no change in 65,2% (the majority had incapacity degree = 0). The follow-up baciloscopic exam performed in 81 patients who completed the 1st year of surveillance showed: decrease in 45.6% increase in 13.5% and no change in 27.1% when compared with the BI at the end of MDT not realized 13.5%. Among the patients who presented a negative BI at the end of MDT, 4.9% became + during the surveillance (2,45% each year). During the surveillance period 38 (46,9%) of the patient presented reactions: 29.6% in the 1st year and 6.1% in the 2nd year and 11.1% realized in first and second years. Type I reaction occurred in 15.7 % of patients only at the 1st year of surveillance and type II occurred in 76.3%. Isolated neuritis occurred in 7.8% of the patients.

Supported by grants from TDR-WHO.

CH50

INCORPORACION DE LA MULTITERAPIA EN LOS ENFERMOS DE CATALUÑA:RESULTADOS E INCONVENIENTES:

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La población enferma de Cataluña (España),inició la implementación multiterápica hace 6 años.El Trabajo realizado muestra las dificultades de su incorporación así como el resultado positivo en cuanto a la reducción de la población enferma una vez cumplido el tratamiento durante el tiempo preciso.

CH51

THE SLIT SKIN SMEAR IN LEPROSY - AN IMPEDIMENT TO MDT ?

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The launch of the World Health Organisation's two multiple drug therapy (MDT) regimens in 1982 was accompanied by the strong recommendation that skin smear microscopy of acceptable quality be a prerequisite for field programmes to implement MDT. It gradually transpired that an alarmingly small number of centres in leprosy endemic countries were capable of producing accurate and consistant results and the necessity of skin smear microscopy was questioned since it appeared that the absence of smear facilities was partly responsible for delaying the implementation of MDT in some areas. As an aid, particularly to non-medical field workers, various alternative methodologies have been adopted in order to assist in accurate classification in different programmes and a summary of the "body area rule" is presented. It is argued that, if necessary, a competent MDT field programme can be run in the total absence of a skin smear service and hence poor or absent laboratory support should no longer be allowed to impair the implementation of MDT.

CH52

PRIMARY RESISTANCE TO DAPSONE AND RIFAMPICIN

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With the objective of evaluating Primary Resistance to Dapsone and Rifampicin in untreated patients with Multibacillary Leprosy it was decided to carry out a survey with active Lepromatous Leprosy consulting at the Oswaldo Cruz Foundation. The survey was conducted between october 1989 and december 1992. During the study period, 47 skin biopsies were collected. The results showed that none of the strains was resistant to Dapsone and Rifampicin.
M.leprae recovered from 29 patients showed sensitivity to Dapsone and 25 to Rifampicin.
Four strains were non infective and the fourth was inconclusive.
The organisms from 12 patients did not infect mice and the results from 6 specimens were inconclusive because multiplication of M.leprae was observed in only few control mice.

This Investigation received finacial support from UNDP/World Bank/WHO-TRD

CH53

SURVEY FOR SECONDARY DAPSONE AND RIFAMPICIN RESISTANCE IN CUBA.

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A total of 1211 Cuban leprosy patients treated for at least 5 years were clinically and bacteriologically examined. They were being treated according to a two-phase monotherapy regimen with RMP first and DADDS afterwards. On skin smear examination 50 patients were found positive, of them, 9 showed a BI of 3+ or higher at any site. With regard to the clinical status the only cases found with clinical signs of relapse were 5 of 7 long-standing patients with BI of 4+ and 5+. A sixth patient of this high BI group who showed a good clinical condition except for a heavy infiltration of both earlobes was receiving a second RMP course when examined and biopsied for this research. These 9 patients were biopsied and susceptibility tests to RMP and DDS performed. The results showed that in 1 case the M. leprae were resistant to both drugs, the organisms from 2 other patients were susceptible to RMP but low-grade resistant to DDS. Those from another patient were susceptible to RMP and fully resistant to DDS. In 3 other cases the bacilli did not multiply in any of the mice but 1 of these strains was from the patient taking a second RMP course, therefore this strain might also be susceptible to RMP and resistant to DDS. In the last 2 cases multiplication was only observed in 2 of the controls and in 1 of the 0.0001% DDS treated mice, therefore, these experiments were not conclusive and the AFB inoculated into fresh mice to repeat the tests but failed to multiply.

CH54

RELAPSES AFTER DAPSONE MONOTHERAPY: AN ANALYSIS OF 769 CASES IN JIANGSU PROVINCE, CHINA

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From 1949 to 1988 the leprosy patients cured in Jiangsu Province totalled 41,594, of whom 1,069 cases relapsed with a relapse rate of 2.55%. This article investigated 769 relapse cases (652 males, 117 females) who had received dapsone monotherapy for 1 to 24 years with a regular treatment rate of 86.4%. The dapsone monotherapy was also given during the observation period. The interval between cure and relapse averaged 4.30 years for the MB cases and 4.69 years for those of PB. 94.8% of the relapse patients were over 25 years of age when they developed signs of relapse and the disease course was all found to be longer than 6 months. Of all the MB relapse cases, 36% had more than three skin lesions on first visit, apparently higher than the control group (26.9%). The clinical features of the MB relapse cases were mostly the reactivation of old skin lesions and the deterioration of old nerve impairment and the deformity rate was 10.79%, while a large portion of the PB's developed new skin lesions and nerve impairment,and the deformity rate was 24%. It has been shown that the main precipitating facts causing relapse are overwork, life and mental load and excessive drinking. 84.56% of the cases were detected by personnel and 13.29% by basic health care system or by the patients themselves. The authors held that the dapsone monotherapy cannot provide a solution to the problem of relapse, on which early diagnosis and treatment may have a greater effect.

CH55

AN EVALUATION OF RE-TREATMENT OF 13,477 LEPROSY PATIENTS CURED WITH DDS IN JIANGSU PROVINCE, CHINA

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In order to prevent cured patients from relapse, 13,477 cases cured with DDS monotherapy were re-treated with MDT in Jiangsu province from 1984 to 1991. Three thousand four hundred and fifty seven of them were MB and 10,002 were PB. Two thousand two hundred and twenty seven patients were re-treated with three drugs in combination and 11,250 cases with two drug combination regimen. All patients were followed once or twice a year after the completion of the re-treatment. 3,520 cases of them (26.12%) have been released from re-treatment for 5 or more than 5 years. By the end of 1991, no relapse was detected. But during the same period (1984-1991), 457 relapses were found in 22,488 DDS-cured but not re-treated patients, giving a relapse rate of 2.03% (MB 13.95%, PB 0.8%).

CH56

COMBINED CHEMOTHERAPY AND IMMUNOTHERAPY FOR TREATMENT OF HIGHLY BACILLATED BL/LL CASES

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Viable as well as dead bacilli are known to persist in BL/LL cases even after 2 years of currently recommended MDT. Our earlier studies showed that BCG had a potential immunotherapeutic effect when used in BL/LL patients. In this study, we have investigated the therapeutic response of combined immunotherapy alongwith MDT in BL/LL patients. Untreated BL/LL patients with the initial BI of 4 to 6+, were serially alloted to three treatment groups. Group I patients received a slightly modified WHO regimen (Rifampicin once a month, Clofazimine & Dapsone daily) and BCG 0.1 mg/dose. Group II cases were administered the same MDT and Mycobacterium w. (2×10^8 killed bacilli/-dose) and group III received the same MDT with 0.1 ml of distilled water. Vaccination was repeated every 6 months. Biopsies were taken from the local site of vaccination and from a distant site i.e. back. The progress was monitored periodically by using, clinical, histopathological and bacteriological-BI, mouse foot pad, ATP and other viability parameters. The vaccines were well tolerated. There were no serious side effects. In cases of combined chemotherapy and immunotherapy, no viable bacilli were demonstratable by mouse foot pad and ATP measurements at 6 months and afterwards. However in some of the control cases on MDT alone, viable bacilli could be detected even upto 2 years. With 30 months of treatment, the mean BI decreased from 4.6 to 2.45 in the group on MDT alone (control): 4.9 to 0.08 in the MDT+BCG group and 4.7 to 0.05 in the MDT+M.w group. Immunotherapy appears to have a significant effect on killing and clearance of bacilli in these cases.

CH57

INTRODUCTION OF SINGLE DOSE OF RIFAMPICIN FOR THE TREATMENT OF LEPROSY PATIENTS IN OUT REACHED AREA

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WHO had undertaken a BCG vaccine trial in Singu township of Upper Myanmar (1964-75) to see its effectiveness against leprosy. Overall prevention rate after 10 years trial period showed only about 14%.

In addition, epidemiology of leprosy was studied and incidence was not abated with the dapsone monotherapy. So combined drugs using rifampicin, lamprene and dapsone were considered for further trial.

During the trial operation, (1976-1984), patients in outreached area (about 70%) were unable to be covered with the standard trial regimen.

So, if not the best, an alternative regimen using a single supervised dose of 1500 mg of rifampicin and self administered daily dose of dapsone was introduced for 5 years.

The results were satisfactory; morphologically all of them were zero after one year and bacteriologically most of them were negative after 5 years.

And thus a feasible operation using a single dose of rifampicin per year for 5 years in outreached area was considered helpful to change the leprosy epidemiological pattern in an area where standard regimen was inoperable.

CH58

EXPERIENCE GAINED IN NEPAL WITH COTRIFAZID

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This is not a report on a trial in which a new leprosy therapy was evaluated. Such a trial had been carried out earlier in Paraguay (Ref.). The aim was to check the effectiveness of out-patient Cotrifazid treatment (Rifampicin + Cotrimoxazol + Isoniazid) under the difficult outer conditions prevailing in Nepal. Depending on the severity of the case, treatment duration varied from 2 to 6 months. The high tolerance and compliance and the excellent result of this therapy are discussed in detail. Cotrifazid, which might be termed a fixed broad-spectrum combination, offers the great advantage that no additional medication is required for treating concurrent infections often encountered in leprosy patients, e.g. tuberculosis, "atypical" mycobacterial diseases, enteritic diseases, staphylococcae etc.

Summary: So far we have not heard of any other therapy allowing to overcome such a complex of difficulties.

Ref.: A New Short-term Combination Therapy of Leprosy. E. Freerksen, A.E. Alvarenga, O. Leguizamón, Maria Victoria de Morra, L.A. Reyes, W. von Ballestrem. Chemotherapy 1991, 37, 353-363

CH59

ON THE NECESSITY OF ALTERNATIVE THERAPIES FOR THE TREATMENT OF LEPROSY

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The varying severity of leprosy is due to the large ethnic and genetic differences, the different state of nutrition, and the wide differences in age of the leprosy patients. Hence there is an urgent need for alternative forms of therapy for the treatment of leprosy.

In addition to the treatment scheme propagated by the WHO, whose advantages and disadvantages are known, fixed combinations of up to four drugs (i.e. the components have been integrated in one tablet) are presently available. These combinations are highly effective, tolerated well, easy to administer, at low cost.

A report is made on the use of "Isoprodian" (INH + PTH + DDS), "Isoprodian-RMP" (INH + PTH + DDS + RMP), "Cotrifacid" (SXT + INH + RMP), "Emdetine" (SXT + PTH + RMP), Ofloxazin + INH + DDS + RMP, and a combination of PTH and DDS in more than 1970 cases of leprosy.

CH60

BACTERICIDAL ACTIVITY OF OFLOXACIN AGAINST Mycobacterium leprae

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Sixteen patients with infiltrated lesions of lepromatous leprosy were enrolled in this trial. The microscopic examination of their lepromata yielded bacterial indexes in from 4+ to 5+ (according to Ridley's logarithmic scale) and morphological indexes higher than 70%. The histological study of the lesions revealed typical LL leprosy granuloma. Patients presented disseminated erythematous plaques, papules, nodules and macules. The mouse footpad inoculation and estearase tests were positive in all patients. Supervised multi-drug treatment (standarized by WHO) taken during at least 2 years had failed in all cases, as proven by clinical and bacteriological controls. Then, a six-month monotherapy with ofloxacin (2 daily 200 mg doses) was initiated. The drug was kindly provided by Cilag Pharmaceutical. During the progress of ofloxacin therapy, 2 patients presented type II reaction (nudosum erithema), other side-effects were absent. After 2 months treatment, only granular bacilli were found by smear examination; the estearase and the inoculation tests were negative in all 16 cases. Remission (n=7) and flattening (n=2) of the lesions was observed in the 9 patients who completed the chemotherapy. They were followed-up for 4 to 6 months and no reactivation occured.

CH61

K-130: A NEW INHIBITOR OF *M.LEPRAE* DIHYDROFOLATE REDUCTASE

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Bacterial dihydrofolate reductase is a well known target for antibacterial drugs like trimethoprim and related compounds. No compound of this type has until now become an antileprotic drug because of low effectivity. Therefore several diaminopyrimidine derivatives were sythesized with the aid of molecular modelling to derive compounds with improved properties. The aims were, 1) to increase the affinity against the target enzyme, 2) to increase the ability of permeation through the highly lipophilic nycobacterial cell wall and 3) to possibly combine two principles of folate synthesis inhibition (dihydropteroate synthase and dihydrofolate reductase inhibition respectively) by combining dapsone derivatives with a diaminopyrimidine derivative in one "autosynergistic" acting molecule.

All of these aims have been achieved successfully. Among the derivatives synthesized K-130 is the most promising. Its high activity has been demonstrated on the isolated enzymes as well as *in vitro* against *Mycobacterium lufu* (a model strain) and *M.leprae*, respectively.

The *in vitro* efficacy was convincingly confirmed in mouse foot pad experiments. On the basis of these results toxicity studies in rats and monkeys were performed at the Central Drug Research Institute in Lucknow (India), showing that the drug is safe up to the highest concentrations tested. The data have been submitted to the Indian drug contollers for permission to initiate phase I clinical trials.

CH62

GANGLIOSIDES(CRONASSIAL)& LEPROSY NEUROPATHY. A Randomized,Placebo controlled trial.

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Gangliosides are been used for the last 14 years in the treatment of various forms of peripheral neuropathies.

Method:Randomized double-blind placebo controlled trial of Cronassial conducted in 6 centres in India.Of the 120 patients who entered the trial only 114 completed it as per protocol.Only BB,BL, LL types were selected because their neural damage is similar,& an earlier open-trial suggested that these patients would benefit the most.

Other criteria for selection:1)Age between 18 & 50.(2)At least 2 nerves have moderate to severe damage as assessed with Pasricha's instruments, WHO thermal tester,skin thermometre,VMT.(3)The damage must be of not less than 2 years duration,so as to rule out spontaneous recovery.

The therapy:40mgs.Cronassial i.m.daily for 60 days.The placebo vials were identical in appearance to the drug.The patients were assessed with objective & subjective methods for sensory/motor/sympathetic loss at baseline,and after 30,60,180 days;some could be checked after 360 days. Results:the drug group showed much better results (statistically significant)than the placebo,in sensory,motor & sympathetic functions.Circa 45% of Cronassial patients recovered "in toto" all sensory modalities:touch,2-point discrimination, pin-prick,temperature,as against the placebos of which only 19% had improvement of one or two sensory modalities.The VMT score & the sympathetic functions were significantly better in the the drug-group.A follow-up of 2 years in 30% of cases showed that the placebo had a poorer score (compared to their last one)while the Cronassial group had consistent or even better results.

CH63

CLINICAL AND BACTERIOLOGICAL EFFECT OF TRYPTOPHAN-ENRICHED DIET IN MULTIBACILLARY LEPROSY - A PRELIMINARY COMMUNICATION

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Anti-leprosy effect of deoxyfructolserotonin for which evidence is available prompted trials of tryptophan-enriched diet "Nourriture Anti-Lepre" (NAL) administered to multibacillary leprosy patients to study the clinical and bacteriological effects, attributable to the enhancement of the concentration of free tryptophan as serotonin precursor in blood. A trial group of 12 MB patients with BI $\geq$ 3.0 receiving NAL 50 gms per day for 6 months was compared with 12 patients put on WHO MDT regimen and 12 others on WHO MDT along with NAL.

Assessment of photographs objectively carried out in a "blind" manner by independent observers showed that there was 75% improvement in 1 patient, 50% in 7 and 25% in 4, in the trial group. Comparable improvement was noticeable in the two other groups as well. Clinical scores assessed before and after treatment also showed perceptible decline in all the groups.

Mouse foot pad innoculations prior to the trial and six months after diet therapy showed loss of viability of M.leprae in 9 out of 12 in the NAL group.

This presentation has clearly shown that tryptophan augmentation in diet is effective against leprosy and results are comparable to the control MDT group.

CH64

ALTERNATIVE TREATMENT FOR DRUG-RESISTANT LEPROSY AND TUBERCULOSIS

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Rational chemotherapy of an infectious disease involves identifying an essential metabolic activity of the causative agent and suppressing that activity with an appropriate inhibitory compound. We discovered derepression of the enzyme, β-lactamase, in M. leprae multiplying in armadillos treated with penicillin G benzathine. M. tuberculosis has been reported to contain a constitutive β-lactamase. M. leprae is able to develop resistance against the generally used antileprosy agents. To overcome this problem, multidrug therapy is being promoted widely, and has had remarkable successes. When M. tuberculosis became resistant to individual drugs, combination therapy was adopted to treat the disease. Now multidrug-resistant (MDR) tuberculosis is spreading in many countries, especially with the emergence of AIDS. One cannot safely deny the possibility of the emergence of MDR leprosy.

Mycobacteria, in general, synthesize β-lactamase and are insensitive to penicillins and cephalosporins. We screened the effect of β-lactam/β-lactamase-inhibitor combinations on growth of M. leprae in mouse foot pads, and on M. tuberculosis H37Ra, H37Rv, M. avium, and BCG (drug-susceptible as well as drug-resistant strains). We tested four different drug combinations: ampicillin/sulbactam (Pfizer), ampicillin/YTR 830H (Taiho), amoxicillin/clavulanate (SmithKline Beecham), piperacillin/tazobactam (Cyanamid). All of them suppressed growth of the bacteria, including that of drug-resistant mycobacteria. Ampicillin/sulbactam showed better activity than the others in which the proportion of inhibitor to antibiotic is higher than in amoxicillin/clavulanate or piperacillin/tazobactam. Apparently, β-lactam/β-lactamase-inhibitor combinations could serve as effective alternative therapy for MDR tuberculosis and drug-resistant leprosy.

CH65

COMBINED DISTRIBUTION-TOXICITY STUDY OF TWO NOVEL PHENAZINES

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Clofazimine is an antibacterial phenazine which has principally been used in the treatment of leprosy. Although a very efficacious agent, its prolonged use has a number of associated problems. A number of novel phenazine agents have been synthesised to produce a more widely effective agent with less side-effects.

Two of these agents (B4090 and B4100) have been shown to be particularly promising. Before further investigation of the therapeutic potential of these compounds, we have investigated the tissue distribution and some elements of the sub-chronic toxicity of these agents as compared to clofazimine. Toxicity was measured by monitoring serum enzyme levels, routine haematology and urine analysis, including urinary NMR markers. The tissue distribution and toxicity of these newer agents in the model used are discussed.

CH66

IMPROVED HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC ANALYSIS OF SYNTHETIC PHENAZINE COMPOUNDS INCLUDING CLOFAZIMINE

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Clofazimine (B663) is an anti-leprosy agent which has also been successfully used to treat other mycobacterial diseases, including *M. avium* infection in AIDS. In an attempt to optimise and increase the therapeutic potential of B663, a number of compounds have been synthesised with different chemical substituents on the parent phenazine molecule.

We have developed a reverse-phase ion-paired HPLC procedure for the measurement of clofazimine and other phenazine compounds. The chromatographic system consists of a C_{18} column with a mobile phase of THF : Water : Acetic acid (400 : 594 : 6) with 2.5 mM hexane sulfonic acid and UV detection at 285 nm.

Phenazine compounds (B663, B749, B3954, B4090 or B4100) were extracted from biological samples into dichloromethane containing another phenazine with a suitably different retention time as internal standard. Using peak height ratios, the extraction ranges were linear in the range 0-50ug/ml.

This method uses an easier extraction protocol for phenazine agents than has previously been reported and coupled with the use of an internal standard, make this method suitable for routine analysis of these compounds from biological samples.

CH67

RELAPSES OF 1,445 LEPROSY CASES CURED WITH DDS MONOTHERAPY

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A follow-up physical and bacteriological examination of 1445 leprosy patients cured with DDS monotherapy before 1986 in 22 counties in Hubei province was carried out in 1990. Among them 35

relapsed cases were detected with a relapse rate(RR) of 2.42% (MB 31/1,084; PB 4/361).

Among 1,084 MB cases followed up,RRs in those with a disease duration less or more than 10 years were 2.58% and 10.53% respectively; RRs in those with a treatment duration of 1-6 years (555 cases)and 7-14 years (281 cases)were 4.49% and 2.14% respectively. No relapse was found in those with a treatment duration more than 15 years. As for the relationship between RR and the duration after clinical cure, it was 2.16% in 6-9 year group, much higher than that in group of 1-5 year(0.83%),but it was high up to 6.74% in those of more than 15 years after clinical cure.

The RR was likely to be closely related to the duration of contineous treatment (CT) after cure. Among 774 cases with CT of 5 or more than 5 years, 26(3.82%) cases relapsed. No relapse was detected in 254 cases with CT of more than 10 years. It was high up to 8.93% in those without CT.

The authors suggest that inadequate or irregular treatment, development of bacterial resistance to DDS and reproduction of persisters are possible causes of relapses for cured patients with DDS monotherapy.

CH68

CLOFAZIMINE DISTRIBUTION IN HUMAN MILK

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Clofazimine, (3-(p-chloroanilino) - 10-(p-chlorophenyl)-2,10-dihydro- 2-(isopropylimino) phenazine), is used in chemotherapy of leprosy. In addition it exhibits anti-inflammatory properties when used in higher doses for treating lepromatous leprosy in reactive phase. We have worked out the distribution of clofazimine in human milk as the knowledge of the amount of drug present in milk will help in deciding about the safety of breast-feeding during maternal ingestion of the drug.

Eight female leprosy patients who were on clofazimine 50 mg daily or 100 mg on alternate days for periods ranging from 6 months to 2 years and were lactating at the time of study formed the subjects of the study. 2-3 timed aliquots of milk and corresponding blood samples were collected. The drug levels were estimated by HPLC and spectrophotometric procedures.

Clofazimine is excreted in milk to such an extent as to colour the milk. The preliminary data is suggestive of a milk to plasma ratio of 1:1.5 for the drug with milk drug levels of 1.5 - 2.5 ug/ml.

The amount of drug ingested by the infants through breast-feeding (0.2 to 0.5% of maternal daily dose) is not likely to be harmful. The high liposolubility and moderate binding of the drug to plasma proteins are the key factors that may decide the distribution of clofazimine in human milk.

CH69

THE CHAULMOOGRA OIL WAS ALREADY USED TO TREAT LEPROSY BY TRADITIONAL CHINESE MEDICAL DOCTORS IN THE PERIOD OF SOUTHERN SONG DYNASTY

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It has been proved that traditional Chinese medical doctors had treated leprosy with Chaulmoogra oil even in Southern Song Dynasty (from 12th to 13th century).The following evidences are considered as major arguments, 1) Bai Yuchan(1193-1229), a famous Taoist priest, poet and doctor, treated leprosy with chaulmoogra oil and his prescription was collected in the monograph--"Jie Wei Yuan Su"written by Shen Zhiwen in the Ming Dynasty;2)Some medical works, such as "Renzhai Zhi Zhi Fang", in which the mentioned prescription was collected, were lost in the Ming Dynasty, but fortunately it had been collectecd in "Yi Fang Lei Ju" and "Xiang Yao Jicheng Fang", edited by Korean doctors in the 15th century and published by the Japanese afterwards;3)Evidences of importing chaulmoogra oil could be found in some historical literatures, such as "Si Ming Annals"; 4) Some historical relics from harbour ruins of Quanzhou Bay also provide evidences. The author suggest that the implementation of open policy in the field of trade and culture in Southern Song Dynasty resulted in the introduction and application of chaulmoogra oil and many other valuable medicinal materials.

CH70

TREATMENT COMPLIANCE IN THE SOUTH SULAWESI LEPROSY CONTROL PROGRAMME, INDONESIA

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Since 1991, the leprosy control programme of South Sulawesi Province, Indonesia, has aimed at providing all its patients in need of chemotherapy with MDT, regardless of their ability to come to the monthly clinic. Patients are allowed to send someone else to collect MDT -including the monthly dose- for them. Selected patients are treated with blister calendar packs of unsupervised MDT for up to 3 months. Although not encouraged, leprosy workers are allowed to deliver MDT to the patients' home. To assess whether this policy is in fact acceptable, urine samples of 588 patients were examined with a spot test for dapsone in the urine. Overall compliance was 78.8%.
There was no difference in compliance between patients who came to the clinic in person and those who sent someone else to collect their drugs. However, it appeared that patients who had their medication delivered at home by a fieldworker, and those being treated with blister calendar packs, were less compliant than the other patients.
Sex, age, classification, disability grade, mode of detection and duration of treatment, had no significant effect on compliance.

CH71

A BIOASSAY TO DETECT NANOGRAM CONCENTRATIONS OF RIFAMPICIN

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Mycobacterium bovis, strain 44 (BCG P_3 vaccine strain) was incubated with ^{14}C-palmitic acid in an axenic culture. Release of $^{14}CO_2$ was detected by liquid scintillation using Whatman No.42 filter paper soaked in liquifluor concentrate; PPO; Triton X 100; 4 N NaOH. Rifampicin at concentrations of 2.0, 0.2, 0.02, 0.002, 0.0002, 0.00002, 0.000002 μg/ml was added to the cultures on the first day. The evolution of $^{14}CO_2$ was monitored daily for 5 days. Rifampicin significantly inhibited the ability of BCG to oxidize ^{14}C-palmitic acid and release $^{14}CO_2$. All concentrations of rifampicin were significantly inhibitory ($p < 0.01$) after 2 days in culture (Dunnett's T test). Cultures incubated with the lowest concentration of rifampicin (2 ng/ml) showed inhibition of metabolism of BCG at the 4th and 5th days of incubation (Dunnett's T test $p < 0.001$).

This bioassay is being utilized in Ethiopia to screen extracts of plants, used in traditional medicine, for their mycobactericidal activity; and to estimate the concentration of rifampicin in various body fluids and tissues.

CH72

EFECTOS INDESEABLES PROVOCADOS POR LA RIFAMPICINA.

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Se estudian los efectos secundarios más importantes provocados por la Rifampicina en dosis unimensual en enfermos de Hansen tratados con multiterapia.

Se hace especial mención a los efectos secundarios renales y hepáticos.

CH73

ELECTRON MICROSCOPY, POLYMERASE CHAIN REACTION AND SERODIAGNOSIS AS TOOLS FOR ASSESSING LEPROSY TREATMENT.

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This study was done on diagnosed leprosy patients receiving the WHO regimen of treatment (MTD) for more than two years. Biopsies were taken from skin lesions and sections were prepared and stained for electron microscopy. PCR tests were done using two and four primers to increase the sensitivity of the tests. Serodiagnosis was done using (ND - O. BSA) by the indirect ELISA test.

The bacteriological and the immunological investigations showed significant results which will be discussed and presented.

CH74

THE EFFECT OF ANTILEPROSY DRUGS ON BIOLOGICAL RYTHMS

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Rythmical arrangement of physiological functions in a living organism and their disarrangement caused by endogenous factors including medicines attract an increasing attention of the investigators. The appearance of new rythms, development of desynchronoses, resulting in the formation of different pathological states and toxic complications have been described. The effect on biological rythms of DDS given by gavage to outbred white rats in doses of 2-20 mg per kg of body weight for a year was studied. Untreated animals served as controls. Total blood count and biochemical analyses of blood from caudal vein were performed monthly. The results were processed with using cosinor-analysis. All the parameters of homeostasis under investigation in control animals had their own rythms of fluctuations. Erythrocyte count, glucose and hemoglobin concentrations were changed according to circannual rythm. Rythmical fluctuations of other blood indices differed from circannual rythms. Prolonged administration of DDS caused desynchronization of the previously synchronized rythmical fluctuations of erythrocyte, leucocyte and lymphocyte counts and hemoglobin concentrations as well. In view of the evidence obtained an experimental study was begun to investigate the influence of DDS alone and combined with other antileprosy drugs on seasonal and circadian biorythms. The preliminary results suggest new potentialities of development of antileprosy multidrug regimens in terms of chronobiological factors.

CH75

Leprosy Clinical Trial of Fusidic Acid

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A clinical trial of film-coated fusidic acid (Fucidin) in leprosy was undertaken based on impressive *in vitro* activity vs. *Mycobacterium leprae* in the BACTEC system together with existing documentation of human pharmacokinetics, safety and efficacy in other infections. Untreated lepromatous patients were treated as inpatients with either A) 500 mg Fucidin daily for 8 weeks (5 patients) or B) 750 mg Fucidin daily for 4 weeks followed by 500 mg daily for 4 weeks (5 patients). Skin biopsies were taken just prior to treatment and at 2, 4, 6 and 8 weeks post-treatment. Clinical response (graded according to erythema, diffuse infiltration and size/elevation of nodules and plaques) at the end of 8 weeks treatment was judged moderate in 6 patients and marked in 3 patients. No reversal reactions were noted. Bacilli recovered from skin biopsies showed a mean decrease in radiorespirometric activity of 84%, 96% and 99.5% at 2, 4 and 6 weeks treatment, respectively. Serum phenolic glycolipid-1 titers showed a time-dependent decrease in all patients. No significant difference was noted between patients receiving 500 mg or 750 mg. Mouse footpad infectivity and PCR results are pending. Based on results obtained thus far, fusidic acid appears promising as an anti-leprosy agent.

CH76

LEPROSY CLINICAL TRIAL OF CLARITHROMYCIN

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Clarithromycin is a new semi-synthetic erythromycin derivative with superior activity, pharmacokinetics and gastric tolerance. Both by radiorespirometry and the mouse footpad assay, clarithromycin had been found to be the most active macrolide against *M. leprae*, its *in vitro* activity being roughly equivalent to that of rifampicin. Clarithromycin was evaluated in 9 previously untreated lepromatous patients with the following regimen: 1500 mg x 2 on day 1, no treatment on days 2-7, 1000 mg daily on days 8-22 and 500 mg daily on days 23-56. Skin biopsies and serum were collected just prior to initiation of therapy and after 1, 3, 5 and 8 weeks treatment. Clarithromycin was tolerated well with resolution of skin lesions by the 4th week. Serum PGL-1 antigen titers of all 9 patients declined significantly during therapy. All patient biopsies (data currently available for 6 patients) were rendered non-infectious for Balb/c mice after 2 weeks of 1000 mg/day (total of 17 doses). Radiorespirometric activity also became undetectable at this time. Clarithromycin appears to be very rapidly bactericidal and should be seriously considered in any new multi-drug regimen for leprosy.

CH77

LEPROSY CLINICAL TRIAL OF SPARFLOXACIN

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Sparfloxacin is a new fluoroquinolone which has demonstrated greater *in vitro* and *in vivo* activity than ofloxacin against *M. leprae*. Based on these findings and known human pharmacokinetics, sparfloxacin was evaluated in nine untreated lepromatous patients. Patients received a single 400 mg loading dose followed by 200 mg daily for 8 weeks. Skin biopsies and serum were collected just prior to initiation of treatment and at 2, 4, 6 and 8 weeks post-treatment. Patient response was monitored by clinical photography, serum PGL-1 antigen, radiorespirometry and mouse footpad assay. Moderate clinical improvement was noted in 8/9 patients after only 2 weeks treatment. At 8 weeks post-treatment 8/9 patients showed marked improvement. Skin biopsies became non-infectious for Balb/c mice at 2 weeks (3 patients), 4 weeks (five patients) or 6 weeks (one patient) post-treatment. Radiorespirometric activity correlated well with the mouse footpad data; all biopsies becoming negative by 4 weeks post-treatment. Serum PGL-1 antigen showed a time-dependent decline in all patients. Overall, the results with daily 200 mg sparfloxacin appear to be comparable with that found previously in trials of 400 mg ofloxacin.

CH78

MINOCYCLINE IN THE TREATMENT OF LEPROMATOUS LEPROSY - PILOT STUDIES OF POSSIBLE REGIMENS.

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Although WHO MDT covers the needs of most patients, some refuse clofazimine because of its effect on skin colour, which they fear will result in discovery of their diagnosis. Because of the relatively high incidence of toxic side-effects, including both gastrointestinal symptoms and jaundice, seen with prothionamide/ethionamide therapy, we are now using minocycline in those new patients who refuse clofazimine or reject clofazimine once their skin colour alters.

We are also using minocycline in the two year MDT course given before stopping chemo-therapy to longstanding LL and BL patients, of whom many had received thiambutosine in the past, and therefore might have developed cross resistance to the thioamides.

Side-effects encountered will be reported, and the different practical drug combinations used and the duration of treatment with the minocycline component will be discussed.

CH79

IMMUNOTHERAPY OF MB LEPROSY PATIENTS WITH THE ANTI-LEPROSY VACCINE MYCOBACTERIUM W

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Phase III immunotherapeutic trials with the anti leprosy vaccine, Mycobacterium w, have been in progress in Delhi since 1987.

Subjects inducted are untreated, BI positive, lepromin negative MB patients. In double blind study, the patients are randomly divided into 2 groups. Group I patients receive MDT+M.w vaccine i.d. every 3 months for 2 years. Group II receive MDT+placebo. At determined intervals, patients are assessed by clinical scores, BI, histopathology of lesions and lepromin reactivity. Over 400 patients have been included in the study.

Results on approximately 280 patients have been analysed and are presented. At 2 years, in vaccinated patients, lepromin conversion of 100% for BB, 72% for BL and 70% for LL has been noted. 60/109 high BI MB patients became BI=0 after 8 doses of vaccine. 82/130 demonstrated histological upgrading along the spectrum and/or complete clearance of dermal granuloma. There was slightly higher incidence of type 1 reactions, although type 2 reactions were less frequent and severe. The incidence of neuritis and deformity was less, associated with rapid regression of lesions and shortening of treatment duration. Chemo-immunotherapy, thus brings about rapid bacterial clearance and immunological upgrading without exacerbation of tissue damage.

CH80

IMMUNOTHERAPY WITH MYCOBACTERIUM W VACCINE IN MB LEPROSY PATIENTS SHOWING SLOW RESPONSES TO MDT

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Immunotherapy with Mycobacterium w (M.w) vaccine brings about accelerated regression of lesions and rapid bacterial clearance when used along with MDT in multibacillary (MB) leprosy patients. A study was done to see the effect of M.w vaccine in MB cases who were slow responders to MDT.

13 MB patients, (BL or LL), who had taken MDT from 18 months to 5 years without appreciable improvement, were inducted. Seven (5 LL and 2 BL) received MDT+M.w vaccine and six LL patients received MDT+placebo. Detailed clinical charting and biopsy were done every 6 months, BI and lepromin were performed every 3 months. The vaccine was given at 3-monthly intervals.

All 7 patients receiving MDT+M.w showed rapid fall in BI. 5 were rendered negative. Histological upgrading was seen in patients of BL and none in LL. 5 showed conversion to lepromin positivity after 2-8 doses of vaccine. These findings were in accordance with clinical improvement. Two experienced mild to moderate Type 2 lepra reaction following vaccination. None of the 6 patients in the control group recorded appreciable improvement. Some had severe reactions accompanied by neuritis.

CH81

SUBCELLULAR LOCALIZATION OF DDS AND RIFAMPICIN IN THE SKIN AND NERVE OF MULTI-DRUG TREATED CASES OF LEPROSY

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One of the important but not adequately answered questions is whether anti-leprosy drugs reach a subcellular location such as Schwann cells where there is preferential multiplication and persistence of M.leprae.

Subcellular localization of dapsone and Rifampicin was carried out in skin and nerve lesions obtained from MDT treated cases of leprosy using a immunocytochemical technique. Intracellular localization of drugs specifically in macrophages and Schwann cells was carried out with polyclonal (rabbit) anti-DDS and Anti-Rifampicin antibodies in an indirect immunoperoxidase assay.

Our study records both intra and extracellular staining in the skin and nerve lesions obtained from MDT treated MB and PB cases of leprosy. All the nerves under investigation had moderate to severe pathology; hence a broken barrier leading to free diffusion of the drug. A graded difference was seen in staining intensity in relation to integrity and cellularity of the nerve lesion. It was also noted that the drug (metabolite) persists over a long period of time (>6 mths) after stopping treatment particularly in nerves of MB patients.

CH82

INVESTIGATION OF LYMPHOEDEMA AS AN ADVERSE EFFECT OF CLOFAZIMINE THERAPY IN LEPROSY

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Pedal edema as an adverse effect of clofazimine therapy in leprosy was first described in 1990. 140 patients who were on clofazimine for the treatment of lepromatous leprosy were examined. 19 of these patients were observed to have significant pedal edema on one or both feet after the clofazimine therapy was started.

Systemic causes of pedal edema were ruled out in these patients on the basis of clinical and laboratory parameters.

Lymphangiography was done in ten of these patients. Lymphangiographic evaluation showed lymphatic block, lymph node enlargement, nodal filling defects and collateral lymphatic channel circulation.

Lymphangiographic evaluation on patients with tuberculoid leprosy showed normal lymphatic drainage.

The blockade of lymphatic vessels seems to be the probable mechanism of pedal edema in the first group of patients.

The kinetics of clofazimine and the role of the lymphatic drainage in these patients will be discussed.

CLINICAL

CL1

PREDNISOLONE TREATMENT IN LONGER STANDING SENSATION LOSS.

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Three patients were seen with late reactions involving the nerves of the hands. Prednisolone treatment was given and besides the recovery of the nerve function in the hands, they also regained most of the sensation in their feet which was lost for at least 4 to 8 years(ballpoint method).
Since then we treated all new and some old patients with nerve function loss, when willing with prednisolone, regardless the reported duration of the loss. Out of 11 patients thus treated, who had reported loss for 1 year or longer,3 did not improve or improved only slightly,4 improved moderately and 4 made good improvement. In general sensation of the feet improved more than sensation of the hands. Muscle function in general did not improve considerably. Four patients who had sensation loss on detection and could not be treated with prednisolone did not improve.
We belief that although these results need verification, there is an indication for more extensive use of prednisolone in longer standing sensation loss.

CL2

ANALYSIS OF POTENTIAL PROGNOSTIC FACTORS IN PAUCIBACILLARY LEPROSY

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With the multidrug treatment (MDT) the overall results have been satisfactory. However, the problems of residual activity, worsening of residual activity, late reactions/-relapses after the stoppage of treatment specially in case of fixed duration of 6 month regimen have been reported by several investigators. In this study, the data of over 600 cases of paucibacillary leprosy (as defined by the WHO criteria of 1982) has been analysed using multivariate statistical techniques to assess the relationship of the factors like the type and duration of treatment regimen, clinical type of leprosy, number of lesions, lepromin status, clinical type of leprosy, number of lesions, lepromin status, bacterial positivity with parameters like inactivity rates at different treatment intervals, clinical course of residual persisting activity, late reactions and relapses. These patients were treated with WHO recommended regimen of 6 month duration, modified 12 month regimens as well as Prothionamide containing regimen reported by us earlier. It was observed that the treatment duration as well as regimen had statistically significant relationship with these assessment parameters. The clinical type, immunological status, number of lesions and occasional bacteriological positivity did not have close association as reported in the dapsone monotherapy days and in some of the studies later. The significance of these findings need to be debated and investigated by further studies.

CL3

A "QUICK" VMT AND ST FOR THE HANDS COMPARED TO A STANDARD VMT AND ST.

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A "quick" Voluntary Muscle Test (VMT) and Sensory Test (ST) for the ulnar and median nerves has been used by the author in field programmes; the "quick" VMT compares left and right muscle strength for the ulnar and median