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CONGRESS ABSTRACTS

As a cost-saving measure, the abstracts of the XII International Leprosy Congress have been photoreproduced from the book of abstracts distributed at the Congress without editorial changes.—RCH

ABSTRACTS

SESSION I
CLINICAL ASPECTS

Chairman: Schaller, K.F.
Rapporteur: Teera, R.

MONDAY, 20TH FEBRUARY, 1984

Auditorium 14.00–17.00

Abstracts

A* : 1-14
P* : 15-24 and 28
T* : 25-27 and 29

*A : accepted for reading
*P : for poster presentation.
*T : for title reading.

I/1(A) LEPROSY IN CHILDREN UNDER ONE YEAR OF AGE

Merlin L. Brubaker and Wayne M. Meyers
Armed Forces Institute of Pathology, Washington, U.S.A.

The incubation period in leprosy is a medical curiosity, often reported in years rather than days, weeks or months as for most other infectious diseases. Failure to recognize early symptoms or signs may contribute to an assumed prolonged incubation time in some patients. Our hypothesis for this study was: if we could establish that large numbers of infants (children 12 months old or under) had leprosy, it would demonstrate that the incubation period could be shorter than generally assumed and that intrauterine infection was possible.

To determine the global experience of leprosy in infants, we searched the world medical literature and the files of the Leprosy Registry at the Armed Forces Institute of Pathology and surveyed, by letter, members of the International Leprosy Association and others who have had an opportunity to diagnose leprosy in infants.

Patients confirmed by clinical and histopathologic findings are, to date, as follows: AFIP files - one case, and the mail survey - eight cases. The youngest patient was 2½ months. Our correspondents have identified a number of additional patients by clinical and/or skin smear results.

The final results of our survey and a review of the literature with relevant correlations will be presented.

I/2(A) INDETERMINATE LEPROSY IN A POPULATION SURVEY AND IN THE SUBSEQUENT FOLLOW-UP OF CHILDREN

L.M. Bechelli
Brazil

The paper discusses various aspects of indeterminate (I) leprosy in the initial total population survey undertaken in the Burma BCG trial (69242 inhabitants) and in the annual examinations of 28220 children in the trial followed up over periods of five to eight years. The diagnosis of I leprosy was made on clinical examination.

Age-specific rates in the initial mass survey are presented. In total 1914 leprosy cases were detected (6.2% I, 76% T and 16% L). Among the children in the BCG trial, 768 leprosy cases were detected. 255 (33%) of them had the I form. Of these 255 I cases only 4.3% had a negative or doubtful lepromin reaction. Two-thirds of these 255 cases evolved to the tuberculoid pole in less than one year. No L cases appeared in the trial population until ten and eleven years after the start of the trial.

It is concluded that whereas a high proportion of indeterminate leprosy cases regress spontaneously or evolve towards the T form, the indeterminate lepromin negative cases are important in the dynamics of the disease because of a proportion of them, if untreated, tend to evolve towards the L form. This stresses the importance of detection and treatment of I cases at an early stage in an effective strategy for controlling leprosy.

I/3(A) CHANGING PROFILES OF FIRST LESIONS IN LEPROSY PATIENTS ATTENDING A REFERRAL HOSPITAL

Rachel Mathai, Mary Jacob and P.S.S Rao
Christian Medical College, Vellore, INDIA

The clinical profiles of newly registered leprosy patients at a large referral hospital were compared between two time periods, ten years apart, viz., between 1972-73 and 1982-83. The profile for each patient included the presenting lesions with their distribution and duration, the findings at clinical examination and the results of histology and bacteriological tests. Further, the reasons that brought each patient to seek medical attention at the hospital were also ascertained and the details of any previous diagnosis made and treatment taken.

In the light of intensive anti-leprosy campaigns carried out in India during the past decade, especially in the endemic areas and with the establishment of peripheral clinics and SET Centres, one would expect a general decline in patient attendance at a referral hospital, a lower incidence of early cases, and a proportionately higher number of patients with complications. Against such expectations, the changes actually observed in the clinical features between the two time-periods are presented and discussed in relation to demographic and other relevant factors.

I/4(A) A SINGLE SKIN LESION – AN UNUSUAL PRESENTATION OF LEPROMATOUS LEPROSY

Leo J. Yoder, R.R. Jacobson and C.K. Job
National Hansen's Disease Center, Carville, U.S.A.

Lepromatous leprosy presenting as a solitary lesion with a high bacterial count is a rare occurrence. Such a case has been followed at Carville since 1977. The lesion was approximately 3 cm in diameter, located on the left elbow and had been present for about nine months. The bacterial index in the lesion was 5+ and histopathology was that of lepromatous leprosy with a BI of 5+ and a MI of 2%. Slit-skin smears from six additional sites including the ears were negative. The lepromin skin test was negative. The patient was placed on dapsone monotherapy with a satisfactory response. This case illustrates the importance of a biopsy in the evaluation of new leprosy cases. Without such information, this case would have been considered tuberculoid or borderline tuberculoid, and would have received limited treatment. Secondly, histopathologically, immunologically and bacteriologically this single lesion must be classified as lepromatous. Yet this patient's immune system was able to limit the disease to one lesion only while bacilli were able to multiply to a level of 5+ in this localized area. This case suggests there are factors yet unknown which play a significant role in determining host response to exposure to *Mycobacterium leprae*.

I/5(A) SYPHILIS IN LEPROSY PATIENTS: VERIFICATION WITH TREPONEMAL HEMAGGLUTINATION

K.A. Murray, S.A. Larsen and S.E. Keas
Center For Disease Control, Atlanta and National Hansen's Disease Centre, Carville, USA

As we found that syphilis and Hansen's disease (HD, leprosy) coexist in approximately 10% of HD patients, we attempted to define the HD population at greatest risk for concurrent syphilitic infection and the best serological tests for doing so. Specimens from 725 patients from the National HD Center in Carville, Louisiana, were tested with the rapid plasma reagin (RPR) card test and the fluorescent treponemal antibody absorption (FTA-ABS) test. The microhemagglutination assay for *T.pallidum* antibodies (MHA-TP) using sheep erythrocytes was performed on 63 patients.

Seropositive Syphilis, with reactive RPR and reactive FTA-ABS tests, often with clinical syphilis, was found in 71 patients (9.8%). Isolated RPR reactivity or false positive serology appeared in another 52 cases (7.2%), and isolated FTA-ABS reactivity occurred in 27 cases (3.7%). The MHA-TP was reactive in 36/42 patients tested with seropositive syphilis and nonreactive in all 12 patients tested with false positive serology. We found the sensitivity and specificity of the MHA-TP and FTA-ABS tests similar in HD patients with active syphilis as well as in those with false positive serology. Thus the MHA-TP represents a simple and inexpensive treponemal test for diagnosing syphilis in HD patients.

HD patients with syphilis were similar to other HD patients with respect to age, sex, leprosy class and disease activity, but they were less likely to be having ENL reactions (13% vs 25-28%) and were most often of the black race (27% vs 6-8%).

I/6(A) "GONADAL INVOLVEMENT IN LEPROSY" (STUDY OF TESTICULAR AND EPIDIDYMAL INVOLVEMENT AND GYNAECOMASTIA)

R.D. Mukhija, Pranesh Nigam, S.G. Dayal, B.M. Goyal
B.R.D. Medical College & Nehru Chikitsalaya, Gorakhpur, U.P., India

Sixty male leprosy patients, selected at random, were studied for their gonadal involvement. Of these 32 were lepromatous, 10 dimorphous and 18 tuberculoid. Their ages ranged from 14 to 50 years and the duration of illness from 3 months to 18 years. 34 were married. Only those with lepromatous and dimorphous leprosy developed testicular and epididymal changes. Nine patients with lepromatous leprosy and three with dimorphous leprosy showed decreased sexual functions and nine of these developed gynaecomastia. Nodular thickening with preserved testicular sensation was observed in 11 cases while diminished size of the testes with impaired sensation was detected in 7 cases and atrophy of testes without testicular sensation in 3 cases. Spermogram revealed azospermia in 31 cases and oligospermia in 16 cases.

These changes were believed to be due to the altered gonadal state in lepromatous and dimorphous leprosy. Patients with oligospermia (10 out of 16 cases) responded well to Tentex forte and Speman (indigenous herbal preparation of Himalaya Drug Co.) and the sperm count returned to normal with three months' therapy with these indigenous preparations along with other antileprotic agents.

I/7(A) INCUBATION TIME FOR RELAPSE IN MULTIBACILLARY LEPROSY

Nollet E., Janssens L., Groenen G., Bourland J., Pattyn S. and The Collaborative Study Group on the Treatment of Leprosy,
Leprosy Service, Kisangani, Zaire

In order to judge the value of therapeutic regimens in multibacillary leprosy, knowledge of the incubation time of relapses is essential, as this will define the length of time patients have to be followed after treatment has been stopped. In a previous study, we have shown that in paucibacillary leprosy 50% of relapses occur within 3 years, and stated that the mechanisms of relapse in multibacillary leprosy being the same, the figure should be identical for multibacillary leprosy. Observations on 40 cases in Central Africa confirmed this hypothesis. Follow-up after studies on finite treatment in all forms of leprosy can thus be concluded 3 years after the end of treatment.

I/8(A) INCUBATION TIME OF RELAPSES AFTER TREATMENT OF PAUCIBACILLARY LEPROSY

J. Bourland, L.Janssens, G. Groenen, S.R. Pattyn and The Collaborative Study Group on the treatment of leprosy
The Leprosy Service, Bujumbura, Burundi

Data are presented on the incubation time of 21 relapses after stopping dapsone monotherapy in paucibacillary leprosy in Central Africa. The results are comparable with those of other studies: 50% of relapses occur during the first 2-3 years. This figure is most important in the analysis of the results of drug trials in paucibacillary leprosy. This figure should also be relevant to regimens including drugs that are more bactericidal than dapsone since the bactericidal activity has a bearing on the minimal necessary duration of treatment, but not on the incubation time of relapses.

Since the same mechanisms prevail in relapses in multibacillary leprosy, their incubation periods should be identical.

I/9(A) HEARING PROBLEMS AMONG LEPROSY SUFFERERS

K.P. Srinivasan
Mac Quarie University, Australia.

Leprosy, an ancient systemic disease, is highly endemic in the developing countries. *Mycobacterium leprae* causes protean disorders.

Hearing in leprosy sufferers is neglected. In this study, 700 leprosy subjects and 742 normals were audiologically tested, using a calibrated two channel diagnostic audiometer, in Tamil Nadu, India. On comparison and analysis, hearing was found impaired in 82% of the leprosy population with a 60% preponderance over the normals. 90% lepromatous patients, 80% of borderline and 75% of tuberculoid showed hearing loss.

Hearing loss does not appear before two years of the onset of leprosy. Moderate degree severity, conductive type nature and a flattened audiometric pattern are the dominant features of hearing loss in leprosy sufferers. The greater the cell-mediated immune response in a patient, the less his hearing impairment. Compared to other sensory modalities, hearing is the most affected.

Hyperacusis/phonophobia is significantly experienced among leprosy sufferers, indicating paralysis of the nerve to the stapedius. There is no audiological evidence for retrocochlear lesions in leprosy. The insidious patho-physiological spread into the middle ear, causing hearing loss, needs further study in microbiology, audiology and oto-rhino-laryngology.

Appropriate otological and audiological services are recommended for the leprosy sufferers in Tamil Nadu, India.

I/10(A) A STUDY OF RELAPSE IN NON-LEPROMATOUS AND INTERMEDIATE GROUPS OF LEPROSY IN THE ELEP LEPROSY CONTROL PROJECT, DHARMAPURI

T.D. Pandian, M. Sithambaram, Ravindra Bharathi and G. Ramu
Dharmapuri, India

Cases of leprosy belonging to the non- lepromatous group consisting of maculo-anaesthetic, tuberculoid and polyneuritic types and intermediate groups comprising indeterminate and borderline were released from control from 1971 onwards. A total number of 11,345 cases consisting of 11,092 non-lepromatous and 253 intermediate group cases, were so released. Uptill 1982, 263 of these cases have relapsed, giving an overall relapse rate of 2.31%. Factors associated with the occurrence of relapse are discussed.

I/11(A) ULCERATIVE CUTANEOUS MYCOBACTERIOSIS BY *M. ULCERANS* IN MEXICO: A STUDY OF FOUR CASES.

Lavalle, P., Novales, J., De Ovando, F. and Huerta, M.A.
Pascua Dermotological Centre, Mexico

The first author (P.L.) presented to the VI International Leprosy Congress (Madrid, 1953), a case of ulcerative cutaneous mycobacteriosis caused by *M. ulcerans*, which was the first case in Mexico and the American Continent. Recently, we have studied three other cases from the same geographic area, situated in the central eastern region of the country.

A comparative study was carried out from 4 cases from the clinical, histopathological and bacteriological points of view and the results of the treatment administered. We also considered the epidemiological data which permitted us to outline the characteristics of the source of this ulcerative cutaneous mycobacteriosis, one of the few cases known in America.

Finally, we compared this Mexican experience with those obtained from other countries, mainly in Africa and we explained the name adopted for this infection caused by *M.ulcerans*.

I/12(A) REVERSAL REACTION IN BORDERLINE LEPROSY

Tulip Tan
Middle Road Hospital, Singapore

The incidence and treatment of reactions were studied in 56 new cases of borderline leprosy diagnosed over a period of three years. Of 25 patients (45%) who developed reactions, all except one had reversal reaction. Half the patients developed it at the time of diagnosis of leprosy (Group A). In 41% of those who developed reactions after treatment of leprosy (Group B), it occurred more than a month later.

In Group A, 7(58%) had BT leprosy, 5 (42%) had BL (4) and BB(1) leprosy. The reverse ratio was seen in Group B.

Seven Group A patients (58%) required one to two months of prednisolone alone to control the reaction. Four patients (33%) with severe reaction had both prednisolone (average four months in 3 patients) and clofazimine (average five months in 3 patients) therapy.

Group B patients controlled with prednisolone alone (58%) had an average of 6 months' therapy.

Five of Group B patients who had both prednisolone and clofazimine therapy also required longer periods of treatment (average seven months prednisolone and fifteen months clofazimine).

The reasons for the difference in the duration of treatment required to control the reactions are discussed.

I/13(A) REACTIONS IN LEPROSY : A STUDY OF 30 PATIENTS

Zobeida Lovio, Alfredo Abreu, Lourdes Gonzalez
Cinadad dela Habane, Cuba

The behaviour of reactions in leprosy, (erythema nodosum leprosum and reversal reaction) was studied in 30 patients in this clinical picture in the last five years, in Dermatological Service of the Comandante Fajardo Teaching Hospital.

The following data were collected: age, sex, colour of the skin, type of reaction, number of erythema nodosum leprosum reactions, symptoms of the first erythema nodosum leprosum and its development and symptoms of the reversal reactions.

It was observed that all patients that showed erythema nodosum leprosum were LL and those that showed reversal reaction were BB, BT and BL.

The erythema nodosum leprosum appeared in the majority of patients after one year of treatment and the reversal reaction after six months of treatment.

The specific treatment for the disease was not suspended.

The erythema nodosum leprosum was treated with thalidomide and the reversal reaction with prednisone and analgesics.

The improvement in all the cases was satisfactory.

I/14(A) LUCIO'S PHENOMENON IN SOUTH AFRICAN PATIENTS

E.J.Schulz and S.H. Kok,
West Fort Hospital, Pretoria

The histological differentiation of Lucio's phenomenon (LP) from erythema nodosum leprosum (ENL) is not always clear-cut. The main criteria for diagnosing LP are necrosis of the epidermis, thrombosis in dermal vessels and the presence of solid bacilli. In both LP and ENL *M. leprae* may be found in the walls of blood vessels and a polymorphonuclear infiltrate occurs in the dermis. Immunofluorescence findings reported in the literature are similar and do not help to distinguish between the LP and ENL. The clinical picture of Lucio's phenomenon in which angulated eschars are preceded by bullae and followed by ulcerations is however characteristic and resembles skin lesions seen in intra-vascular coagulation (IC). We have seen several cases in which the clinical picture of LP could be supported by histological findings which excluded ENL and IC. These Lucio-like phenomena occurred mainly in patients with diffuse untreated lepromatous leprosy.An additional infection seems to play a precipitating role in some of the patients.

I/15(P) REACTION PATTERNS IN CONTACTS OF HANSEN'S DISEASE

Ruth Annamalai
Department of Dermatology and Leprosy, Stanley Medical College, Madras, INDIA

100 cases of early forms of Hansen's disease seen at the Dermatology centre of the Government Stanley Hospital, Madras are presented herein.

Astute probe revealed in all cases, contact history of Hansen's disease in the immediate relatives or neighbours. The reaction patterns met with in these cass were: 1. Pityriasis rosea 2. Pityriasis rubra pilaris 3. Alopecia of beard and/or scalp 4. Knuckle pads and ichthyosis confined to legs 5. Traumatic fissures of feet and ichthyosis of legs 6. Callosities of feet and ichthyosis 7. Recurrent impetiginised leg ulcers with ichthyosis. Recognised clinical types of Hansen's disease were conspicuous by their absence in them. Multiple slit-smear studies from various sites were negative for A.F.B.H. and E section of skin and radial cutaneous nerve showed a tuberculoid granuloma, but was negative for A.F.B. The lepromin test and F.L.A. - A.B.S. test were of value in early recognition of Hansen's disease when present, details of which are discussed. Dapsone therapy caused complete resolution in some, amelioration of signs and symptoms in others, in whom the therapy was continued. Each case was assessed with V.D.R.L., G.T.T. and immunoglobulin studies to detect or rule out other immune deficiency diseases, in addition to routine blood and urine analysis.

I/16(P) PREGNANCY AND LEPROSY: THE CONSEQUENCES OF ALTERATIONS OF CELL-MEDIATED AND HUMORAL IMMUNITY DURING PREGNANCY AND LACTATION.

Duncan, M.E., Pearson, J.M.H., Ridley, D.S., Melsom, R. and Bjune, G.
MRC Leprosy Project, Addis Ababa; Ethiopia; NIMR London

One hundred and fourteen women with leprosy and 33 healthy controls were studied through 120 and 36 pregnancies respectively and followed up with their babies during lactation. Fifty five mothers showed deterioration of their leprosy status(overt leprosy, relapse in cured cases and deterioration in those on treatment) during pregnancy and the first year of lactation: 31 (56%) during the third trimester of pregnancy.

Forty women were diagnosed as having reversal (type I) reaction; in 20 (50%) the first occurrence was during the first 6 months of lactation. Twenty-eight women had erythema nodosum leprosum (type 2) reaction, which in 19 (68%) first occurred during the third trimester of pregnancy or the first 6 months of lactation. Reaction in skin was a feature of pregnancy while reaction involving nerve was a marked feature of lactation. The most serious effect of these reactions was nerve damage. Nearly half of the leprosy patients showed loss of sensory and/or motor nerve function during a single pregnancy/lactation: all mothers were at risk.

These observations are attributed to some non-specific suppression of cell-mediated immunity (CMI), possibly due to serum-factors, maximal during the third trimester of pregnancy which comes off soon after delivery.

I/17(P) CLINICAL AND HISTOLOGICAL EVALUATION OF 1098 SUSPECTED CASES OF HANSENIASIS.

Miriam Peres, Gisela del Pino, Maria da Graca Busko, Jose Grossi Netto and Lucio Bakos.
Estado do Rio Grande Do Sul, Brazil.

A total of 1098 suspected cases of Hanseniasis reported in Rio Grande do Sul State, Brazil, between 1 November 1974 and 31 August 1982 is analysed. New cases diagnosed only on clinical grounds by dermatologists and general practitioners are analysed separately. All cases are submitted to an anatomo-pathological test. Cases diagnosed clinically and cases confirmed by histological examination and clinical findings demonstrate that differences between the two classifications are not significant.

Many suspected cases of indeterminate leprosy were eliminated during the study, either because they were not confirmed as being due to Hanseniasis (Leprosy) or because they revealed a granulomatous histological structure.

These findings reduced the proportion of this clinical form.

This paper is an up-to-date version of the paper presented at the XI International Congress of Leprosy, in Mexico City.

I/18(P) NASAL SEPTAL PERFORATION IN LEPROSY

B. Koteswara Rao
Government T.B. & I.D. Hospital, Waltair, India

204 adult leprosy patients under treatment for periods of 1 month to more than 10 years (mostly lepromatous and some borderline) were examined clinically. Nasal examination was performed with Thudicum's speculum, forehead mirror and Bull's eye lamp. Nasal smears were taken and studied along with skin smears.

About 16% of the cases had nasal septal perforations. All the perforations exhibited a characteristic anterior limitation. This limitation pattern of septal destruction is explained on the basis of the compartmental anatomy and embryology of the nasal septum.

In the non-perforated cases, the appearances of nasal septum are described and correlated with activity of the disease on the basis of bacteriology. Those appearances also conform to the anterior limitation pattern and might be regarded as indicating the underlying pathology.

The paper will be illustrated with about 10 slides.

I/19(P) LEPROSY THE GREAT SIMULATOR

Roshdy Mohareb
Director, Leprosy Control Department, M.O.H. of Egypt, Cairo.

Early detection of leprosy depends on knowledge of its various skin manifestations which simulate all known skin diseases. This study demonstrates by slides skin conditions commonly confused with leprosy, starting with the small hypopigmented macule of indeterminate leprosy and proceeding through papular lesions, nodular, infiltrated, bullous and ulcerative lesions etc.

Leprosy lesions of the mucous membrane of the mouth and tongue are also demonstrated and compared with those due to other skin diseases.

Neurological and dystrophic manifestations are discussed briefly with special reference to the rare condition of congenital indifference to pain, of which 3 cases are shown.

I/20(P) THE PRIMARILY PIGMENTED TUBERCULOID LEPROSY

V.R. Mehta
Department of Dermatology, Venereology & Leprology, L.T.M.M. College and L.T.M.G. Hospital, Sion, Bombay, India

D.M., male, 29 years came to our notice in May 1972 with a 4 year history of pigmentation of the right leg. It started on the outer aspect of the ankle and

spread to the dorsum of the foot and front and outer surfaces of the leg. It was accompanied by dysaesthesia and shooting pain in the affected area.

A diffuse dry, atrophic, bluish black skin over the lower half of the anterior and lateral aspects of the right leg and dorsum of the foot was found on examination. The affected area was anaesthetic. A thickened and tender lateral popliteal nerve was palpable below the fibular head.

The H.E. stained section of a 5 mm punch biopsy revealed patchy epidermal atrophy with flattening of the rete ridges. Bands of a lympho-histiocytic infiltrate surrounded the neurovascular tissue in the mid-reticular parts and the sweat glands. The Fontana-Masson preparation showed clumping of melanocytes at the epidermo-dermal junction; processes of the adjoining cells seemed to fuse at the interface giving it a festooned appearance. Pigment extrusion through the epidermis was in the form of granules in groups. There was very little incontinence of pigment into the dermis. The Fite stain as expected did not reveal leprosy bacilli.

The patient was treated during the first year with 300 mg of thiacetazone and 600 mg of isoniazid, combined with 20 mg of prednisolone daily initially, tapered down to 10 mg in 6 months. At the end of the year, there was marked improvement in sensation and the pigmentation began to be replaced by hypomelanosis. At this point, 100 mg of dapsone per day was given to replace the previous therapy.

Comment: This is the only case of tuberculoid leprosy, with hypermelanosis as the initial manifestation, seen by the author.

I/21(P) PHYSICAL PARAMETRIC CONSIDERATION FOR CUTANEOUS SENSORY TESTING

Frank Kanatani
National Hansen's Disease Centre, Carville, USA

Published articles have presented clinical studies on cutaneous sensory testing with currently available instruments. The articles reveal the need for base-line data and definitive clinical reference.

Standardization of cutaneous sensory testing instrument is a priority item. Standardization implies defining design criteria and quality control of production . Establishing criteria suggest that the relation of two physical parameters, force and pressure, is understood.

Criteria considered in the design of the author's steel wire pressure aesthesiometer were: 1. Steel wire would be selected. 2. Diameter would be consistent. 3. The tip configuration would be flat. 4. The whole tip area would be in contact with the skin surface throughout the period of application. 5. One instrument would encompass the full range of normal pressure through pain threshold.

The poster exhibit represents a comprarison of engineering tests on two types of skin contact sensory testing instruments. The descriptive aspect shows design differences and application principles for the benefit of the clinician.

I/22(P) RELIABILITY OF THE SEMMES-WEINSTEIN MONOFILAMENTS IN HANSEN'S DISEASE

David S. Sims, Jr. James A Birke
National Hansen's Disease Centre, Carville, USA

In 1898 Von Frey introduced the use of horse hairs of varying thickness as a clinical method of determining the sensory threshold of the skin. Semmes and Weinstein modified this method in the early 1960's, by substituting a set of 20 nylon monofilaments. Many clinicians are currently using the Semmes-Weinstein monofilaments; however, there is a lack of information regarding their reliability.

The purpose of this study was to determine the reliability of the Semmes-Weinstein monofilaments in the foot of Hansen's Disease patients. Three repeated measurements of sensory threshold were made on selected sites by two therapists in 20 patients.

The variability between testers was found to be only slightly greater than variability within testers. The 95% confidence interval was calculated to determine the minimum interval between successive monofilaments during testing. The critical interval was found to be every 4th monofilament.

I/23(P) A STUDY OF BUCCAL MUCOSA IN VARIOUS TYPES OF LEPROSY

Sharma, N.K., Goel, V.K., Shakunthala, R and Pratap, N.K.
L.L.R.M. Medical College, Meerut, India

Clinical observation, and histological and histochemical changes observed in mucosal biopsies in 50 patients with various types of leprosy, seen in the Meerut area, are presented and discussed in the light of review of the relevant literature on the subject.

I/24(P) "SPOT THE DIAGNOSIS" (Intended for Poster Presentation as a QUIZ)

Phyllis M. Taylor and Sigmoni Arunthathi
Schieffelin Leprosy Research & Training Centre, Karigiri, India

Case history, photographs, photomicrographs of FIVE patients will be presented.

Answers will be available at the time of Conference with one of the authors.

Case Abstracts are attached (not to be printed).

I/25(T) "CASE TAKING" IN LEPROSY

K. Ramanujam
India

Leprosy, in the majority of instances, is diagnosable on the basis of a proper clinical examination alone. Hence it is mandatory that a set pattern is followed in the examination of an individual for the presence of leprosy. This procedure is "CASE TAKING" in leprosy.

The prerequisites for undertaking this procedure are: to remember that leprosy is no respecter of persons; awareness of the occurrence of leprosy in the community, especially in areas where leprosy is endemic; a pair of observant eyes; an unbiassed mind; an attitude that will never take things for granted; and lastly, familiarity with the early manifestations of leprosy and the clinical signs of the disease.

"CASE TAKING" comprises of:

1. Interrogation –
   - (i) Collection of biodata of the individual, such as name, age, sex, occupation and place of residence.
   - (ii) Family history of leprosy.
   - (iii) History of contact with cases of leprosy.
   - (iv) Details of previous treatment for leprosy, if any.
   - (v) Prsenting complaint or symptom.
2. Clinical examination –
   - (i) Inspection of the body surface, to the extent that is permissible, in good natural light for the presence of suggestive or tell-tale evidence of leprosy.
   - (ii) Palpation of the commonly involved peripheral and cutaneous nerves at the sites of predilection for the prsence of enlargement and/or tenderness.
   - (iii) Testing for evidence of damage to the sensory or motor modalities, such as (a) sensory changes in the skin patches or the peripheral parts of the limbs; and (b) paresis or paralysis of the muscles of the hands and feet, leading to the disabilities or deformities.

The "CASE TAKING", as far as possible should be supplemented by the taking of smears from the skin and the nasal mucosa by standard methods, which are then examined for the presence of *M. leprae*. This will enable the detection of very early lepromatous cases which, otherwise, will be missed.

I/26(T) HYDRATION OF STRATUM CORNEUM IN LEPROSY

Okhandiar, R.P.
Skin & Leprosy Institute, Bhagalpur (Bihar), India

Lesions of leprosy are dry, inflexible, brittle and form fissures and cracks in winter, presumably due to destruction of sympathetic nerve fibres impairing sweating, thus limiting water supply to its stratum corneum (SC).

The SC water-content, essential for its softness, pliability and extensibility, is dependent upon sensory factors and also such factors as water-loss and atmospheric conditions like relative humidity, temperature, wind-speed, etc.

However, a qualitative defect in SC, inherent or acquired, may impair its water-holding/water-binding power. To study this, the dried pulverized callus of the anaesthetic foot adjacent to the trophic ulcer representing pure SC (unprocessed callus- UC), was washed with ether (EWC), and with both ether and water (EWWC); and water-uptake and water-loss were measured at 100% humidity and 37°C. Significant poor water-uptake and water-loss were recorded by UC and EWC as compared to the normal SC (callus of controls, a defect not recorded after both ether and water-washing (EWWC).

The findings suggest a qualitative alteration in the SC in leprosy lesions, mostly in its water-soluble protein fraction. A defect in keratinization process due to nerve damage is postulated, which renders the SC brittle and prone to trophic ulceration.

I/27(T) ELECTROCARDIOGRAPHIC CHANGES IN LEPROSY

N.S.V. Jagga Rao, and B. Narisimha Rao
Visakhapatnam, India

Electrocardiograms (ECG) were studied in fifteen patients with Hansen's disease. Fourteen patients had lepromatous leprosy and one patient had borderline type disease. The mean duration of the disease was 19 years (5 to 45 years).

In three patients, the disease process was very active and in one it was inactive.

One patient had a history suggestive of angina pectoris and one patient had hypertension. Twelve-lead electrocardiograms revealed a normal QT interval.

There was no discordance of QRS-T angles. The resting ECG in one patient with ischaemic heart disease showed ST-changes consistent with ischaemia. Four patients showed plane ST-segment changes in lateral leads, while two patients had similar changes in inferior leads. While awaiting more detailed investigations in a larger group of patients with various types of leprosy, it seems that there are no changes in ECG, unique to lepromatous leprosy.

I/28(P) LUCIO'S LEPROSY, CLINICAL AND HISTOPATHOLOGICAL CHARACTERISTICS

Rodrigues Obdulia and Novales Josefa
Centro Dermatologico Pascua, S.S.A, Mexico, D.F., Mexico

The authors present a historical-synthesis of Lucio's Leprosy, since the first paper in which it is mentioned *(de la Pascua, 1844)*, as far as the more recent immunological studies. They analyse briefly the masterly description of *Lucio and Alvardo (1852)*, and the data which have been added since its identification. Clinical features of this form of lepromatosis are described : *Diffuse general infiltration that never transforms into nodules*. Slow but total loss of eyelashes, eyebrows and downy hair. Rhinitis, panneuritis and visceral lesions. The typical lepra reaction of these cases (erythema necrotisans, with Lucio's phenomenon), is also described.

The main histopathological data in these cases are: In superficial and intermediate dermis, lepromatous infiltrates in samll foci around vessels and appendages. Infiltrates are more dense in the deep dermis and hypodermis. In ear lobes, they are similar to those found in nodular leprosy and are separated from the epidermis by Unna's band.

During lepra reaction (Lucio's phenomenon), there is epidermal necrosis, ulceration and intraepidermal bullae. Vasculitis of small and medium calibre blood vessels surrounded by polynuclear foci with numerous bacilli are seen in all cases. There is destruction of elastic fibres, the reticular ones are increased, and the collagen fibres are normal. Finally some of the histopathological changes in liver, testis, epididymis and mammary tissue biopsies, are described.

I/29(T) DIAGNOSTIC DIFFICULTIES OF LEPROSY – ASSOCIATED WITH OTHER SKIN DISEASES

M.H. Mobayen
Department of Dermatology, Medical Faculty, Tabriz University, IRAN

Leprosy is one of the ancient indigenous diseases in Iran. The diagnosis of leprosy is not difficult in areas known to be contaminated. But when cases of leprosy are associated with other skin disease, diagnostic difficulties may arise. Thus, leprosy may be assoicated with, or mistaken for, discoid lupus erythematosus psoriasis, lupus vulgaris, systemic fungal diseases, it may be confused with congenital anomalies, ichthyosis, scleroderma, vitiligo, basal or squamous-cell carcinoma. It may be present together with superficial tungal disease such as tinea capitis, tinea circinata, candidiasis, pityriasis versicolor, microsporum, epidermophyton, candida - albicans and malassezia furfur; or with viral infections and chronic contact dermatitis. In all these cases, for accurate diagnosis we need to use such examinations as microscopical, pathological, serological and immunological.

SESSION II
IMMUNOLOGY (A)

Chairman: Bloom, B.R.
Rapporteur: Azulay, R.

MONDAY, 20TH FEBRUARY, 1984

Commission Hall 'G' 14.00–17.00

Abstracts
A* : 30- 47

IMMUNOLOGY (B)

Chairman: Convit, J.
Rapporteur: Godal, T.

TUESDAY, 21ST FEBRUARY, 1984
Commission Hall 'H' 08.30-12.00

Abstracts
A* : 48- 65

IMMUNOLOGY (C)

Chairman: Talwar, G.P.
Rapporteur: Hastings, R.C.

TUESDAY, 21ST FEBRUARY, 1984
Commission Hall 'H' 13.00-16.30

Abstracts
A* : 66- 83
P* : 84-104
T* : 105-134

*A : accepted for reading
*P : for poster presentation.
*T : for title reading.

II/30(A) THE IMMLEP PROGRAMME OF THE UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES

B.R. Bloom, S.K. Noordeen, and H. Sansarricq
Albert Einstein College of Medicine, New York, USA

The goals of IMMLEP programme are to foster development of: 1) anti-leprosy prophylactic and therapeutic vaccines; 2) immunological methods for detection of specific serologic and cellular immune responses to *M. leprae;* and 3) greater understanding of immunopathological mechanisms responsible for unresponsiveness and tissue damage. A continuing effort remains to provide and disseminate information on research progress to investigators around the world, to develop useful protocols for laboratory and field studies, and to make available vital reagents, such as purified *M. leprae,* monoclonal antibodies and specific antigens, as available to qualified investigators. Possibilities for use of monoclonal antibodies and recombinant DNA techniques for seroepidemiologic studies and future vaccine studies will be discussed.

II/31(A) COMPARATIVE ANTIGENIC ANALYSIS OF *M. LEPRAE* USING ISOELETRIC FOCUSSING

R.G. Navalkar, C. Ibegbu and L. Graham
Morehouse School of Medicine, Atlanta, U.S.A.

Isoelectric focussing (IEF) represents a major advance in the field of high resolution separation of proteins and other amphoteric macromolecules. It is an equilibrium method in which proteins are segregated according to their isoelectric points (pi) in pH gradients.

We have employed this technique to determine various protein antigens of *M. leprae* and other clinically relevant mycobacteria. Various preparations of *M. leprae* such as post-ATP extraction, autoclaved, gamma-irradiated and untreated, showed significant differences in their protein content as determined by the number of bands stained. Such differences were also noted between *M. leprae* and other mycobacteria not only in the number of bands but also their location within a given pH range. Bands of all mycobacteria, including *M. leprae,* located themselves in acidic pH range when Polyacrylamide gel (PAG) plates at pH 3.5 to 9.0 were used. Subsequently, when PAG plates with pH 4.3 to 6.0 were used, other mycobacterial bands were seen between pH 4 and 5.0. However, only *M leprae* bands extended to pH 6.5.

This property of *M. leprae* now permits identification of the organism from all mycobacteria including *in vitro* grown *M. leprae*. In addition, it also permits recognition of immunogenic components of the organism, because of the differences seen between each of the *M. leprae* preparations, especially the autoclaved and gamma irradiated ones.

II/32(A) ANALYSIS OF THE MAJOR ANTIGENIC DETERMINANTS OF THE CHARACTERISTIC PHENOLIC GLYCOLIPID FROM *M. LEPRAE.*

Brett, S.J., Payne, S., Draper, P., and Gigg, R.
Medical Research Council, London, England

Antibodies to a phenolic glycolipid purified from *M. leprae* have been demonstrated in sera of leprosy but not tuberculosis patients, using an ELISA. The major antigenic determinants on this molecule were investigated using anti-sera raised in rabbits to the purified glycolipid. A small, but significant, cross-reaction was observed with the glycolipids from *M. bovis* and *M. kansasii*, which contain the phenolphthiocerol dimycocerosate part of the molecule but have different sugars, and also with a semi-synthetic 'attenuation indicator lipid' which shares the phenolphthiocerol but has no sugars. There was, however, no cross-reaction with phthiocerol dimycocerosate. The disaccharide, corresponding to the two terminal sugars of the *M. leprae* glycolipid and the trisaccharide, have been chemically synthesized and shown to inhibit the reaction between glycolipid and antibody in the ELISA. The cross-reactivity observed with *M. bovis* and *M. kansasii* glycolipids was not inhibited by the synthetic oligosaccharides. These findings suggest that the cross-reactivity is associated with the phenol ring and implies that the trisaccharide may be a unique antigenic determinant of *M. leprae*.

It is hoped to conjugate the trisaccharide to a protein to produce an *M. leprae* specific synthetic antigen. This will be used to determine antibody levels in leprosy patients and contacts providing, it is hoped, a method of detecting sub-clinical infections.

II/33(A) SYNTHESIS AND ACTIVITY OF AN ARTIFICIAL ANTIGEN BASED ON PHENOLIC GLYCOLIPID I FOR DIAGNOSIS OF LEPROSY.

Fujiwara, T., Hunter, S.W., Cho, S.N., Aspinall, G.O., Chatterjee, D., Gelber, R.H., Ray T.H. and Brennan, P.J.
International Leprosy Association, Fort Collins, Colorado, U.S.A.

The structural requirements within the species specific 3,6-di-0 methyl-ß-D glucopyranosyl (1→4)2, 3-di-0-methyl-∝-L-rhamnopyranosyl (1→2) 3-0-methyl-∝-L-rhamnopyranose of the specific phenolic glycolipid I antigen of *M. leprae* for binding to anti glycolipid immunoglobulin M from human leprosy sera were examined. Use was made of chemically defined partially deglycosylated fragments of phenolic glycolipid I, of two other minor *M. leprae* specific phenolic glycolipids, those containing 6-0 methyl-ß-D-glucopyranosyl (1→4)2, 3-di-0 methyl-∝-L-rhamnopyranosyl (1→2) 3-0-methyl-∝-L-rhamnopyranose, or 3,6-di-0-methyl-ß D-glucopyranosyl (1→4) 3-0-methyl-∝-L-rhamnopyranosyl (1→2) 3-0-methyl-∝-L rhamnopyranose, and of phenolic glycolipids from other myco bacteria. Additionally, the trisaccharide corresponding to that in phenolic glycolipid I, and the 3,6-di-0-methyl-ß-D-glucopyranosyl (1→4)2,3-di-0-methyl-∝-L-rhamnopyranose, the 6-0-methyl-ß-D-glucopyranosyl(1→4) 2,3-di-0 methyl-∝-L-rhamnopyranose, and ß-D-glucopyranosyl (1→4) 2,3-di-0-methyl-∝-L-rhamnopyranose disaccharides were synthesized, charaterized, and their activities examined. The phenolic glycolipids containing 3,6-di-0-methyl-ß-D glucopyranose at the non-reducing terminus were highly active in binding leprosy anti glycolipid immunoglobulin M, and the 3,6-di-0-methyl-ß-D-gluco-pyranosyl-containing di-and trisaccharides were the most effective in inhibiting this binding. Thus, the 3,6-di-0-methyl-ß-D glucopyranosyl substituent was recognized as the primary antigenic site in phenolic glycolipid I. With this information, bovine serum albumin containing reductively aminated 3,6-di-0-methyl-ß-D-glucopyranosyl (1→4)2,3-di-0-methyl-L-rhamnose was prepared and shown to be highly active in the serodiagnosis of leprosy and to show excellent correspondence to the actual phenolic glycolipid antigen.

II/34(A) FURTHER CHARACTERIZATION OF MONOCLONAL ANTIBODIES TO *M. LEPRAE*

Thomas P. Gillis
Marshall University, School of Medicine, USA

Monoclonal antibodies have been produced to *M. leprae*. Antibodies have been isolated which bind common mycobacterial antigens, and others react only with *M. leprae* determinants. Radioimmunoprecipitation and immunoblotting analysis with some of the monoclonals indicated that four of the antibodies were reactive with an *M. leprae* protein that has an apparent molecular mass of 68K daltons. This molecule is present in other species besides *M. leprae* (e.g. *M. tuberculosis* and *M. smegmatis)* and experiments are in progress to purify this molecule from cultivable species of mycobacteria using the monoclonals. Experiments are also in progress to gain information on the chemical nature of the molecule, carrying the antigenic determinants defined by the monoclonals which react only with *M. leprae*. Initial studies indicated that these monoclonals were directed at determinants on the phenolic glycolipid I of *M. leprae*.

II/35(A) FURTHER STUDIES OF MONOCLONAL ANTIBODIES DIRECTED AGAINST DEFINED MYCOBACTERIAL ANTIGENS PRESENT IN *M. LEPRAE* AND OTHER MYCOBACTERIA

Richard A Miller, Thomas P. Gillis, Saroj R. Khanolkar, Douglas B. Young, Thomas M. Buchanan
University of Washington, USA

A panel of murine monoclonal antibodies have been produced that are directed against protein and polysaccharide antigens of *M. leprae*. Some of these monoclonals were cross-reactive with many species of mycobacteria, recognizing antigen epitopes which are widely distributed within the genus; others had a more restricted spectrum, and two were specific for *M. leprae*.

BALB/c mice immunized with partially purified, intact *M. leprae*, a lithium acetate extract of *M. leprae*, or with arabinomannan purified from *M. smegmatis* were fused with NSI/1 myeloma cells in the presence of polyethylene glycol. Screening of the fusion products was performed by an enzyme-linked immunosorbent assay (ELISA). Species specificity of the immunoglobulins produced by the stable hybridoma lines was determined by screening against antigen preparations from 18 species of mycobacteria in an ELISA. Antigen specificity was demonstrated by western blot or gel-radio-immunoassay (GIRA) methodologies.

The majority of the monoclonals whose specificity has been determined bind to epitopes present on a 68,000 dalton protein. At least five distinct epitopes have been detected on this protein, some unique to *M. leprae* and others common to many species. One monoclonal antibody was specific for arabinomannan, a carbohydrate antigen found throughout the mycobacterial genus, and another was specific for a low molecular weight protein of approximately 14,000 daltons.

Monoclonal antibodies against defined antigens of *M. leprae* may prove useful in the purification of important antigenic proteins and in research into the pathogenesis of human leprosy.

II/36(A) IDENTIFICATION OF *M. LEPRAE* ANTIGENS USING MONOCLONAL ANTIBODIES

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The Wellcome Research Laboratories, Department of Experimental Immunobiology, Beckenham, UK

Previous studies with polyclonal antisera suggested the existence of antigens specific for *M. leprae*, but failed to establish widely applicable techniques for the assay and purification of corresponding molecules. Here we report on the definition of two quasi species-specific (MY1, MY2) and two cross-reactive (MY3, MY4) antigens from the supernatant fraction of sonicated *M. leprae* using murine monclonal antiboidies. The representation of these antigens was examined in twenty different species of mycobacteria. The molecular size determined by immunoblotting from polyacrylamide electro-phoresis gels and the epitope specificity of antibodies was analysed by binding competition assays between pairs of antibodies.

A protein antigen, MY1 of molecular size of 12K reacted with antibody ML06 without demonstrable cross-reactivity for any of the other species of mycobacteria. Antibodies to antigen MY2, however, showed a very marginal degree of binding also to *M. avium, M. kansasii* and *M. paratuberculosis*. Antigen MY3, represented by about five protein bands (35-70K) present in several mycobacterial species, probably originated from the bacterial cell wall structure, since repeated sonication selectively increased its yield in the supernatant fraction. Finally, a protease-resistant molecule MY4 (40-50K), presumably rich in carbohydrate content, displaying two distinct cross-reactive epitopes, has been established. The described monoclonal antibodies could be valuable for the immunoassy and for the purification of antigens which may be explored towards prophylactic or therapeutic immunisation against leprosy.

II/37(A) MONOCLONAL ANTIBODIES TO TUBERCULOSIS, *M. LEPRAE* AND *M. BOVIS-BCG.*

A.H.J. Kolk, M.L. Ho, T.A. Eggelte, P.R. Klatser and S. Kuijper
Royal Tropical Institute, Amsterdam, The Netherlands

A battery of monoclonal antibodies (Moab) specific for the different mycobacteria would provide an extremely useful tool for the rapid diagnosis of active disease. To produce such antibodies BALB/c mice were immunized with either sonicated or heat killed mycobacteria and boosted 4 days before the fusion with SP 20 mouse myeloma cells. Hybridomas were selected on the basis of the highest degree of specificity in a micro-enzyme immuno-assay using Terasaki plates (EIA) coated with intact or sonicated mycobacteria. Most clones secreting antibodies with a high specificity were obtained from fusions with spleen cells from mice, immunized with intact mycobacteria.

The activity of 25 Moab were characterized using *M. tuberculosis* H37Rv, *M. leprae*, *M bovis-BCG*, nine other mycobacteria and PPD from *M. tuberculosis*. One Moab reacted only with H37Rv, two Moab reacted only H37Rv and H37Ra. Four Moab reacted only with *M. tuberculosis* and *M. bovis-BCG*. One Moab reacted with a chloroform-methanol-water extract of BCG and the other eighteen showed unique patterns of reactivity by EIA. In addition, several of the 25 Moab were characterized by a reaction in an enzyme immuno-assay on longitudinal slices of sodium dodecysulphate polyacrylamide gels, on which mycobacterial sonicates were separated. Moab reacting with low molecular weight and high molecular weight proteins were detected. We plan to use these monoclonal antibodies to isolate their specific antigens which can be utilized in an EIA for serodiagnosis.

II/38(A) MONOCLONAL ANTIBODIES TO *M. LEPRAE*

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Clinical Immunology Research Centre, Sydney, Australia

Monoclonal antibodies (MAbs) which recognize the antigens of sonicated M. leprae were obtained by fusion of mouse myeloma cells with splenocytes from mice immunised to both *M. bovis* and *M. leprae*. Of five MAbs raised to *M. bovis*, two crossreacted with *M. leprae;* whilst at least one of the five other MAbs raised to *M. leprae* crossreacted with *M. bovis*. A number of the remaining antibodies demonstrated apparent monospecificity for the two immunising antigens used. Studies in progress include competitive binding assays to determine epitope specificity. In particular, we are examining whether epitopes recognized by the *M. leprae* crossreactive MAbs raised to *M. bovis* are the same as those recognized by MAbs from the reverse immunisation. The relation of epitopes recognised by human antibodies and those by MAbs is being explored with sera from lepromatous patients in inhibition experiments.

Initial characterisation of these MAbs defined determinants is underway using immunoblotting techniques.

II/39(A) THE PRODUCTION OF HUMAN MONOCLONAL ANTIBODIES AGAINST *M. LEPRAE*

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The hybridoma technique has provided monoclonal antibodies for the diagnosis and potential therapy of many infectious diseases and as molecular probes for elucidating the biological mechanisms of infection. Leprosy is a very poorly understood disease that poses severe health problems mainly due to the lack of reliable and sensitive diagnostic methods for early detection. We report here a system which has the potential of generating human monoclonal antibodies against species specific antigens of *M. leprae* for use in the early diagnosis of leprosy.

B-cell lines from lepromatous leprosy (LL) patients were established by Epstein-Barr virus (EBV) transformation of peripheral blood lymphocytes. These LL-lines were fused with the GM-1500-derived, B-lymphoblastoid cell line, KR-4, which is ouabain resistant and HAT sensitive. 10^7KR-4, cells were fused with 10^7 LL cells and hybrid cells were selected in HAT medium containing 10 uM ouabain. Supernatants from surviving hybrids were tested for anti-*M. leprae* antibody production using the enzyme-linked immunosorbent assay (ELISA). Positive hybrids were subcloned and tested for anti-*M. leprae* antibody production. In the ELISA screening tests, we used three different *M. leprae* antigen preparations, namely, *M. leprae* soluble sonicates (MLS), *M. leprae* SDS extracts of the pellets obtained from centrifugation of sonicates (MSE), and a purified glycolipid preparation from *M. leprae* (M-GLIP), kindly provided by Dr. Patrick Brennan. Out of 1651 hybrid supernatants tested against MLS and MSE, 92 were positive for anti-MLS antibody production and 243 were positive for anti-MSE antibody production. Upon subcloning the hybrids, we found that out of 792 subclones, 73 were positive for MLS and 88 for MSE. These have been recloned at very low cell densities (0.5 cell/well). We also screened 176 hybrids for anti-M-GLIP antibody production and out of these, 9 were positive. These were subcloned and out of 220 subclones, 21 were positive. In preliminary experiments to test the amount of cross-reactivity in these hybridomas, we screened supernatants from the positive subclones against all three antigen preparations from two other mycobacteria, *M. tuberclosis* and *M. smegmatis*. In these experiments, a few of the clones showed specificity for each separate mycobacterium while some others cross reacted between two or all mycobacteria. The final clones will be selected for *M. leprae* specificity, using a much larger panel of mycobateria.

Human monoclonal antibodies specific to *M. leprae* will have a diagnostic potential in clinical and sub-clinical leprosy infections. Furthermore, the use of human monoclonal antibodies as therapeutic agents in certain clinical cases is a matter for consideration.

II/40(A) EVALUATION OF THE SIGNIFICANCE OF ANTIBODIES TO PHENOLIC GLYCOLIPID OF *M. LEPRAE* IN LEPROSY PATIENTS AND THEIR CONTACTS

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Dept. of Biochemistry, University of Peradeniya, Sri Lanka and Immunology Research Laboratory, Seattle Public Health Hospital, Washington, USA

An immunoassay that measures antibody predominantly to the unique trisaccharide of the phenolic glycolipid PG of *M. leprae* might prove useful for the detection of subclinical infection and for the early diagnosis of leprosy. To test this possibility, the ELISA employing deacylated PG, as described by Young and Buchanan, was used to evaluate 245 patients and 1096 patient household contacts from Sri Lanka.

The 245 patients were characterised according to the Ridley-Jopling criteria and consisted of 85 TT, 61 BT, 27BB, 27 BL and 45 LL patients. The absorbance level and percent positivity of antibody to PG showed a direct relationship to type of disease (TT –.10, 36%+ve, BT–.33,62% BB –.48, 77%, BL–.72, 88% and LL–.67, 87%+ve) and was found to decline with chemotherapy (84% positive in untreated patients, compared to 68% in treated patients).

The overall seropositivity for household contacts was 34% (378/1096). Three or more serum samples collected over a period of 2½ years were available from 127 contacts. Of these 72 (57%) remained consistently negative, 28 (22%) had one positive sample and 27 (21%) showed consistent seropositivity. Two serial blood samples, collected at approximately 6 monthly intervals over a period of 1-2 years, were available from 411 contacts. Of these, 200 (49%) remained negative throughout, 124 (30) had one sample positive and for 87(21%) both sera were antibody positive.

During the follow-up period, 4 contacts developed clinically evident leprosy infection. Two were diagnosed as TT (A_{492}0. 12-0.19, 0.38-0.43), one as BT (A_{492}0.11-0.83) and the fourth as LL (A_{492} 0.91-1.1).

II/41(A) IMMUNE RESPONSES OF LEPROSY PATIENTS TO SELECTED GLYCOLIPID ANTIGENS OF *M. LEPRAE* AND PERIPHERAL NERVE

E.T. UMLAND, C. TEUSCHER, F.T. KOSTER, K.S.K. TUNG, P.J. Brennan, V. Suriyanond, P.Vithayasai, D.Scollard, K.E. Nelson,
University of New Mexico, USA.

Leprosy patients, particularly those with lepromatous leprosy (LL and BL), demonstrated antibodies to a specific glycolipid of *M. leprae* (phenolic glycolipid I, PGL-I). PGL-I also stimulated in vitro proliferation of peripheral blood mononoclear cells and/or T cells of 7 of 14 US leprosy patients. Only two of the seven responders also produced antibody to PGL-I. Of 125 untreated, non-reacting Thai patients of all clinical-pathologic classifications, 79 (63%) had antibody to PGL-I detected by radioimmunoassay using *S. aureus* Protein A. 100% of LL patients had antibody, while 38% of TT patients had antibody with a lower median binding ratio. Patients having reversal reactions tended to relatively higher prevalence and/or level of antibody of PGL-I than most non-reacting patients of similar classification. Control of the humoral and/or cellular immune response to PGL-I antigen may be involved in the pathogenesis of reversal reactions. Antibody reactive with nerve glycolipid (galactocerebroside, GC) was found in 60% of untreated lepromatous patients, but only 8% of borderline and tuberculoid patients. Antibody levels to GC did not appear to change in relationship to leprosy reactions. An immune response to GC may play a role in the demyelination damage to sensory nerves in untreated lepromatous leprosy, similar to demyelination in experimental allergic neuritis mediated by antibody to GC.

II/42(A) SPECIFIC *M. LEPRAE* ANTIGENS RECOGNIZED BY LEPROSY PATIENTS

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Royal Tropical Institute, Amsterdam, Netherlands.

The isolation of *M. leprae* specific antigens relevant for leprosy might provide the basis of a clinically useful serodiagnostic test. For this purpose, we separate antigen-mixtures of sonicated mycobacteria on SDS-polyacrylamide gels. The gels are then sliced into thin longitudinal sections. After fixation of the proteins and removal of fixative and SDS, each section can be incubated with a different antiserum (patient-serum). The indirect immunoperoxidase method then permits easy visualization of antigen-antibody complexes (SGIP-assay).

Using this SGIP-assay with patient sera absorbed with an insoluble BCG-pellet fraction (after sonication), we were able to demonstrate *M. leprae* specific antigens.

Seven out of nine lepromatous leprosy patient sera reacted with a 38 kD, a 33 kD and a 28 kD glycoprotein present in *M. leprae* sonicate and not pre-

sent in other mycobacterial sonicates (*M. tuberculosis* H37Rv, *M. bovis* BCG and *M. vaccae*) or in normal armadillo liver homogenate. The same reaction pattern was found with one of four borderline/lepromatous patient sera. The other sera, also including 4 borderline tuberculoid leprosy, 4 tuberculoid leprosy and sera from 10 tuberculosis patients and 5 healthy individuals were all negative. In addition, all leprosy patient sera reacted with *M.leprae* protein at the top of the gel (MW > 200.000).

The antigens were not recognized by a rabbit-anti-armadillo antiserum.

The *M. leprae* specific antigens will be isolated with monoclonal antibodies.

II/43(A) APPLICATION OF ANTI-*M. LEPRAE* MONOCLONAL ANTIBODY BASED RADIOIMMUNOASSAY IN THE SEROLOGY OF LEPROSY

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A serological test for leprosy has been devised on the basis of inhibition of binding of ^{125}I labelled *M. leprae* specific monoclonal antibody ML04 by serum. Serial dilutions of test serum and fixed activity of ^{125}I ML04 are incubated on solid phase (polvinyl microtitre plates) bound *M.leprae* sonicate antigens. Bound radioactivities are counted and results are expressed in terms of ID_{50}(i.e. the serum dilution causing 50% inhibition of ^{125}I ML04 binding). A serum was considered to be antibody positive, if its ID_{50} was 1 : 5 or more.

Material comprised of 106 leprosy sera from 29 cases of TT/BT/BT (R), 6 cases of BB/BB(R) and 71 cases of BL/LL/L (R) leprosy. In addition, 12 sera from cases of pulmonary tuberculosis and 14 sera from healthy laboratory staff served as controls. 52% of TT/BT/BT (R) cases, 100% of BB/BB(R) cases and 97% of BL/LL/L(R) cases were positive for specific antibody, whereas none of the control sera was positive. Antibody titre was highest in the BL/LL group (ID_{50}> 1 : 1000 in most cases) followed by BB and TT/BT cases. Reactional cases of all types of leprosy showed higher titre of antibody, as compared to non-reactional cases of the corresponding type. Follow-up study in certain cases showed a decrease in antibody titre, after chemotherapy. Significance of these findings will be discussed.

II/44(A) SECRETORY IMMUNE RESPONSES IN LEPROSY

Abe, M., Yoshino, Y., Minagawa, F., Miyaji, I., Sampoonachol, P., Ozawa, T., Sakamoto, Y. and Saito, T.
National Institute of Leprosy Research- Tokyo, Japan.

The levels of immunoglobulins and their antibody activities against *M. leprae* in the serum and the saliva collected from leprosy patients were investigated by using the techniques of immunodiffusion and flourescent leprosy antibody absorption (FLA-ABS) test. The average levels of serum IgG, IgM and IgA were not significantly different among 50 patients with lepromatous leprosy, 24 with borderline, and 36 with tuberculoid. Salivary IgG and IgA levels and their ratios to those in the serum were also not different significantly, according to the classification of leprosy. The results of FLA-ABS test indicated that *M. leprae*-specific antibodies in the serum were mainly found in IgM but less frequently in IgA. On the contrary, salivary IgA antibodies against *M. leprae* were found in a significant number of specimens, whereas IgG and IgM antibodies were scarcely found. However, the percentage of positive FLA-ABS test caused by salivary IgA antibodies was higher in the patients with tuberculoid or borderline leprosy than in those with lepromatous. These findings coincide with the result of our previous study on the nasal secretions collected from leprosy patients and suggest an important role of secretory antibodies in the local defense mechanism of mucous membrane against *M. leprae*.

II/45(A) FIELD SURVEY OF LEPROSY CONTACT CHILDREN IN KOREA - CLINICAL FOLLOW-UP OBSERVATION, TESTING SKIN REACTION TO DHARMENDRA ANTIGEN AND FLA-ABS

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National Leprosarium, Japan

Children of leprosy contacts had been examined repeatedly in the Korean National Leprosarium, as a mass survey before 1973. Since 1973 however, findings of skin, sensation and peripheral nerves have been individually recorded every time at annual examination, even though the findings were subclinical. The total number of examined children from 1973 to 1983 is 1420, a quarter of whom are under long term follow-up observation. FLA-ABS test which uncovers subclinical infection of *M. leprae* was performed on 150 cases, out of which 70 were positive, including very strongly positive cases.The skin test by Dharmendra antigen was also used. Long term clinical follow-up observations, FLA-ABS tests and skin reaction to Dharmendra antigen were analysed from the view point of subclinical infection of *M. leprae*, in relation to the leprosy control programme.

II/46(A) ANTIBODY TO SOLUBLE ANTIGEN OF *M. LEPRAE* AND PHENOLIC GLYCOLIPID I IN PATIENTS WITH LEPROSY AND CONTACTS

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Two ELISA systems, employing a soluble antigenic extract of *Mycobacterium leprae*, and phenolic glycolipid I generously supplied by Dr. P. Brennan, have been used to study circulating anti-mycobacterial antibodies in patients with leprosy and in skin-test positive and negative contacts. Sera studied include 299 from skin-test negative healthy contacts, 102 from skin-test positive contacts, sera from active and inactive LL, and serial samples taken before and after immunotherapy with a *M. leprae*-BCG mixture. Both SA-ELISA and GL-ELISA revealed high levels of antibody in small, partially overlapping percentages of skin-test negative contacts (2.3 and 4.7%, respectively); the subsequent response to vaccination with a *M. leprae*-BCG mixture in these groups will be discussed. Studies of individual classes of antibody in the SA-ELISA system revealed high levels of IgG and IgM antibodies in patients with active LL; inactive disease was associated with a more marked decline in IgM antibody levels than in IgG. Seventy percent of LL patients had titers of IgM greater than 1:2000 in GL-ELISA, in spite of variable periods of chemotherapy; IgG antibody titers were almost invariably lower (37%> 1:1000). CMI response to immunotherapy was not correlated to initial levels of anti-glycolipid anitbody of either class nor accompanied by a dramatic reduction in titer in a period of two years.

II/47(A) DIAGNOSTIC VALUE OF ELISA IN LEPROSY

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Diagnostic test-systems based on using indirect peroxidase-linked immuno assay to determine anti-*M. leprae* antibodies in blood sera from leprosy patients and armadillos with experimental leprosy infection are developed. Sonicated *M. leprae* passed on rats and isolated from infected tissues according to Draper were used as an antigen. Sera from newborns, blood donors and the patients with tuberculosis served as controls. The reaction was read by optical density of substrate using enzyme-meter MR 590 (Dynatech) at 490 nm. High sensitivity and specificity of the test developed for detection of antibodies against mycobacteria in sera from leprosy patients were revealed. The dependence of ELISA on activity of leprosy process is indicated by the ratio of the titres of IgG : IgM antibodies to a specific antigen. The test is suggested for trials in seroepidemiological studies for the early detection of subclinical leprosy infections. The possibility of predicting the results of experimental infection in armadillos is reviewed, depending on the increase in intensity of antibody reactions according to the dynamics of the development of the disease. Serological data were subsequently confirmed by the appearance of subcutaneous lepromas and AFB in skin smears in armadillos.

II/48(A) EPIDEMIOLOGICAL STUDIES WITH *M. LEPRAE* SOLUBLE ANTIGEN SKIN TESTS

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The availability of *M. leprae* soluble antigen preparations for skin testing holds considerable promise for studies of the epidemiology of *M.leprae* infection. This paper will describe extensive experience with two such antigens, prepared by different methods, and applied in a leprosy-endemic population in Northern Malawi. Indurations are generally not sharply defined as with tuberculin (RT 23), and frequency distributions of indurations may differ between populations; but a clear bimodality of indurations and rising prevalence rate of "positivity" with age suggests these skin tests are specific for some mycobacterial experience. Tests in biopsy-confirmed cases, in household contacts, and in persons with no known leprosy contact provide measures of sensitivity and specificity of these skin tests for infection with *M. leprae*. Specificity appears to be higher at 72 than at 48 hours. Interpretation of reactions is complicated by differences in sensitivity and specificity between batches of antigen and by cross-reactions with BCG and with several environmental bacteria. Detailed analysis of survey results with such tests allow inferences concerning the distribution of *M.leprae* infection in endemic populations, but there is still room for improvement in preparation methods, standardisation, sensitivity and specificity of these tests.

II/49(A) *IN VITRO* LYMPHOCYTE STIMULATION IN CONTACTS OF LEPROSY AND IN NON-EXPOSED CONTROLS WITH AN ANTIGEN FRACTION PREPARED FROM *M. LEPRAE* AND TUBERCULIN PPD

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An antigen fraction prepared from *M. leprae*, called MLW1, which is shown to induce both humoral and cellular immune responses in leprosy pa-

tients, was used as stimulator in the lymphocyte stimulation test in comparison with tuberculin PPD. The test was performed in three groups of contacts of leprosy patients with various degree of exposure: 1) close contacts 2) occupational contacts and 3) non-close contacts, and in addition a group of BCG-vaccinated and non-exposed controls. At 0.1 ug/ml. the MLW1 preparation induced moderate to strong responses in all three groups of contacts, but only weak or no response in the control group. Although the PPD responses showed a wide variation in all groups, a significant depression was observed in the group of close contacts. Using the △cpm as estimator of the MLW1 response, both the degree of cross reactivity between MLW1 and PPD and the magnitude of the response to MLW1 are taken into account.The median △cpm response was seven to nine times higher in the group of close contacts than in the two other contact groups. The group of non-exposed controls showed significantly lower △cpm responses than the others, indicating that the intensity of the specific response increases with the closeness of contact with patients.

II/50(A) STUDIES OF VACCINES AGAINST *M. LEPRAE*

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In continuing studies of leprosy vaccines in mice, we have used normal mice and *M. leprae*-tolerant mice (induced by intravenous injection of a 10^7 *M. leprae)*. Normal mice respond to intradermal injection of 10^7 heat-killed *M. leprae* by developing delayed-type sensitization (as measured by footpad challenge with 10^7 *M. leprae*) and by developing immunity to infection with living challenge. The tolerant mice do not respond significantly to intradermal immunization with *M. leprae*. They respond to intradermal BCG (living) by developing a partial sensitization to M. leprae without significant protection against infection. Addition of heat-killed *M. leprae* to the BCG vaccine has no effect.

Two other cultivable mycobacteria (ICRC strain C44 and *Mycobacterium w.*, both of which have been classified as members of the *M. avium-intracellulare* complex) have been proposed as leprosy vaccines, and we have begun studies with these. In normal mice, these mycobacteria can produce sensitization to *M. leprae*, depending on the way they are killed. Results bearing on protection against infection wil be available in the fall of 1984. Results of a comparison of these cultures and BCG in tolerant mice should be available by the time of the Congress.

II/51(A) A PRELIMINARY EVALUATION IN THE LEBANON OF TWO ADDITIVES TO BCG VACCINE

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A comparative study of 3 vaccines against mycobacterial infections has been commenced in two districts of North Lebanon. In one of these districts there are no known cases of leprosy and very few cases of tuberculosis. In the other, there is a low prevalence of leprosy and a moderate prevalence of tuberculosis. The people vaccinated were approximately 1500 village children between the ages of 7 and 18 years who were tuberculin negative. The vaccines used were BCG (Glaxo) alone, BCG (Glaxo) + killed *Mycobacerium vaccae* and BCG (Glaxo) + killed *M. leprae*.

Prior to vaccination, all children were tested with tuberculin, leprosin A, vaccin and scrofulin, and subsequently at yearly intervals cohorts of vaccinees were retested with the same reagents. 1.7% and 2.7% of children in the 2 districts respectively were tuberculin positive and excluded from vaccination.

Among the tuberculin negative children who were vaccinated, 1% and 6% were Leprosin A positive in the 2 districts ($P< 0.001$).

All these vaccines produced an acceptable level of tuberculin conversion. The vaccine scar sizes averaged between 3.4 and 4.9 mm and were not significantly different for the 3 vaccines. The detailed results obtained in the 3 annual follow-ups completed so far will be presented.

II/52(A) ICRC 'ANTI-LEPROSY' VACCINE

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ICRC bacillus, a mycobacterium that has been repeatedly cultivated from human lepromata, shows cross reactivity with *M. leprae* specially with reference to CMI antigens. A vaccine containing ICRC bacilli, killed by gamma irradiation, has been administered, during the last 3 years, to a number of LL and BB/BL patients. By 10 months of vaccination, lepromin (Mitsuda) conversion was observed in 57.7% of LL patients. In some cases there were associated changes in tissue morphology consistent with upgrading of lesions. Lepromin conversion was not only persistent but with time, an increasing number of vaccinated patients exhibited lepromin positivity. Very high rates of conversion (about 90%) were observed in the vaccinated BB/BL patients and Mitsuda-negative healthy subjects who represent a high-risk group. The minimum effective dose of the vaccine appears to be close to 1.6×10^7 bacilli/person, since a reduction of the dose to this level resulted in conversion in only 45% of the healthy lepromin-negative individuals; the intensity of the reaction was also low. The vaccine is safe and has been found to be non-toxic in different species of animals. No untoward effects have been observed during the 3-year observation period. Different batches of the vaccine have consistently induced lepromin conversion, indicating antigenic stability of the organism. Being given as a single dose, the vaccine has high acceptability. The results of the vaccine are comparable to those obtained by Convit and co-workers using a vaccine containing a mixture of *M. leprae* (heat killed) plus BCG. The ICRC vaccine thus meets the requirements of a 'candidate' vaccine which could be used both in immunoprophylaxis as well as immunotherapy of leprosy.

II/53(A) ALLIED MYCOBACTERIUM INDUCED LEPREMIN CONVERSION IN SUBSIDED LEPROMATOUS CASES AND ITS RELATION WITH COMPETENCY OF CLEARING *M. LEPRAE*

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The specific non-responsiveness to M. leprae cases appears to be life-long and such patients rarely become Mitsuda-positive, even after prolonged period of bacteriological negativity and life-long therapy. These cases are also prone to frequent relapses. Attempts have been made to build up specific immunity (lepromin conversion) in lepromatous cases against *M. leprae* by mycobacteria antigenially closely related to *M. leprae* or by passive transfer of immunity. But the authenticity of lepromin conversion and *in vitro* and other tests as indicators of C.M.I. against *M. leprae* is now under question; and the test for competency of clearing *M. leprae* (C.C.B. test) is preferred as better direct evidence of C.M.I. against this organism. Thirty-two bacteriologically negative and persistently lepromin negative lepromatous patients were given injection of an allied mycobacterium of A.I.I.M.S. Twenty of them showed clinical as well as histopathological lepromin conversion with improvement in LMIT and LTT. The converted cases were given 640×10^6 dead human *M. leprae* in 0.1 ml dose intradermally. Biopsies from injected sites were examined after 6 weeks for competency of clearing bacilli (CCB test). Eight cases showed bacterial clearance.

II/54(A) VACCINATION OF CONTACTS, NORMALS AND LEPROSY PATIENTS

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In recent years, there has been a growing interest in developing vaccine for leprosy using *M.leprae, M.vaccae, Mycobacterium W* and ICRC bacilli with or without additive such as BCG. The main purpose of any vaccine is to modulate protective immune response in that segment of the population which might develop the disease if exposed and to activate the macrophages in lepromatous leprosy to enable them effectively to bio-degrade *M. leprae* so as to prevent the bacilli from acquiring drug resistance. Since 1980, considerable evidence has been accumulated in our laboratories concerning this,and 655, Leprosin-A negative (including Mitsuda negative contacts,normals and leprosy patients) were vaccinated once or repeatedly with a mixture 1×10^7 killed *M. leprae* and BCG 10^8. Clinical, histopathological and immuno-histochemical criteria were applied to assess the vaccine efficacy in the individuals. The results and the significance of these findings will be discussed.

II/55(A) HLA-LINKED CONTROL OF LEPROSY TYPE

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The HLA-linked control of predisposition to polar tuberculoid (TT) leprosy has been clearly established. For several reasons, the dogma has been, that this HLA-linked control is confined to TT leprosy. One of the main reasons is, however, that no or only few data have been collected for the other leprosy types. We will present data from two large family studies performed in Venezuela and China, which convincingly show that predisposition to lepromatous leprosy also is controlled by HLA-linked genes. Moreover, these studies clearly show that susceptibility to leprosy *per se* is not, and only the predisposition to certain leprosy types is controlled by HLA.

Finally, we will present data of *in vitro* studies in search for the mechanism of this HLA-linked control of leprosy type.

II/56(A) A PRELIMINARY STUDY OF ASSOCIATION BETWEEN HLA PHENOTYPE OR HAPLOTYPE AND LEPROSY PATIENTS OF HAN NATIONALITY IN CHINA

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HLA-A, -B typing was performed in 61 cases of lepromatous and 48 cases of tuberculoid leprosy patients of Han nationality in Jiangsu and they were compared with 116 healthy controls of the same nationality matched for locality, age and sex. In the above individuals, 37 lepromatous and 32 tuberculoid patients and 65 healthy controls were typed for HLA-DR. It was observed that the frequency of HLA-A1, AW 30+31 and B17 was significantly decreased and of DR2 was significantly increased in lepromatous leprosy, even after correction for the number of antigens tested. In tuberculoid leprosy, significantly decreased frequency of HLA-Bw54, Bw60 was observed but showed no significance when corrected. Slightly increased frequency of DR2 was found, but it was not statistically significant.

In a total of 378 haplotypes, the relative delta parameters of the tri-locus linkage disequilibrium between HLA-A,B, or -A, DR or -B, DR and the supposed leprosy susceptibility gene were calculated with the Porta-McHugh's formulas by computer, according to AR model.Eight haplotypes relatively susceptible to leprosy were found,namely All-DR2, A9-B13 and All-B17 to lepromatous, A9-DR2, All-DR5, Bw60-DR3, All-B15 and A28-Bw54 to tuberculoid.

The results obtained indicated that the susceptibility gene of leprosy is very likely linked with HLA region and indirectly demonstrated that the gene might be on the DR side.The fact that lepromatous and tuberculoid patients were associated with different HLA haplotypes, suggested that two types of leprosy appeared to be of heterogeneous nature.

II/57(A) *M. LEPRAE* INDUCED ALTERATIONS IN THE MACROPHAGE MEMBRANE

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The structural, functional and regulatory mechanisms of human mØ membranes were studied in polar leprosy patients and normals. The Fc receptor represented membrane integrity, the function being studied by antigen mediated mØ-lymphocyte interaction. Bacterial adherence to mØs was examined at 4°C. Correlation between structure and function was attempted by monitoring of membrane HLA-Dr antigen.

Specific changes were seen on exposure to *M. leprae* or supernatants of LL mØ cultures of freeze-thawed extracts of infected LL mØs. Amongst these were a reduced ability to rosette with sensitized SRBC and a negative mØ-lymphocyte interaction. The former was obtained with viable *M. leprae* only and not with any other mycobacteria,host cell viability being a prerequisite. *M. leprae* adherence to mØs was lowest in active lepromatous patients. HLA-Dr antigens and bacterial adherence resembled the Fc marker in that the *M. leprae* induced reduction in their expression was reversed by trypsin and colchicine, thus implicating microtubules as the cause for membrane alterations. The two sub-cellular factors were found to be distinct entities: the washate action being indomethacin sensitive, the action of lysate being indomethacin resistant.

These studies suggest the mØ as a centrally defective cell in leprosy. Moreover, monitoring of the membrane Fc receptor lends itself to screening of immunomodulating agents and anti-leprosy drugs.

II/58(A) IMMUNOGENETICS OF SUSCEPTIBILITY TO LEPROSY: INDICATION OF GENE ACTION BY MONITORING OF *IN VITRO* ALTERATIONS IN THE MACROPHAGE PLASMA MEMBRANE

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Three approaches were formulated to examine extent of gene involvement in mØ response to *M. leprae* (a) Study of mØ *in vitro* parameters in familiar contacts of leprosy patients, viz., expression of membrane Fc receptor and HLA-Dr antigens and antigen mediated mØ-lymphocyte interaction. (b) Somatic cell hybridization between lepromatous and normal mØs and resultant *in vitro* mØ functions in hybrids. (c) Evidence for pre-existing defect in lepromatous mØs before establishment of intracellular infection.

These studies delineated two independent gene systems functional within a "susceptible" mØ (reduced expression of Fc and/or negative interaction). When compared to lepromin, the sensitivity of the *in vitro* tests was substantially greater in identification of individuals "at risk" before disease symptoms become manifest and is an instance where the mechanism of gene action is identified.

"Susceptibility" genes seemed to be inherited in a heterozygous dominant form, the "susceptibility : resistance" ratio being 3:1. Dominance of lepromatous properties was also noted in somatic hybrids for the Fc receptor alterations. This indicated an irreversibility in gene expression after exposure to *M. leprae*.

Finally, manipulations during *M. leprae* phagocytosis viz., temperature shifts, treatment with Cytochalasin B and dual particle systems presented additional evidence for an intrinsic defect in lepromatous macrophages.

II/59(A) MACROPHAGE FUNCTION IN MYCOBACTERIAL INFECTIONS

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It has been established that macrophages play an important role in cell-mediated immunity to a number of intracellular infections (e.g. Listeria, Brucella, Mycobacteria). Activation of macrophages is known to be mediated by lymphokines and is accompanied by enhanced bactericidal capacity.

We have studied various parameters of peritoneal macrophage activity during experimental infection in mice with *M. marinum, M. bovis,* and *M. leprae* and have shown that macrophage activity varies with the stage of infection. By comparing infection in nude and normal mice, the role of the T-lymphocyte has been implicated in this process. The soluble products of T-lymphocytes from these animals were also examined for their ability to stimulate macrophage activity.

Our results show that in normal mice, macrophage activity parallels infection. However, in the nude mouse although a higher initial level of activity is observed, this is subsequently depressed whilst infection ultimately causes death.

II/60(A) ROLE OF LANGERHANS CELL IN LEPROSY

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Langerhans cell (LC) is one of the dendritic cells of epidermis. These cells bear FC and C_3b receptors and express Ia antigen on their surface. Role of LC in the induction of contact hypersensitivity to various chemicals is well established. However, their status in infectious disease remain largely unexplored. In the present study LC population was counted in 12 normal, 13 TT, 24 BT, 10 BL and 50LL patients. LC count was near to normal in TT (856.15± 154.75) and significantly decreased in LL (465.30± 234).

It seems that the mode of entry of organisms in two polar forms of leprosy is different. In TT organism enters through epidermis where it is processed in LC and results in activation of cell mediated immunity. In LL, organism may find entry directly to blood through oral, respiratory or directly through nerve and bypasses LC. Once the organism reaches central lymphon, it activates humoral immune response and suppressor T-cells. Humoral antibodies form immune complexes with circulating antigens and destory LC. Low count of LC in LL also explains poor induction of contact sensitivity to chemical and delayed graft rejection. Better understanding of LC will help in reinforcing specific cellular immunity against lepra bacilli.

II/61(A) *IN VIVO* EXPERIMENTAL INDUCTION OF THE LYSIS CAPACITY TO THE VIRCHOWIAN MACROPHAGES

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Three negative virchowian treated cases were intradermally inoculated with:

1 – PPD (5U)
2 – Bacillary lepromin (640×10^6 *M. leprae* per ml)
3 – Liophilised BCG (0.1mg/ml) + Bacillary leprmin 640×10^6 M leprae

Answers:

No. 1: all the three patients presented a 72 hours positive reaction.

No. 2: all the three patients presented a small nodule which showed a macrophage reaction with many bacilli in the cytoplasma of the macrophages.

No. 3: all the three patients presented larger nodules which showed a tuberculoid picture without bacilli.

Conclusion: 1) The macrophages of a virchowian patient is unable to induce lysis of *M. leprae;* 2) The macrophages of a virchowian patient is able to acquire the lysis capacity toward *M. leprae* when activated by BCG specific lymphokines.

II/62(A) CHARACTERIZATION OF T-CELL CLONES TO *M. LEPRAE*

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Recent technological achievements in the use of cloned T-cell lines which maintain antigen specificity and biological functions for long periods of *in*

vitro cultivation are providing a valuable tool for dissection of cell-mediated immune responses. By cloning homogeneous subsets of T-cell types, it is possible to focus attention on investigating the nature and specificity of antigen recognition, and on regulatory interactions between cells. We are applying this approach to dissection of the immune response to *M. leprae*.

Inguinal lymph node cells from BALB/c mice immunized intradermally with 10^8 ^{60}Co-irradiated *M. leprae* were cloned by limiting dilution. Lymphocyte growth was found to be critically dependent on this presence of *M. leprae*, accessory cells and Interleukin-2. *In vitro* proliferation of cloned cell lines was characterized by a marked preferential response to *M. leprae*, although cross-reactivity with other mycobacteria was observed. Cellular fractions of *M. leprae* were tested for antigenicitry and different clones were found to respond to different fractions. Phenotypic analysis showed the clones to be predominantly Lyt 1^+ $^-2$, with helper activity determined by IL-2 production on exposure to antigens. Functional features of the clones have been investigated with respect to lymphokine production as well as their role *in vivo* delayed-type hypersensitivity reactions.

Overall the results of the study indicate that the T-cell response to *M. leprae* is polyclonal, with *M. leprae*-specific T-cells contributing multifunctional roles.

II/63(A) ABERRANT IMMUNOREGULATION OF T LYMPHOCYTES IN LEPROSY PATIENTS

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A reverse hemolytic plaque-forming cell (PFC) assay was used to study immunoregulatory effectrs of T lymphocytes on polyclonal B lymphocyte function in leprosy patients prior to treatment. A gradually widening range of abnormally high and low individual patient PFC responses was seen from borderline turberculoid (BT) to lepromatous (LL) in 12 BT, 5 borderline (BB), 6 borderline lepromatous (BL), and 20 LL patients. However, PFC responses of 7 tuberculoid (TT) patients were all within the range of 22 healthy individuals. Co-culture of normal T-lymphocytes with BL-LL patients' lymphocytes increased the PFC responses of the "Low Responder" patients and decreased PFC responses of some of the "High Responders". On the contrary, when T-lymphocytes from LL or BL patients were mixed with normal lymphocytes, the PFC response of the normal cells was not altered. This demonstrates aberrant suppressor and helper T-Cell function in lepromatous leprosy. However, T-Cells from TT patients were able to increase PFC responses of normal lymphocytes with initially low-normal responses, suggesting that T-cell function in TT patients is intact. Together, these observations indicate increasingly aberrant immunoregulation from BT to LL leprosy, the cause of which is thus far undetermined.

II/64(A) EVIDENCE FOR THE PRESENCE OF *M. LEPRAE* ANTIGEN REACTIVE T CELLS IN SOME LEPROMATOUS LEPROSY PATIENTS

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Macrophages (Mo) derived from lepromatous patients were unable to support *M. leprae* antigen-induced lymphoproliferation of HLA-D identical responder individuals. However, those Mo derived from tuberculoid patients could support lymphoproliferation of other tuberculoid patients. Such Mo improved the responses of lymphocytes (Ly) from HLA-D identical lepromatous patients. Studies conducted with Ly and Mo sharing partial identity indicated that Mo from different tuberculoid patients supported lymphoproliferation of lepromatous Ly to varying extent. The co-cultures indicated that nylon wool column purified T cells (NWC) gave better reponses as compared to 2-hr plastic non-adherent cells (NAC). As allogenic effects could not be ruled out in non-identical co-cultures, studies were done using autologous Mo-Ly combinations. All tuberculoid individuals tested gave improved responses. Pulsing of Mo with antigen prior to combining with Ly gave better responses similar combinations in lepromatous patients. Gave improved responses in 9 of the 16 patients. Preliminary studies with IL-2 (a T cell lymphokine) indicated that addition of IL-2 along with antigen improved lymphoproliferative responses in some lepromatous patients.

From these studies, it would appear that some lepromatous patients have T cells which can be induced to proliferate in response to *M. leprae* antigens *in vitro*.

II/65(A) SPECIFIC RESPONSIVENESS OF IMMUNE LYMPHOCYTES TO *M. LEPRAE* PHENOLIC GLYCOLIPID (PGL-I)

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Understanding the cellular immunologic phenomena of leprosy has been hampered by the lack of specific antigens. The discovery of a phenolic glycolipid (PGL-I) unique to *M. leprae* may fill this need, if it stimulates specific T-cell proliferation. We studied peripheral blood lymphocytes (PBL) from 11 Mexican and Asian patients followed inthe US, including 5 with LL or BL, 6 with BT leprosy, and 10 healthy U.S. controls. In a standard lymphocyte proliferation assay, PGL-I was dried on to the bottom of microtiter wells, and proliferation was measured by an 8-hour pulse of tritiated thymidine on the fifth day of culture. PBL from 4 patients responded to PGL-I with stimulation indices (SI) ranging from 2.2 to 4.0. In contrast, no control lymphocytes responded (SI less than 1.0). Two responders studied against six months later retained responsiveness to PBL-I. Purified T cells from two responders, and two additional patients whose unfractionated PBL did not respond, responded to PGL-I. The concentration of PGL-I producing maximal stimulation was 0.1 mcg/ml (20 ng/well). These preliminary results suggest that PGL-I stimulates modest but significant lymphocyte proliferation, that the responding cells are T cells, and that dose-response curves indicate the requirement for very low concentrations of antigen. PGL-I may be a tool to dissect specific T cell directed-phenomena in clinical leprosy.

II/66(A) CHANGES IN THE T-CELL CONTENT OF DERMAL GRANULOMAS AND PERIPHERAL BLOOD DURING THE COURSE OF LEPROSY

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Imbalances in the distribution and activity of T-cell subpopulations are important in the pathogenesis of leprosy. It has also been suggested that these imbalances might be implicated in the onset of erythema nodosum leprosum. We have studied the content of peripheral blood (PB) in T-cells, and the content of dermal granulomas (DG) in T-cells and granulocytes, in 4 tuberculoid patients (Tub), 12 lepromatous patients (LL) without erythema nodosum leprosum (ENL) and 6 patients with ENL.

Monoclonal antibodies specific for all T-cells (OKT 3 and Leu 4), T-helper cells (OKT 4 and leu 3a), T-suppressor cells (OKT 8), and granulocytes (Leu M1) were used, and detected by an indirect immunofluorescence technique.

Tub. DG contain many lymphocytes, and are mainly composed of cells with the T-helper phenotype; the suppressor cells are rare, and can be found only around the granuloma. The H/S ratio is 1.65 ± 0.3 in DG and 1.42 ± 0.07 in PB.

LL patients exhibit different patterns of T-cell distribution according to their therapeutic status. In untreated patients, the DG contain few lymphocytes, mainly of the suppressor phenotype. The H/S ratio in these patients is 0.58 ± 0.08 in DG and 0.91 ± 0.15 in PB. In treated patients, we found an increase in the content of helper cells in the DG : the H/S ratio is 1.65 ± 0.21 in DG and 1.88 ± 0.24 in PB.

ENL lesions contain more lymphocytes than non-ENL DG. Suppressor cells are rare in ENL-DG and the H/S ratio is 2.72 ± 0.8 in DG, and 1.97 ± 0.16 in PB.

Granulocytes are numerous in ENL - DG and very rare in the other leprous DG.

Several conclusions can be drawn : (1) in Tub DG, suppressor cells are separated from the helper cells, which appear to be located close to epitheloid cells. (2) LL-granulomas are almost devoid of helper cells in untreated patients, and this pattern reverses when an efficient therapy has been instituted. (3) ENL lesions contain few suppressor cells.

The imbalance in T-cell subsets has already been demonstrated in the PB patients with leprosy; can also be demonstrated at the local level, where it appears to be more accentuated than in the PB.

II/67(A) THALIDOMIDE INDUCES IMBALANCES IN T-LYMPHOCYTE SUBPOPULATIONS IN CIRCULATING BLOOD OF HEALTHY MALES

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The effect of thalidomide on circulating T-cells, T-suppressor cells, T-helper and natural killer cells was assayed by immunofluorescence using the fluorescein conjugated monoclonal antibodies Leu-1, Leu-2a, Leu-3a, and Leu-7, respectively.

Ingestion of 200 mg of thalidomide/day for 4 days induced significant decrease in the T-helper to T-suppressor cell ratio (H/S ratio) in the blood of healthy males. The post-treatment H/S ratio returned to pre-treatment levels, two weeks after thalidomode was stopped. The decreased H/S ratio ($p < .005$, paired t) was due to a decrease in the percentage of absolute numbers of circulating T-helper cells and an increase in the percentage of absolute numbers of T-suppressor cells. The percentage and absolute numbers of natural killer and B cells was not altered.

Lepromatous leprosy patients experiencing erythema nodosum leprosum (ENL) have a significant increase in their H/S ratio. Thus, site of action of thalidomide in the management of ENL may be in correcting imbalances in T-cell subpopulations.

II/68(A) EFFECT OF DAPSONE ON CELL-MEDIATED IMMUNE STATUS IN BORDERLINE LEPROSY PATIENTS.

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Two groups of borderline leprosy patients receiving 1 mg/Kg body wgt/day and 4mg/Kg body wgt/day of dapsone were followed up at regular intervals viz., before treatment, 1 month and 2 months after treatment and on clearance of dapsone from the blood for cell-mediated immune responses to PHA-P, *M. leprae* (whole bacilli) and *M. leprae* (sonicated) using the Leukocyte Migration Inhibition Test (LMIT). Suppressor cells (T_s) were also enumerated. The clinical status was evaluated on each occasion an immunological test was done, and the blood dapsone level measured. Biopsies were performed at the start and at the end of the study. Preliminary results indicated a significant suppression ($p < 0.02$) in cell-mediated immune response to sonicated *M. leprae* after treatment in four out of five patients on high dosage group, whereas no change was observed in 10 patients receiving dapsone in lower dosage. Clinical improvement was more marked in patients receiving the high dosage. The possible immuno-suppressive effect of dapsone and its implication in preventing borderline reactions will be discussed.

II/69(A) A STUDY OF NATURAL KILLER CELL ACTIVITY FROM THE PERIPHERAL BLOOD OF LEPROSY PATIENTS

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The K562 tumour cell is a highly susceptible target for natural killer (NK) cell lysis by the lymphocytes of human peripheral blood. In an experiment with blood samples of leprosy patients,the natural killer cell mediated cytotoxicity (NKMC) against ^{51}Cr-K562, as a target cell was studied in 39 leprosy patients (12 with lepromatous, 11 with tuberculoid and 16 with borderline leprosy) and 11 normal controls.

In a comparison between the effector/target cells ratio as 50:1, the NKMC was seen to be more significantly reduced in lepromatous and borderline leprosy (mean ± S.D.; 24.9± 4.9, 28.5± 8.6) than those in normal controls (mean ± S.D.; 39.2± 13.3). In the cases of lepromatous leprosy, it was significantly reduced compared to tuberculoid leprosy (mean ± S.D.; 34.5± 7.6), but in tuberculoid leprosy, NKMC was not much lower than that in normal subjects.

A possible explanation for the low NK cell activity in lepromatous patients could be the blocking of such activity by immune complexes. It does, however, indicate a useful role for the NK system as an additional parameter for the evaluation of cell-mediated immunity (CMI) and as a prognostic monitoring tool in leprosy.

II/70(A) THE ROLE OF CYTOTOXIC CELLS IN *M. LEPRAE* INFECTIONS

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The current concept of dealing with intracellular pathogens such as *M. leprae* is that macrophages are activated by T cells and these activated cells then kill the intracellular organisms. Thus, before the immune system can effectively deal with these types of pathogens, they must enter either an activated macrophage, or one capable of adequate activation, before killing can occur. However, one of the features of *M. leprae* infections is that there is a wide variety of possible host cell types and a large proportion of the bacilli may be inside cells which are incapable of activation and killing. Two possible mechanisms of dealing with these "protected" bacilli are:

a) To induce a change in the metabolism of the host cell so as to kill the intracellular pathogen. Although there is some evidence that it may occur in haemoprotozoa infections, no investigations have been undertaken with mycobacteria and, in view of the long generation time and low metabolic activity of *M. leprae*, this possibility may be unlikely.

b) To release the bacilli by a cytotoxic mechanism thus allowing them to be taken up by cells capable of killing. Two cytotoxic cell types have been investigated; natural killer cells (NK cells) and antibody dependent cytotoxic cells (K cells). The level and activity of these cytotoxic cell types have been assessed in both treated and untreated leprosy patients and in patients with reversal reaction and erythema nodosum leprosum. While K cell activity does not alter dramatically, NK activity is high in reactional patients and correlates with changes in interferon production. The role of these cell types and the interaction of K cells with anti-mycobacterial antibodies will be discussed in terms of resistance and recovery from *M. leprae* infections.

II/71(A) MYCOBACTERIAL ANTIGEN-SPECIFIC SUPPRESSOR T CELLS. INDUCTION AND MODE OF ACTION

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Mycobacterial antigen-specific suppressor T-cells were induced *in vitro* from lymphocytes of BCG vaccinated healthy individuals. Optimal antigen and monocyte concentrations, as assessed by proliferation during induction phase, also resulted in maximum suppression. Suppressor cells could exhibit their activity only when added within 24 hours of the fresh cell activation. Suppressors did not absorb any significant amount of 1L2 and the cells preincubated with 1L2 containing supernatants were equally suppressive. 1L1, 1L2 or interferon antibodies exogenously added to the culture system did not abrogate suppression. 1L1 production from adherent cells in response to BCG was not affected, whereas, 1L2 production by T-cells was considerably reduced in presence of suppressor cells. In addition, the suppressor cells inhibited the expression of 1L2 receptors on fresh cells and the responsiveness of cells to standard 1L2 preparations.

Further analysis of the system using T cell clones will also be presented.

II/72(A) MECHANISM OF IMMUNOSUPPRESSION IN LEPROMATOUS LEPROSY - ROLE OF MACROPHAGE SUPPRESSOR FACTOR(S)

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The study focuses on the importance of the macrophage as a suppressor cell in lepromatous leprosy. The effect of lepromatous mØ-derived intracellular product on normal mononuclear cells was studied. This permitted the study of immunosuppressive mechnisms in the absence of *M. leprae*.

The observations indicate that factor(s) from lepromatous mØs negatively modulate *in vitro* cellular immune functions. MØs and T-lymphocytes were altered by the factor(s). These induced normal mØ membrane alterations reflected in a reduction of Fc, Con A and *M. leprae* adherence receptors. Drugs inducing reversal of the above changes were studied with positive results. Factor(s) also generated T-suppressors *in vitro* from normal mononuclear cells. The study of intracellular factor(s) from normal and tuberculoid mØs and the use of metabolic inhibitors in production of factor(s) suggest that it is an interaction product of *M. leprae* and lepromatous mØs. Data are presented on the specificity of action and production of the factor(s). Time kinetic studies are discussed delineating the mechanism of suppression and progressive action of the factor(s). The factor(s) appears to be a glycoprotein, non-dialysable and heat-stable. Production of antisera to the suppressor factor(s) has been possible and its neutralizing effect on the factor(s) is examined.

The results therefore strongly suggest a mechanism of mØ suppressor factor mediated immunodepression in lepromatous leprosy acting on both cell types, the mØ and the T-lymphocytes.

II/73(A) SUPPRESSOR CELLS IN LEPROSY REACTIONS

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Antigen-induced suppressor cell activity in leprosy patients with Type I and II reactions has been evaluated by means of *in vitro* co-stimulation with *M. leprae* - and PHA. In the lepromatous form (BL/LL) of leprosy, *M. leprae* - generated suppressor cells inhibited PHA responses to a lesser degree than at the tuberculoid end of the disease (TT/BT). However, during reactional states, two distinct patterns emerged. High resistant (TT/BT) patients in reaction show little or no less of suppressor activity, as compared to the uncomplicated TT/BT group. In contrast, BB/BL patients with Type I reaction and BL/LL patients with Type II reaction gave evidence of increased suppressor cell activity compared to the non-reactional patients with similar types of the disease. Many of these patients, when tested after subsidence of reaction, gave evidence of abrogation of suppressor activity.

II/74(A) CHARACTERISATION OF A FACTOR IN LEPROSY SERUM WHICH INHIBITS THE GROWTH OF MITOGEN-STIMULATED NORMAL HUMAN LYMPHOCYTES

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A factor capable of inhibiting the growth of mitogen-stimulated lymphocytes from normal donors was detected in the serum of 41 of 72 chronic leprosy patients. The inhibitory activity was detected with similar frequency in patients with tuberculoid or lepromatous leprosy. This factor interfered with volume growth in the first 24 hours after stimulation, with RNA synthesis during the first 3 days of culture and with DNA replication in 72-hour cultures. The inhibitory factor was shown to be macromolecular, since it eluted completely in the void fraction of a Sephadex G25 column: on Sephadex G200, the factor co-eluted with IgG. The inhibitory factor stable to heating at 56°C, but labile at 100°C, could be removed from serum by immobilised Staphylococcal protein A and copurified with IgG through standard purification procedures. None of the inhibitory activity appeared in the void volume of G200 columns, so it is not an immune complex. We conclude that the inhibitory factor is an antibody and suggest that it may be an autoantibody since the sera inhibit the growth of all donor lymphocytes we have tested.

II/75(A) MECHANISM OF T. CELL UNRESPONSIVENESS IN LEPROMATOUS LEPROSY IS RELATED TO FAILURE OF LYMPHOKINE PRODUCTION

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The basic immunologicgal defect of patients with lepromatous leprosy is the specific T-cell unresponsiveness, both in *in vivo* and *in vitro* to *Mycobacterium leprae*, while in general maintaining responsiveness to other antigens. Recent studies have shown that T cells with functional capabilities after initial triggering with antigen can be maintained in a state of proliferation *in vitro* when cultured in interleukin-2 (IL-2) rich T-cell conditioned medium. Based on this concept we did experiments which demonstrate that lepromatous T cells failed to produce IL-2 after exposure to *M. leprae*. However, they can proliferate in response to *M. leprae* when cultured in T-cell conditioned medium, suggesting that the unresponsiveness in lepromatous patients results from a deficiency of production of IL-2 or related factors and not due to the lack of *M. leprae* - reactive T-cells. The implications of these findings will be discussed.

II/76(A) IMPAIRMENT OF INTERLEUKIN 1 (IL-1) PRODUCTION BY PERIPHERAL BLOOD MONONUCLEAR CELLS FROM PATIENTS WITH LEPROMATOUS LEPROSY

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The production of IL-1 by peripheral blood mononuclear (PBM) cells from 21 leprosy patients was investigated to explore the hypothesis that the deficient cell-mediated immune (CMI) responsiveness of patients with lepromatous disease may result, in part, from impairment of IL-1 production. Patients ranged in age from 19-69 years and were either untreated or treated for less than one week prior to IL-1 assay. Normal controls were age and sex-matched. PBM cells were added to 35 mm cultures plates and, after 4hr incubation, non-adherent cells were removed. IL-1 inducing agents added to the adherent cells were LPS, 20μg/ml or Con A, 2 μg/ml or phorbol myristate acetate (PMA) 100 ng/ml. Supernatants were removed 24 hr later, dialysed and assayed in a comitogenic assay system utilizing C3H/HeJ thymocytes and a suboptimal concentration of PHA. IL-1 in the supernatant was quantitated by comparison with a standard preparation. PBM cells from all eight patients with TT/BT and BB leprosy produced IL-1 when stimulated. Moncytes from five of these patients produced IL-1 spontaneously. PBM cells from five of 13 (38.5%) BL/LL patients did not produce detectable IL-1 and none secreted IL-1 spontaneously. Cells from 20 normal donors secreted IL-1 (including controls shipped with cells from patients) and none released IL-1 spontaneously. The finding of markedly impaired IL-1 production by PBM cells from a substantial proportion of BL/LL patients suggests that amplification of T-cell mediated immune responses may be impaired in these patients.

II/77(A) DEFICIENT γ-IFN PRODUCTION IN PATIENTS WITH LEPROMATOUS LEPROSY: RESTORATION OF PRODUCTION IN LEPROMATOUS PATIENTS WITH INTERLEUKIN-2

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Antigen and mitogen induced release of γ-interferon (γ-IFN) was measured in peripheral blood mononuclear cells from leprosy patients. Lepromatous (BL and LL) patients were found to be deficient in their capacity to release γ-IFN in response to *M. leprae*, as well as Concanavalin A. Chemotherapy for as long as 10 years did not seem to revert this immunological unresponsiveness. Tuberculoid (BT and TT) patients generated increased amount of γ-IFN in response to both antigen and mitogen. Normal controls did not respond to *M. leprae* with release of γ-IFN, but had good responses to Concanavalin A. Addition of a purified human Interleukin-2 preparation to lepromatous patients' mono-nuclear cells restored their ability to release γ-IFN, in response to the specific antigen or mitogen.

Antigen-induced γ-IFN release in leprosy patients correlated positively with a ratio of "helper"/"suppressor" T cells in skin lesions, as measured by fluorescent staining with OKT4 and OKT8 monoclonal antibodies as previously reported.

M. leprae-induced γ-IFN release demonstrated to be a meaningful and sensitive functional assay for the diagnosis of the immunological status of patients with leprosy. Its role in evaluating contacts at risk of developing lepromatous disease is being investigated.

II/78(A) T-LYMPHOCYTE SUBSETS IN BLOOD AND TISSUES OF PATIENTS WITH LEPROMATOUS LEPROSY AND ERYTHEMA NODOSUM LEPROSUM

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To study further the immunopathology of lepromatous leprosy (LL) and erythema nodosum leprosum (ENL), we have studied T lymphocyte subsets in LL patients with or without ENL and controls. Monoclonal antibodies were used in conjunction with flow cytometry to examine blood or a modified immunoperoxidase technique to eavluate frozen tissue sections.

In blood 22 LL without ENL patients, as compared with 22 controls, were significantly and proportionately lymphopenic ($p.<01$), pan T cytopenic ($p< .001$), helper/inducer cytopenic ($p <.001$) and suppressor/cytotoxic cytopenic ($p<.01$), but had no abnormality in the helper: suppressor ratio. In contrast, the T lymphocyte subsets in 18 LL with ENL patients did not differ significantly from the controls.

In tissues of LL with or LL without ENL patients, the helper/inducer and the suppressor/cytotoxic phenotypes were both admixed with the histiocytes. The 10 LL without ENL tissues showed a predominance of the suppressor/cytotoxic phenotype and a mean helper: suppressor ratio of $0.6\pm:4$. In contrast, the 12 LL with ENL tissues showed a predominance of the helper/inducer cells and a mean helper:suppressor ratio of $2.1\pm:4$, significantly greater than in LL without ENL, $p< .01$.

Our data indicate that active cell-mediated immune mechanisms may be important in the pathogenesis of LL without ENL, where the suppressor/cytotoxic lymphocyte predominates, and of ENL, where the helper/inducer lymphocyte predominates.

II/79(A) ISOLATION AND ANALYSIS OF CIRCULATING IMMUNE COMPLEXES FROM LEPROSY PATIENTS

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Circulating immune complexes (CIC) were detected and then isolated by 2 antigen non-specific methods from 60 patients belonging to borderline tuberculoid (BT) and lepromatous (LL) types with and without leprae reaction. LL patients in reaction (LR) were further classified into (a) those with only arthritis and (b) those with only predominantly skin manifestations as part of their reaction.

CIC were elevated in BT patients with reaction (BTR) as well as in LR. CIC from BTR consisted largely of IgG and C3, whereas those from LR had CRP also. In addition, IgM and rheumatoid factor were demonstrated in the CIC of LR patients. Antimycobacterial antibody was seen in two-thirds of the LR patients who had only skin manifestations.

II/80(A) AUTOANTIBODIES TO DNA IN LEPROSY: ANTIGENIC SIMILARITIES BETWEEN DNA AND MYCOBACTERIAL PHOSPHOLIPIDS DEFINED BY HUMAN MONOCLONAL ANTIBODIES

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Patients with leprosy produce antibodies against numerous auto-antigens, including nuclear antigens. Our studies deal with the mechanism of production of anti-nuclear antibodies in leprosy, and in particular whether determinants on mycobacteria, through antigenic mimicry, lead to production of cross-reacting antibodies. In leprosy sera, high titers of antibodies were detected to cardiolipin, to DNA and to mycobacterial antigens, assayed by ELISA to sonicated, DNAase treated cell walls from *M. leprae* and *M. bovis* (BCG). Lepromatous patients exhibited highest titers and antibody concentrations fluctuated during erythema nodosum leprosum reactions, suggesting participation of these auto-antibodies in the immune complexes detected during ENL reactions.

Screening of 30 human hybrids derived from blood lymphocytes of a human with anti-DNA antibodies revealed 5 that bound to mycobacteria; of those, 4 also bound to DNA. The cell wall epitope resembling DNA was identified using thin layer chromatography (TLC) of lipid extracts of the cell walls. Autoradiography demonstrated binding of monoclonal anti-DNA to mycobacterial phospholipids on the TLC plate. These results suggest that mycobacterial cell walls contain phospholipid antigens which resemble structures in the sugar-phosphate backbone of DNA and the phosphate-glycerol structure of cardiolipin, offering a plausible explanation for the mechanism of production of anti-DNA antibodies in leprosy.

II/81(A) EFFECTS OF *M. LEPRAE* ANTIGENS ON THE *IN VITRO* RESPONSIVENESS OF MONONUCLEAR CELLS FROM LEPROMATOUS ARMADILLOS TO CONCANAVALIN-A

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Armadillos develop a disseminated infection when experimentally inoculated with *M. leprae*. However, some animals show resistance. Effects of *M. leprae* on Concanavalin-A-induced *in vitro* proliferation of mononuclear cells from armadillos with a disseminated infection with *M. leprae* were compared to armadillos which demonstrated resistance to infectious challenges with *M. leprae*.

There was no significant difference between the infected and resistant groups of animals in their responsiveness to Con-A alone. However, the simultaneous addition of Con-A and sonicated Dharmendra lepromin into replicate mononuclear cell cultures had varying effects when compared to cultures receiving Con-A alone. The *M. leprae*-infected group had blood mononuclear cells which responded to sonicated Dharmendra *in vitro* by suppressing the responses to an intermediate dose of Con-A, enhancing the response to an optimal dose of Con-A, and inducing no significant change in response to a minimal dose of Con-A. In contrast, mononuclear cells from the resistant group of armadillos responded *in vitro* to *M. leprae* by suppressing responses to all three concentrations of Con-A.

II/82(A) IMMUNOLOGIC EFFECTS OF LEPROSY IN MANGABEY MONKEYS (CEROCOCEBUS ATYS).

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Sooty mangabey monkeys (Cercocebys atys) with naturally-acquired or experimentally transmitted leprosy have been studied immunologically in a longitudinal manner for 2-3 years. In advanced, disseminated leprosy near the LL end of the spectrum, decreases occurred in mitogen responsiveness and in pokeweed mitogen-induced immunoglobulin producing plaque-forming cell (PFC) numbers. Treatment of the naturally-infected mangabey resulted in dramatic clinical improvement with decreased *M. leprae* morphologic indexes. Following a lag period of 19-24 months after the initiation of therapy, dramatically increased mitogen responses were noted and PFC responses were in the high normal range.

The percentage of "helper" (OKT4$^+$ and Leu 3a$^+$), "suppressor" (OKT8$^+$) and other subpopulations of lymphocytes were observed. Additional studies, now proceeding, are required to clarify statistically the possible role of these cells in the observed alterations in immune function. Numbers of blood lymphocytes and certain subpopulations in control and infected managabeys varied with an apparent circannual periodicity that must be considered in evaluating the data.

The results indicated that the mangabey will be useful in the study of mechanisms involved in immunologic responses to leprosy.

II/83(A) NK AND K CELL FUNCTION IN LEPROSY PATIENTS: INCREASED NK CELL ACTIVITY IN PATIENTS UNDERGOING REACTION

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Thirty-two leprosy patients were assessed for natural killer (NK) and killer (K) cell function at the Armauer Hansen Institute in Addis Ababa, Ethiopia. Twenty-four of the patients had recently-detected or un-treated leprosy (12 BT, 9 BL, 3 LL); six additional patients were undergoing reversal reactions (RR) and two had erythema nodosum leprosum (ENL). For comparison, five foreign and eight Ethiopian controls without leprosy were also tested. Plastic non-adherent peripheral blood lymphocytes were incubated in tubes with ^{51}Cr-labelled K562 cells in fetal calf serum at ratios of 25:1, 12.5:1, 6.25:1, and 3.125:1 to measure NK activity and with ^{51}Cr-labelled sheep red blood cells (SRBC) and anti-SRBC serum at 10:1, 5:1, 2.5:1, and 1.25:1 for the K cell assay. No differences were found in K cell function.NK cell activity was significantly depressed in newly diagnosed leprosy patients compared with normal controls or patients with RR or ENL; an effector: target cell ratio of 16–29:1 was necessary for new patients to achieve 50% target lysis whereas a ratio of only 5:1 was necessary for controls or for patients undergoing reaction. The differences between patient classifications were not significant. These findings would suggest that NK activity, which can be enhanced by interferon, the production of which can be induced by BCG and other adjuvants, may play an important role in the immunopathogenesis of reactional leprosy.

II/84(P) *M. LEPRAE* ANTIGENS AND ANTI-*M. LEPRAE* ANTIBODIES IN THE URINE OF LEPROSY PATIENTS

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M. leprae antigens were documented in 50% of urine samples taken from patients with multibacillary leprosy using a RIA designed to detect mainly polysaccharide antigens. Results of further analysis of urinary antigens will be presented.

Anti-M. leprae antibodies were documented in urine samples from 90% of multi bacillary leprosy patients with a RIA, and in 50% precipitating antibodies against antigen 5, 6 and 7 was documented by CIE. A positive correlation between serum and urine antibody levels was found.

The possible use of urine as a sample which is collected atraumatically, for detection of *M. leprae* antigen and/or *anti-M. leprae* antibodies in epidemiological surveys will be discussed.

II/85(P) LEPROMIN-REFRACTORY CONTACTS

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The lepromin test offers a useful tool/parameter for detecting individual vulnerability to *M. leprae* infection. The lepromin negative contacts are more prone to get the disease than lepromin-positive ones. The value of lepromin positivity in ascertaining the immune status (C.M.I.) in individuals is well recognised. Consequent on this, various methods are employed for lepromin conversion using a number of antigens. Repeated use of lepromin at intervals in individuals may effect the enhanced immune status. 280 contacts of 46 lepromatous cases were subjected to repeated lepromin testing with both D.L. and M.L. at intervals of 6 weeks. Thirty- three percent of the contacts showed lepromin conversion after first testing, another thirty percent of the remaining contacts showed conversion on the second retesting. Fifty percent of the rest were subjected to lepromin retesting for further periods. Only 8 contacts (thirteen percent) remained lepromin negative even after the fourth retesting; they were in the age group between 11–20 years. *In vitro* L.T.T. and L.M.I.T. performed in these cases revealed interesting findings.

II/86(P) THE LYMPHOCYTE BLASTOGENIC RESPONSE IN LEPROSY PATIENTS AND THEIR SIBLINGS

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Blastogenic response (LTT) to PHA, lepromin and *M. leprae*, Mitsuda's reaction and serum globulins levels, were studied in 34 leprosy patients (17 lepromatous and 17 tuberculoid leprosy), and in 34 of their non–affected siblings, sex-matched and approximate age, in order to verify. (a) the influence of an inherited family character on LTT responses in L and T patients and in their relatives; (b) the correlation between LTT and serum globulin levels. The blastogenic response was assessed by cellular incorporation of 3H-thymidine.

All the lepromatous patients had depression of blastogenic response to PHA, lepromin and *M. leprae* when compared with their non-affected siblings. There was no evidence of family character determining LTT depression in these sibling pairs. The Mitsuda reaction was negative in all lepromatous patients whereas 14/17 of their siblings had positive reactions. There was a positive correlation (99.5%) between LTT response to PHA and the lepromin test in lepromatous siblings, but no correlation between LTT and serum globulin levels.

Lymphocytes of tuberculoid leprosy patients had higher response to PHA, lepromin and *M. leprae* than siblings' lymphocytes. The Mitsuda reaction was similar in tuberculoid patients (positives 15/17) and their siblings (positives 12/17). There was positive correlation between LTT stimulated by PHA, lepromin and *M. leprae*, and the Mitsuda reaction in tuberculoid patients. There was no correlation between LTT and lepromin test in the tuberculoid siblings and no correlation between LTT response and serum globulin levels in tuberculoid patients and their siblings.

From the findings, it seems there was no evidence of an inherited family character determining similar response to LTT in leprosy patients and their siblings.

II/87(P) ERYTHEMA NODOSUM LEPROSUM (ENL). THE ROLE OF EXTRAVASCULAR IMMUNE COMPLEXES

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The centre of the ENL lesion comprises disintegration of macrophages with release of bacterial *(M. leprae)* antigen. The antigen is composed of cell walls, cytoplasm and soluble products which combine first with IgM, then with IgM antibody and complement. The classical pathway of complement is implicated. Acute phase reactants,C-reactive protein, B-lipoprotein and serum amyloid P factor indicate that plasma proteins may be the main connective tissue immune complex forming agents.

The immune complexes are extravascularly deposited at the site of small granulomas. Complexes formed at appropriate ag-ab ratio precipitate the reaction.

Ultra analysis shows that much of the debris antigen is retained in phagosomes which are dispersed widely in the reaction area.

II/88(P) LEUKOCYTE MIGRATION INHIBITION TEST (LMIT) AS A MODEL OF *M.LEPRAE* INDUCED SUPPRESSION

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The effect of *M. leprae* on inhibition of Peripheral Blood Leukocyte (PBL) migration to PHA-P and PPD was studied in 44 leprosy patients. Suppression of PHA-P response was observed in 75% of the tuberculoid patients while the majority of the lepromatous cases showed enhanced response to

the mitogen. The present suppression was highly significant ($p<0.001$) between the two groups of leprosy patients. However, there was no significant difference between the groups in the percent suppression induced by *M. leprae* on responses to a related antigen, PPD. Investigation on healthy contacts is under way. The potential of Leukocyte Migration Inhibition Test (LMIT) as a model for *in vitro M. leprae*-induced suppression will be discussed.

II/89(P) IMMUNO HISTOCHEMICAL ANALYSIS OF KINETICS OF THE IN VIVO RESPONSE TO KILLED *M LEPRAE*

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Eighty biopsies were obtained from B.I. negative patients in the leprosy control programme of the ALERT hospital in Addis Ababa. Biopsies, taken at different stages of the lepromin reaction, allow analysis of the development of the immune response. Biopsies from 20 lepromatous patients with clinically negative early and late reactions show the reaction starts with non-specific inflammatory changes and a moderate infiltrate of round cells and histiocytes around the vessels and sweat glands of the dermis. Small foci of granulocytes are present early in the reaction in some cases, but these disappear as the infiltrate evolves into predominantly foamy macrophages containing ingested bacilli.

Biopsies from 20 tuberculoid patients show more extensive early infiltrates. Often, there are central areas of necrotic collagen and granulocytes. As the reaction progresses, the relative numbers of round cells and histiocytes, and their spatial relationships, change resulting in well formed tubercles at 28 days.

Phenotypes of cells are identified using monoclonal antibodies defining T-lymphocyte subsets ("T-helper", "T-suppressor"), B cells, activated lymphocytes and macrophage subsets. An avidin-biotin horseradishperoxidase technique is used with frozen sections of the biopsies. The phenotypes of the cells involved will be reported.

II/90(P) PATHOLOGICAL OBSERVATION FROM IMMUNODEPRESSIVE VIEWPOINT ON LEPROSY AUTOPSIES

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A total of 230 leprosy autopsies has been studied since 1955. Among these autopsies, there were several interesting cases from the immuno-depressive viewpoint. The cases are Kaposi's sarcoma, pleiosis, hepatis, tracheobronchopathia, chondro-osteoplastica, bacterial tricuspidal valvulitis, laryngotracheal carcinoma, malignant lymphoma, double cancers, triple carcinomas, leukemia, miliary tuberculosis, Klebsiella pneumonia, liver cirrhosis, etc.

Cases of amyloidosis since 1975 will be discussed.

The combination of immunodepressive disorders with leprosy, which itself is typically an immunodepressive disease, is considered to be related to the fact that the lifespan of leprosy patients has been much prolonged with better treatment and health care in Japan.

Selected cases from such patients will be shown.

II/91(P) CHARACTERIZATION OF T SUPPRESSOR CELLS IN LEPROMATOUS PATIENTS

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In view of the serologic cross-reactivity between the protein antigens of *M. leprae* and other mycobacteria, the specific and selective immunological unresponsiveness of lepromatous patients remains a problem. We have suggested that T suppressor cells specific for one or more unique antigenic determinants of *M. leprae* could explain the specific unresponsiveness. We have shown: (i) Dharmendra lepromin induced *in vitro* suppression of the Con A response of lepromatous and borderline, but not tuberculoid patients or normals (ii) two cell populations contribute to the suppression, monocytes and T cells (iii) all the lepromin-induced Ts activity was associated with a 20-30% sub-population of T cells defined by the TH_2, monoclonal OKT5 or OKT8 antibodies (iv) a high percentage of the Ts subset expressed activation markers, Ia and Fc receptors (v) some Ts recognized the unique phenolic glycolipid I of *M. leprae*, which could induce suppression of mitogenic responses *in vitro* as well as lepromin and (vi) no significant suppression *in vitro* was found with lymphocytes from 60 lepromatous patients after immunotherapy with BCG+killed *M. leprae*, and the number of Ia^+OKT8^+ cells returned to normal levels.

II/92(P) ANTIBODIES TO MYCOBACTERIAL SULFOLIPIDS IN LEPROSY PATIENTS

Uma Malik, Gopal K.Khullar and Bhushan Kumar
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The occurrence of antimycobacterial antibodies in the low resistant form of leprosy is well documented. Recently, sulfolipids of *M. tuberculosis* have been shown to be antigenic in nature and further antibodies to these components have been detected in tuberculous patients. In view of the common antigens in *M. tuberculosis* and *M. leprae*, a study was undertaken to examine the presence of antisulfolipids in leprosy patients and to study the effect of antileprosy drug on these antibodies. Antibodies to mycobacterial sulfolipids were demonstrated by agar gel and Kaolin-agglutination techniques. None of the tuberculoid patients or normal subjects showed any reaction with total sulfolipids. The presence of antisulfolipid antibodies in lepromatous patients indirectly suggested the presence of sulfolipids in *M. leprae*. The antibody titre was found to decrease gradually on treatment with dapsone and maximum effect was observed in patients undergoing treatment for more than one year. These observations in relation to their significance in clinical diagnosis will be discussed.

II/93(P) ANTIBODIES AGAINST *M. LEPRAE* SCREENING IN POPULATION OF ENDEMIC AREAS USING ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA)

Abdullahi Sh. Hussein, Tarabini-Castellani Guiseppe Luigi, Hassan Hagi Mahamed and Tarabini-Castellani Giovanni
Somali National University, Mogadiscio, Somalia.

In the Immunologic Department of our University, we are carrying out the serological screening at random system into some village populations who are living mostly on the banks of the river Uebi Shebelli.

These villages are affected with high rates of endemic diseases as malaria, schistosomiasis and intestinal parasites.

Since our patients live in areas where there are some Hansen's disease cases, on the same sera we are going to carry out the IgG connected with *M. leprae* by means of Enzyme-linked immuno-sorbent assay (ELISA).

The results obtained are related in this report. At the end of our study it will be possible to map out the subclinical occurrence of Hansen's disease and then add these to the clinical cases discovered by the control programme.

II/94(P) IMMUNE FUNCTION STUDIES IN A FAMILY WITH A HIGH FREQUENCY OF LEPROMATOUS LEPROSY

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An unusually high frequency of lepromatous leprosy has been found in a partial-descent Aboriginal family from North Western Australia.

The father was admitted to the Leprosarium at Derby, Western Australia in 1968. In 1983, the eldest three of four children were diagnosed lepromatous.

Genetic markers have been ascertained for all members of the family. Immune function studies have included skin tests, *in vitro* lymphoblastogenesis, neutrophil function tests and quantitation of immunoglobulins, antibodies to ubiquitous antigens and C-Reactive proteins.

This report will discuss these findings which have been initiated to identify the unique susceptibility to leprosy in this family.

II/95(P) LYMPHOCYTOTOXIC ANTIBODIES IN LEPROSY

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57 sera taken from unrelated leprosy patients and 33 sera from age and sex matched hospital controls were tested for the presence of cold reacting lymphocytotoxic antibodies (LCAs) at 15°C against a panel of 30 HLA-typed normal lymphocytes. 18 of 57 leprosy sera and 22 of 33 control sera showed reactivity ($p<0.05$, x^2test). Each serum was given a cytotoxicity score by adding the strength of reactivity against each lymphocyte of the cell panel. Comparison of the serum strengths revealed significantly higher reactivity of leprosy sera than of control sera (Wilcoxon Rank sum test, $p<0.01$). With the leprosy group, the lepromatous ($n=27$) and tuberculoid ($n=30$) were equally reactive. The occurrence of LCAs did not correlate with any of the HLA antigens of the cell donor panel or the sex or HBs Ag status of the serum donors. The only two HBs Ag positive leprosy sera (by reverse passive haemagglutination) had no LCA activity. These results differ from one previous report of presence of LCAs in the HBs Ag positive lepromatous sera. The low frequency of HBs Ag in our patients can be due to our cases being non-institutionalized and from a low endemicity area. A biological role for presence of LCAs in leprosy is indicated.

II/96(P) HEPATITIS B VIRUS (HBV) SERUM MARKERS IN GREEK LEPROSY PATIENTS

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The exposure of leprosy patients to HBV and the ability of the exposed leprosy patients to clear up the HBsAg were investigated. The study was based on 217 leprosy patients (135 LL and 82TT) and on 382 hospital controls. In the sera of all patients and controls HBsAg, anti-HBs and anti-HBc were determined by RIA. Effective exposure is characterized by the presence in the serum of any marker of HBV exposure, whereas active infection is characterized by the presence in the serum of HBsAg with or without any other serological marker.

The main findings are as follows: (a) effective exposure to HBV was significantly higher among patients with Hansen's disease than among controls ($P<10^{-6}$). On the other hand effective exposure to HBV was not significantly different between patients with LL and TT (b) the ability to clear HBsAg from the circulation among persons exposed to HBV was not different in any group of patients with Hansen's disease compared to other hospitalized patients. These findings indicate that the reported higher prevalence of HBsAg among leprosy patients reflects their higher exposure to HBV and does not indicate the presence of any generalized immunologic deficiency.

II/97(P) SEROLOGICAL STUDY OF LEPROSY BY ENZYME-LINKED IMMUNOSORBENT ASSAY

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Serological tests are used in epidemiological studies in many diseases. In leprosy, the serological test is also expected to have value in detecting subclincal infection, preclinical manifestation, and follow up of efficacy of drug treatment.The test has to be specific, sensitive and reproducible to be useful for these purposes. We chose the ELISA assay because this test could be done with larger number of specimens and does not require subjective reading. Because of the limitation of the *M. leprae* bacilli, we wanted to find an easy growing mycobacterium which would share the *M. leprae* specific antigen. If the mycobacterium is found, it would be a great advantage in that it could be cultivated *in vitro* in large amounts. To find this out, we prepared cultures of upto 9 different mycobacteria for the absorption and for the ELISA assay. Pooled LL sera and pooled pulmonary tuberculosis sera were studied. Both sera were absorbed with each mycobacterium and tested with each mycobacterium. It was found out that absorption with *M. marinum* and testing with *M. fortuitum* will remove the antimycobacterium antibody in the pulmonary tuberculosis sera, but the sera from pool LL gave positive antibody to mycobacterium.We therefore used *M. marinum* as absorbent and *M. fortuitum* as test antigen in our studies. It revealed that after absorpiton, all blood bank donors and pulmonary tuberculosis gave negative (OD<0.2) results. Most of the LL and BL patients were positive. However, another batch of sera from pulmonary tuberculosis patients was assayed, higher amounts of *M. marinum* were needed in the absorption to obtain the OD<0.02. The sera from the leprosy patients with severe ENL, mild ENL, severe reversal reaction and mild reversal reaction were assayed, after absorption with the higher amount of *M. marinum*. It revealed that even the LL sera gave negative results. We therefore concluded that any assay for antimycobacterium leprae which required the removal of the common antimycobacterial antibody needs to be evaluated properly, otherwise it could not be said to be specific for detecting antimycobacterial leprae.

II/98(P) DEVELOPMENT OF AN ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA) TO MEASURE ANTIBODIES TO THE PHENOLIC GLYCOLIPID OF *M. LEPRAE*

Douglas B. Young, Thomas M. Buchanan
University of Washington

A phenolic glycolipid derived from *M. leprae* has been found in large amounts in leprosy-infected tissues of human and armadillo origin and its structure has been elucidated. The unique trisaccharide portion of the molecule suggested that the glycolipid maybe an *M. leprae*-specific antigen and we have developed an ELISA procedure which measures antibodies to the lipid in human sera.

In initial experiments we found that using purified phenolic glycolipid to coat microtiter plates under a variety of conditions resulted in only a limited exposure of the antigenic carbohydrate portion of the molecule. However, when the lipid was deacylated by alkaline hydrolysis, its antigenic properties were markedly enhanced producing a highly satisfactory ELISA system. Using this ELISA test we have shown that the sera from leprosy patients contain antibodies which recognize the *M. leprae* phenolic glycolipid but fail to bind to the related lipid from *M. kansasii* which differs in carbohydrate structure. The dominant class of antibody binding to the glycolipid was found to be IgM. More than 70% of leprosy patients were positive by the ELISA test with the percentage positivity and the mean antibody titer increasing from the tuberculoid to the lepromatous pole of the clinical spectrum. Normal individuals, volunteers recently vaccinated with BCG and patients with tuberculosis and atypical mycobacterial diseases were negative by the ELISA test.

This test has considerable potential as a tool for detection of subclinical leprosy infection.

II/99(P) MONOCLONAL ANTIBODIES TO SURFACE-EXPOSED ANTIGENS OF *M. LEPRAE*

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Monoclonal antibodies are useful as diagnostic reagents and for the identification and purification of antigens. In order to further our understanding of the surface properties of *M. leprae* we have used an ELISA test with whole mycobacteria to screen for monoclonal antibodies reacting with surface-exposed antigens. Cloned cell lines were obtained by fusing spleen cells from mice immunized with purified antigen (phenolic glycolipid) or from athymic mice infected with *M. leprae*.

Antibodies to the *M. leprae* phenolic glycolipid react strongly with *M. leprae* in the whole organism ELISA, but show little or no binding to a panel of 20 other mycobacteria. Binding to *M. leprae* is inhibited by preincubation of antibody with the purified glycolipid antigen. Immunofluorescence studies using monoclonal antibodies show that the phenolic glycolipid occurs as a capsule surrounding leprosy bacilli.These antibodies can be used to visualize bacilli within lesions and also to quantitate the amount of antigen in clinical samples.

Athymic mice infected with *M. leprae* produce a predominantly IgM antibody response to the bacilli and we have used the monoclonal antibody technique to permit detailed investigation of these antibodies. Monoclonal antibodies generated from fusions involving mice at the early stages of infection were directed towards antigens common to all mycobacteria whereas fusions from later stages of infection resulted in antibodies showing differing degree of specificity for *M. leprae* as judged by the whole organism ELISA.

II/100(P) IMMUNOLOGICAL ASSESSMENT OF SENSITIN OBTAINED FROM *M. LEPRAE*

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The results of experimental and clinical trials on sensitin prepared from *M. leprae* passed on rats and isolated from infected tissues according to Draper are presented. The antigenic substance of endotuberculin type is obtained from purified mycobacteria. Biological activity and specificity of sensitin is assayed experimentally in guinea pigs. *In vitro* tests using sensitin revealed a distinct reverse relation between humoral and immune responses in leprosy patients: high titres of antibodies against mycobacteria in indirect haemagglutination test and low levels of specific lymphocytic sensibilization in LTT. 48-72 hours after intracutaneous injection of sensitin in a dose of 0.3 mkg/0.3 ml, the patients with various types of leprosy gave different reactions similar to Mitsuda lepromin test (in 3-4 weeks). The patients with tuberculosis showed negative or weakly positive responses to intracutaneous injections of *M. leprae* sensitin (diameter of nodule <5mm). No correlation was noted between the responses to sensitin and tuberculin in leprosy patients both *in vitro* and *in vivo* tests. The possibilities of using the preparation obtained as an alternative to integral lepromin are discussed.

II/101(P) ENDOGENOUS HYDROCORTISONE AS AN IMMUNE REGULATOR IN LEPROSY

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Serum levels of hydrocortisone, glucocorticoid reserve of adrenal cortex and lymphocyte transformation (LTT) to PHA and PPD were studied in 12 patients with active lepromatous leprosy, 22 improved patients and 23 healthy subjects. It was found that the increase in hydrocortisone levels and decrease in glucocorticoid reserve were related to the activity of the leprosy process and were most evident in patients with active disease ($P<0.05$). These patients showed the deeply depressed lymphocytic response to PPD rather than to PHA. Low values of LTT to PPD in most patients who were clinically improved were accompanied by high levels of hydrocortisone and a decrease in the glucocorticoid reserve. In healthy subjects and leprosy patients with normal glucocorticoid reserve function, lymphocytic response was not related to hydrocortisone concentrations in blood sera. The patients with decreased glucocorticoid reserve in the presence of high basal levels of hydrocortisone in blood showed a strong correlation between hormone levels and intensity of LTT reaction to PPD. This finding reflects the role of endogenous hydrocortisone as a homeostatic

regulator for structure and function of the circulating lymphocytic pool. The increase in serum hydrocortisone level in leprosy patients seems to be a component of neuroendocrine response to the disturbances in homeostasis.

II/102(P) HLA-DR RESTRICTED T CELL LINES, SPECIFIC FOR MYCOBACTERIAL ANTIGENS

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In order to study the cellular interactions and particularly the role of class II products in the immune response against mycobacterial antigens, we grew T cell lines against PPD. Fresh Ficoll isolated peripheral blood lymphocytes of BCG vaccinated individuals were restimulated *in vitro* with PPD for 4-6 days. During the next 10 days, they were cultured and expanded in the presence of 20% IL-2 (Lymphocult-T Biotest).

These cells appeared to be PPD-specific and had lost alloreactivity. By using different allogeneic PBL as antigen-presenting cells, the PPD-specific response was shown to be mainly HLA-DR restricted. We are now trying to develop similar T cell lines specific for *M. leprae*-antigens. Such T cell lines would provide an important tool to resolve further the role of HLA-linked immunoregulatory genes.The first results of this approach will be presented.

II/103(P) THE USE OF TRITIATED URACIL IN A RAPID ASSAY FOR THE ACTIVATION OF ANTI-MYCOBACTERIAL FUNCTIONS IN HUMAN OR MURINE MACROPHAGES BY LYMPHOKINES OR ANTIGEN SPECIFIC, MHC RESTRICTED T-CELL LINES

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Most *in vitro* studies of the immunology of mycobacterial diseases involve lymphoproliferative assays. There is urgent need to assay effector functions that are more directly related to immunity. To assay mycobactericidal or mycobacteriostatic activity, we culture murine peritoneal macrophages or human peripheral blood monocytes in flat-bottomed microtitre wells and infect them with mycobacteria. Concanavalin-A induced or antigen-induced lymphokines are added to some wells. Three or four days later, the macrophages are lysed and a mycobacterial growth medium containing tritiated uracil is added. The tritiated uracil incorporation is linearly related to the number of live organisms present at the time of lysis.

Using *M. tuberculosis* as the infecting organism, we show that lymphokines will induce powerful bacteriostatic effects in murine peritoneal cells and weak ones in fresh human monocytes. Similarly, 3 continuously cultured PPD-specific CBA T-cell lines added directly to infected wells caused marked (>80%) inhibition of growth of *M. tuberculosis* in CBA, but not Balb/c macrophages. As few as 10^3 T-cells were active. A thyroglobulin specific line had no effect.

We feel that this assay represents a useful tool for the analysis of the immunology of the mycobacterioses.

II/104(P) PILOT STUDIES OF IMMUNOPROPHYLAXIS & IMMUNOTHERAPY IN MAN WITH *M. VACCAE, M. LEPRAE* AND BCG

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Two small studies are described which are based on 2 concepts. The first concept is that protection from mycobacterial infection and immunologically-mediated recovery from such infection is associated with the establishment of a pathway of immunity leading to the death of organisms rather than the death of tissue. The second concept is that this protective immunity is triggered by common mycobacterial antigen rather than by the species specific antigens of the invading organisms. One study for which the 2-3 year follow-up is described is of 3 vaccines applied to groups of tuberculin negative healthy school children in a leprosy endemic and tuberculosis endemic region. The 3 vaccines used were BCG (Glaxo freeze-dried) alone, BCG plus 10^7 killed *Mycobacterium vaccae* and BCG plus 10^7 killed *Mycobacterium leprae*. The other study for which 1 year follow up data is available is a controlled trial of 1 reagent, killed *Mycobacterium vaccae*, in immunotherapy of lepromatous patients with very low bacterial indices on long-term chemotherapy. In both studies, quadruple skin-testing with new tuberculins, before vaccination and not less than 1 year after it, has been the principal quantitative criterion of efficacy.

II/105(T) ANTIGEN-SPECIFIC SUPPRESSOR T CELLS STUDIED IN A TWO-STAGE CULTURE SYSTEM

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Peripheral blood lymphocytes from healthy occupational contacts of leprosy patients were cultured 7 d with *M. leprae* (AB 21, protocol 3/77 or AB40, protocol 1/79), BCG, PPD, and SKSD and without antigen. These primed cells were then treated with mitomycin C, washed, and combined with equal numbers of freshly isolated autologous cells. The combined cells, stimulated with the different antigens, were labelled with 3H-thymidine after 6 d culture. In this way, the suppressive effect of cells primed with the second-stage antigen could be compared with that of cells primed with other antigens. Both specific and non-specific suppression were measured relative to control cultures containing mitomycin C-treated cells pre-cultured without antigen. As reported previously, the maximum level of *M. leprae*-specific suppression was observed in individuals exposed to leprosy for about 3 years or more. We now report that the suppressor cell is a non-adherent, SRBC-rosetting cell, possibly a T lymphocyte, and that *M. leprae* preparations AB21 and AB40 differ in their ability to generate suppressor cells. It is possible that lymphocyte proliferation with and without strong suppressor cell generation distinguishes *in vitro* responses that represent protective cell-mediated immunity from those that merely reflect delayed-type hypersensitivity. If so, the two-stage assay for *M. leprae*-specific suppression would be useful for testing the immune response to *M. leprae* leprosy vaccines in healthy individuals previously unexposed to leprosy.

II/106(T) TWO PATTERNS OF SKIN-TEST RESPONSE TO SOLUBLE ARMADILLO-DERIVED *M. LEPRAE* REAGENTS; THEIR RELEVANCE IN THREE DIFFERENT FORMS OF TUBERCULOID LEPROSY

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182 tuberculoid type leprosy patients in Bombay with either single skin (115), single nerve (14) or multiple lesions (53) - 2 or more dermatomes involved - were skin-tested with high (10ug/ml) and low doses (2ug-ml) of LRA 6 and Leprosin-A. Both reagents are sonicates of *M. leprae* extracted from armadillo tissue. LRA6 contains more cell-wall component than Leprosin-A, the reagent now in common usage. Skin tests were applied intradermally, two per forearm in 0.1 ml and induration sizes read at 4, 24, 48, 72 and 168 hours.

All four reagents behaved similarly but high dose Leprosin-A elicited the greatest percentage positivity.Two major response patterns emerged. One was characterised by small size responses present only at 24 and 48 hours. The other larger-size later response began at 24 hours, peaked at 72 hours, but often remained detectable at 1 week. Skin lesion and neural lesion patients showed the highest percentage of early and late responses respectively . Patients with multiple lesions showed low rates of both early and late type reactions and had a significantly lower BCG vaccination rate and a greater percentage of family contacts with smear positive leprosy than the other two groups.

These findings confirm and extend those of earlier Burmese studies with LRA6.

II/107(T) INTERACTION OF MYCOBACTERIA WITH HUMAN COMPLEMENT

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Mycobacteria including *M. leprae* have been shown to activate the human alternative complement pathpay (ACP). Micro organisms which activate the ACP are thought to be non-pathogenic or less pathogenic than those microbes which do not activate the ACP. Therefore, 20 cultivable mycobacteria were first screened for their ability to activate the ACP at the level of C3 by an immunofluorescence technique. The augmenting effect of antimycobacterial antibodies for the activation of ACP by *M. vaccae* and BCG was further examined. In addition, viability studies were performed to find out whether the ACP activation by mycobacteria results in killing of the organisms. The relevance of these findings to mycobacterial infections will be discussed.

II/108(T) T-LYMPHOCYTE PROLIFERATION *IN VITRO* AND ITS RELATION TO *IN VIVO* FUNCTION IN MICE INFECTED WITH *M. LEPRAEMURIUM*

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In vitro proliferation of T-lymphocyte enriched cells from the spleen and their relation to resistance to *M. lepraemurium* infection was studied in two strains of mice, BALB/c and C57BL/6. Two routes of infection, intravenous (i.v) or subcutaneous (s.c.) were used.

T-lymphocytes from i.v. infected mice proliferated significantly to specific antigen stimulation (whole autoclaved organisms), while the cells from the s.c. infected mice proliferated spontaneously in the absence of any antigenic stimulation for a period.

The antigen specific proliferating cells (from i.v. mice) were found to be $Thy1^+$, $Lyt1^+$, $Lyt2^-$. The population which contained the spontaneously proliferating cells (from s.c. mice) on the other hand were $Thy1^+$ and consisted of a mixture of $Lyt1^+$ and $Lyt2^+$ cells.

Adoptive transfer experiments were carried out to investigate the possible *in vivo* function of these T-lymphocyte subsets. In BALB/c which are the more

susceptible strain, significant resistance could be transferred to the recipients with T-lymphocytes from s.c. infected mice (mixture of Lyt1+ and Lyt2+ cells). Lyt1+ cells (from i.v. infected mice were not able to transfer resistance. T-lymphocytes (Lyt1, Lyt123 and Lyt23 cells) from normal BALB/c mice, on the other hand, rendered the recipients significantly more susceptible, indicating the presence of suppressor cells of protection.

II/109(T) COMPARISON OF THREE SEROLOGIC TESTS FOR ANTI-MYCOBACTERIAL ANTIBODIES IN A LEPROSY RESETTLEMENT VILLAGE.

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To elucidate relations between exposure to *M. leprae* and presence of circulating antibody, 226 residents of a leprosy resettlement village in Northern Thailand were studied, with recording of type and duration of leprosy, disease activity, and household contact. Sera were tested by: ELISA using (1) sonicated *M. smegmatis* or (2) sonicated *M. leprae* and (3) RIA using *M. leprae* phenolic glycolipid-I (PGL-I). 74 villagers were patients (all treated) and 152 were healthy; only three patients had positive skin smears. The majority of the patients seropositive by any of the three tests had LL or BL leprosy, and these patients had higher mean and median antibody levels. 83% of patients, 32% of household contacts and 29% of villagers without household contact had substantial levels of antibody detected by both sonicated-whole-organism assays; results were concordant in about 80% of sera tested by these two assays. 32% of patients, 17% of household contacts and 4% of persons without household contact had antibody reactive with PGL-I. Comparing patients and contacts, combination of any two of the three assays gave a sensitivity of 82-90%, specificity of 65-68%, predictive value of one positive test of 73-77%, both tests positive of 85-92%, and both tests negative of 75-85%. The use of 2 serologic assays provides improved sensitivity and specificity in detection of *M. leprae*- related antibodies.

II/110(T) MONOCYTE DERIVED SUPPRESSOR FACTROR(S) IN PATIENTS WITH LEPROMATOUS LEPROSY

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Two-hour plastic adherent cells from 33 lepromatous patients were found to release soluble factors (MoF(s)) capable of suppressing lymphoproliferative responses. Soluble *M. leprae* (AB 40) antigen-induced lymphoproliferation of tuberculoid patients could be suppressed to a greater extent (ranging from 37-87%) as compared to suppressive effects on mitogen-induced responses (ranging from 16-30%). The extent of suppression varied for different lepromatous patients. The adherent cells were found to release spontaneously these factrors (Mean % suppression ± S.D.;62 ± 14.2). Treatment of adherent cells with heat-killed or cryopreserved *M. leprae* did not further increase the suppressive effects. MoF(s) from 5 treated lepromatous patients (who still had residual bacilli in the skin) showed lower spontaneously released suppressive effects (Mean % suppression ± S.D.; 17 ± 7.7). However, treatment with heat-killed *M. leprae* released factors with higher suppressive activity (Mean % suppression ± S.D.; 44 ± 4.8). Tuberculoid adherent cells did not release any suppressive MoF(s)

The lepromatous MoF(s) were heat-stable at 56°C for 30 minutes, were not cytotoxic and had a molecular weight above 25,000 as assessed by ultrafiltration through membrane cones. The release of these factors was not influenced by the presence of indomethacin. Such suppressive factors released by lepromatous monocytes capable of inhibiting lymphoproliferation may play a role in the immunological unresponsiveness observed in lepromatous leprosy.

II/111(T) *IN SITU* CHARACTERIZATION OF T LYMPHOCYTE SUBSETS IN LEPROSY TUBERCULOSIS, SARCOIDOSIS AND RHINOSCLEROMA:

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Immunologic mechanisms are probably important in the pathogenesis of many granulomatous diseases. To evaluate the role of T cell subsets in granulomas, monoclonal antibodies directed against T suppressor/cytotoxic cells and T helper/inducer cells were used to stain frozen sections with an immunoperoxidase technique. Twenty-five specimens of leprosy (15 tuberculoid, 10 lepromatous), three lymphoid specimens of tuberculosis, eight specimens of sarcoidosis (four skin, four lung) and four nasopharyngeal specimens of rhinoscleroma were evaluated. Two immunohistologic patterns were observed. In the tuberculoid leprosy and tuberculosis specimens where the host response is effective in virtual elimination of bacilli and in the sarcoidosis specimens, T helper/inducer cells were found within epithelioid cell aggregates; but, in contrast, T suppressor/cytotoxic cells were located predominantly in the mantle surrounding the granuloma. The lepromatous leprosy and the rhinoscleroma tissues where the host response is ineffective, permitting florid bacillary proliferation, showed a mixture of T helper/inducer and T suppressor/cytotoxic phenotypes distributed throughout the histiocytic granulomas. No mantle of T suppressor/cytotoxic cells was seen. Therefore, the histologic type of granuloma (epithelioid or histiocytic) seems to be associated with a particular microanatomical arrangement of T cell subsets (separated or admixed) and also may reflect the host's response (effective or ineffective) to the foreign invader.

II/112(T) THE NATURE OF INFILTRATING CELLS IN CUTANEOUS LESIONS OF LEPROSY

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Dermal lesions from 23 patients representing the full spectrum of leprosy were studied. The nature and quantities of the inflammatory cells and their bacteria were determined by immunofluorescence and transmission electron microscopy.

The cutaneous infiltrates of patients with lepromatous leprosy (LL and BL) contained predominantly parasitized foam cells with large multibacillary vacuoles. Evidence of phagosome lysosome fusion was obtained. Intact and partially degraded *M. leprae* surrounded by an electron-lucent halo and embedded in an amorphous matrix were always found within membrane-bound vacuoles.

Only small numbers of scattered lymphocytes were found, mostly of the Leu 2a/OKT8 T-cell subset. In borderline patients (BL and BB), smaller numbers of bacilli were found in smaller vacuoles within macrophages. An increase in the numbers of lymphoid cells specifically of the Leu 3a/OKT4 T-cell subset was observed. At the tuberculoid pole of the spectrum (BT and TT), large numbers of T-cells with extremely long and complex filipodia were found closely associated with epithelioid and multinucleated giant cells. Many of the mononuclear phagocytes appeared non-viable and areas of necrosis were evident.

Eighteen months of treatment reduced the bacterial load and the numbers of cells in the cutaneous infiltrates. The numbers and relative frequency of the T-cells and their subsets appeared not to be affected.

II/113(T) ANALYSIS OF THE PROPERTIES OF INFILTRATING CELLS IN LEPROSY LESIONS USING MONOCLONAL ANTIBODIES

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The phenotypic characteristics of the infiltrating cells in the dermal lesions of 85 untreated leprosy patients were studied by indirect immunofluorescence, using monoclonal antibodies defining T cell subsets and fibronectin. Most lymphocytes in the leprosy lesions were positive for OKT3 and Ia-like antigens. Maximal numbers of these cells were seen in tuberculoid lesions in close association with epithelioid cells. A decline in their numbers was observed over the leprosy spectrum with a marked reduction in lepromatous leprosy, where only occasional OKT3+ cells were observed. Furthermore, no difference in the number of OKT6+ Langerhans' cells was observed across the leprosy spectrum. Leu3a (helper/inducer) and OKT8 (suppressor/cytotoxic) positive cells were found frequently within the OKT3+ lymphocytes throughout the leprosy spectrum. The ratio of Leu3a/OKT8+ cells was higher in the granulomas of tuberculoid lesions. It was interesting that OKT8+ Cells were arranged in a ring-like pattern in the peripheral lymphocytic cuff of the tuberculoid granuloma and were rarely seen within the epithelioid cell region. By contrast, Leu3a cells were scattered diffusely amongst the epithelioid cells. This anatomical pattern was maintained in reactional tissues also. Moreover, in ENL lesions, helper T cells were seen in numbers similar to that seen in BT lesions. Macrophages in the granulomas stained intensely with anti-Ia like and with monoclonal antibodies to human fibronectin. Both these antigens were expressed to the same degree on macrophages with or without intracellular bacilli. Interestingly, the subepidermal collagen band in six borderline cases stained intensely with the fibronectin antibodies.

II/114(T) USE OF WHOLE BLOOD FOR ANTIBODY ASSAYS IN LEPROSY

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Thirty patients throughout the leprosy spectrum from the Addis Ababa Leprosy Hospital were initially examined. From each patient, blood was collected simultaneously with EDTA for use as whole blood and without additives for preparation of serum. The samples were kept frozen until examination in three different assays: (1) Radioimmunoassay (RIA) for antibodies to *Mycobacterium leprae* antigen 7, using ^{125}I-labelled antigen and protein A containing staphylococci (2) RIA for IgG antibodies to whole sonicated *M. leprae* antigen, using antigen-coated polystyrol test tubes and ^{125}I-labelled rabbit anti-human IgG, (3) enzyme-linked immunosorbent assay for IgG antibodies to whole sonicated *M. leprae* using antigen-

coated polyvinyl microtiter plates and alkaline phosphatase-conjugated rabbit anti-human IgG.

The antibody activity was virtually identical in all 3 assays when the results obtained with serum were compared with the corresponding frozen and thawed whole blood samples. The assays could also be performed on blood samples collected on filter paper discs, but it was essential to determine both the total IgG content and antibody activity in the eluate to correct for differences in elution of blood from the dried discs. Our data prove the suitability of whole blood for the demonstration of antibodies to *M. leprae* antigen, thus contributing to the adaptation of presently available antibody assays to conditions in the field where large-scale immunoepidemiological studies are urgently needed.

II/115(T) *M. LEPRAE* - AN ANTIGEN LESS MYCOBACTERIUM, A CAUSE OF LEPROSY? A NOVEL HYPOTHESIS AND ITS IMPLICATIONS

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We propose a novel approach to the leprosy puzzle by defining the antigen expression of *M. leprae*. The *M. leprae* specific antigens may be expressed by whole bacilli, in the form of haptens instead of complete antigen. The T-cell recognition will take place only when the latter is expressed and that CMI would be hapten-specific. The complete antigen may be expressed by a few bacilli, or it may occur later *in vivo* by mutation resulting in an *M. leprae* clone, or it may be found in *M. leprae*-culture-isolate. The leprosy bacilli may consist of *M. leprae* strains differing in their hapten profiles. It is hypothesised that the presence of complete antigen in *M. leprae* or the time delay in its expression *in vivo* would determine the clinical expression and immune status in leprosy.

Data on *M. leprae* culture isolates, the ICRC strains, used as vaccine in a clinical trial, lepromin tests, LMI studies in mice sensitised with ICRC strains & ICRC vaccinated LL patients will be presented to demonstrate the possible existence of a mixed *M. leprae* population with different hapten specificities.

The hypothesis explains tne mechanism of action of anti-leprosy ICRC vaccine, its success and failure, and paves the way for the rational design of a potent polyvalent vaccine or a live vaccine against leprosy.

II/116(T) INDUCTION OF UNSUSPECTED ANTINUCLEAR ANTIBODIES IN HETEROANTISERA FROM ANIMALS IMMUNIZED WITH MYCOBACTERIAL ADJUVANTS

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Many immunological tests, including immunohistochemistry and immunoassays, utilize commercial antisera made in animals intially immunized with the relevant antigen emulsified in complete Freund's Adjuvant (C-FA), containing *M. butyricum*. Since leprosy patients produce high titers of antinuclear antibodies, we assayed sequential bleeds from 17 goats immunized with a variety of antigens in CFA and boosted in incomplete FA for antibodies to mycobacterial (BCG) antigens, cardiolipin, casein and single strand DNA, using ELISA techniques. All goats had antibodies against mycobacteria and none had reactivity against a non-specific antigen, casein. Mycobacterial antibodies persisted at high titer for two years, suggesting repeated environmental challenge or persistence of mycobacterial antigens from primary immunization. Antibodies to ssDNA and cardiolipin were detected in all animals, with individual variation in titer, persisting for two years.Selected high titer sera were positive for antinuclear antibodies by immunofluorescence on mouse liver.

These results highlight one of the major problems of using heteroantisera rather than monoclonal antibodies: that is, the un-indentified multiple specificities of crude antisera which need to be affinity-purified or extensively absorbed before use. There are also special problems to beware of when examining tissue or sera of patients with mycobacterial diseases. since mycobacterial antibodies should be expected to be present in all commercial antisera. These observations underline the need for adequate controls when using heteroantisera.

II/117(T) INDUCTION OF DELAYED-TYPE HYPERSENSITIVITY BY ICRC-ANTILEPROSY VACCINE AND THE PASSIVE TRANSFER OF CELL-MEDIATED IMMUNITY IN MICE.

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The immunogenic potency of antileprosy vaccine has been determined by footpad enlargement (FPE) in mice, as described by Shepard *et al.* The test is a good measure of the degree of sensitization and the DTH response (48 hrs.). We have examined several batches of ICRC-vaccine, both irradiated and heat-killed bacilli, at immunizing dose levels of 10^7 & 10^8 organisms - administered intradermally in Balb/c mice. Similarly, live ICRC bacilli, live BCG and a mixture of heat-killed ICRC bacilli and live BCG were also used as vaccines. FPE response to lepromin and ICRC-in and other antigen preparations was measured at 28 days. All the immunizing antigens showed good sensitization against lepromin and better to ICRC-in.

This immunity could be adoptively transferred to normal recipients by sensitized spleenocytes, thus confirming the fact that the immune mechanism involved is cell-mediated. The administration of antigen by I.V. route induced a state of tolerance mediated by suppressor cells, which, when injected to preimmunized mice, suppressed the immune response. We have confirmed the fact that the mouse FPE system provides a good method for testing the potency of an antileprosy vaccine.

II/118(T) ANALYSIS OF SDS EXTRACTS OF *M. LEPRAE, M. VACCAE,* $H_{37}Rv$ AND BCG FOR IMMUNOLOGICAL REACTIVITY WITH HUMAN AND RABBIT SERA.

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Studies were carried out with SDS extracts of whole *M. leprae* (human biopsy derived), *M. vaccae*, $H_{37}Rv$ and BCG to characterize the antigens reacting with different rabbit and human sera. The extracts were analysed by SDS-polyacrylamide gel electrophoresis (SDA-PAGE) and silver staining. The fractionated components were taken on nitrocellulose sheets by the standard procedure of immunoblotting and reacted with different sera followed by 125_I labelled anti-human and anti-rabbit antibodies. With rabbit anti-*M. leprae* serum, *M. leprae* extracts gave one band each at 12-14K and 35K. Pooled sera from lepromatous patients showed a similar reactivity. However, immune complexes separated from sera of lepromatous leprosy patients with 3.5% polyethyleneglycol, when examined by immunoblotting technique, gave 3 bands at 67K, 55K and 22K. One of the bands was unique to leprosy patients and not seen with normal human sera.

II/119(T) REASONS FOR AND CARRYING OUT OF AN ANTILEPROSY PROPHYLAXIS STUDY WITH PURIFIED *M. LEPRAE* FROM ARMADILLO LEPROMIN AND *M. BOVIS* (BCG).

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1. Lepromin test expresses the degree of resistance to *M. leprae* and from negative in new borns, it grows gradually positive in healthy individuals whether in endemic area (our figures - 36.2%) or not (70.3%). In negative healthy individuals, it turns: weakly positive (73%) after retesting; strongly positive (71.4%) after BCG vaccination, but is mostly short-lived; intensely positive (96.1%) with post lepromin scar - p.l.s - (71.4%) after associated antigens vaccination and long (in our research

   already exceeding three years in two cases, showing on each retesting p.l.s., whereas in control case it is negative).

2. If after vaccination with the two associated antigens, the control case changes giving p.l.s. which appears in each retesting, we may think that we have obtained specific and lasting conversion against *M. leprae*. If in a small area of high endemicity, checked with prevalence and incidence indices, we find that those who become p.l.s. positive will show fewer leprosy cases, and of hypoergic form in comparison with non-converted individuals (our study is developing in three villages), it may be considered that a larger scale study be advised. We hope to obtain safe prophylaxis against either leprosy or tuberculosis; it is easy to carry out, and may be applied to infants with a more purified leprosy antigen.

II/120(T) EFFECT OF HEATING ON THE DELAYED TYPE OF HYPERSENSITIVITY (DTH) SKIN REACTION ELICITED BY MYCOBACTERIAL ANTIGENS

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Lepromins of human origin (Lepromin-H) whether it is a Mitsuda or Dharmendra type are generally prepared after heating (boiling or autoclaving) the leproma and *M.leprae* suspension. Recently, two more skin test antigens, lepromin-A and leprosin-A have been prepared from*M.leprae* purified from infected armadillo tissue. In these preparations *M. leprae* is rendered non-viable by Co 60 radiation. The whole idea of exposing the leproma to irradiation rather than to heating is probably for keeping the nature of the antigen unchanged. The present study has been conducted to find out the effect of heating on the quality of immunoprecipitin reaction and on the *in vivo* DTH skin reaction with *M. leprae* antigens. Furthermore, similar studies were conducted with other mycobacterial antigens in experimental animals. An affinity purified antigen of *M. leprae*, MY1 was also included for skin testing.

All these studies have clearly shown that although the number of lines of

immunoprecipitin reactions are reduced after heating of the antigens, the DTH skin reactions are significantly enhanced.

The significance of these observations will be discussed.

II/121(T) ORAL ZINC SULFATE AS AN IMMUNOSTIMULANT IN MULTIBACILLARY LEPROSY

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Oral zinc sulfate in dosage of 220 mg/day was tried in fifteen cases of multibacillary leprosy (7 LLp, 6 LLs, 2BL), as an immunostimulant in addition to conventional antileprosy drugs (Group I) and compared with ten similar cases (6 LLp, 3 LLs, 1 BL) treated with dapsone alone (Group II). All cases were subjected to clinical, bacteriological and histopathological assessment periodically up to 24 months. Cases treated with zinc showed faster clinical improvement, regrowth of eye brows, rapid fall in bacteriological index in skin smears and skin biopsies (B I & BIG). Histopathologically, decrease in granuloma size was nearly similar in both groups but there was early and greater influx of lymphocytes (also in clumps) and neovascularization in granuloma in group I. Upgrading occurred in 6/15 cases (4 LLs, 2 BL) in group I while only one (BL) in group II. Lepromin test became positive after 18 months in 5/6 in group I and one in group II who showed upgrading. No conversion was observed in LLp. The incidence of ENL was low in group I and when seen, it was mild in severity. Serum zinc levels were low (77.2±7.6 ug/100 ml) in all cases before commencement of therapy. At the end of 18 months, zinc levels touched normal (113.5±5.2 ug/100 ml) in group I, while remained low (80.0±5.0 ug/100 ml) in group II.

II/122(T) THE FATE OF *M. LEPRAE* IN MACROPHAGES

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M. leprae continues to elude successful *in vitro* cultivation and the demonstration of growth of this organism depends upon experimental infection in animals. *M. leprae* is normally an intracellular organism being found commonly in macrophages and it has been shown to grow well in the athymic nude mouse, the athymic nude rat and the armadillo. Macrophages from these animals were infected *in vitro* with *M. leprae*, thus focussing our efforts upon cells from donor species that have been shown to develop lepromatous infection. Emphasis was placed upon maintenance of cultures for longer periods than hitherto reported. Fourteen out of a total 36 cultures showed an increase in counts at the end of culture periods of upto 200 days. Examination of cultures infected with live or killed *M. leprae* showed no difference between rates of clearance. Viability of *M. leprae* after various periods of *in vitro* intracellular existence was estimated by the proportional bactericidal method.

II/123(T) ANTIBODIES AGAINST *M. LEPRAE* SEARCHES IN CEREBROSPINAL FLUID OF LEPROSY PATIENTS

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In a preceding study developed in collaboration with the Institute of Nervous and Mental diseases of Catholic University of Rome where the clinical samples were processed, cerebrospinal fluid (CFS), blood serum IgG and albumins of 17 Somali leprosy patients - from Forlanini Hospital Centre, Mogadishu - were examined by means of radiol immunodiffusion. Patients of both sexes and various ages have had the disease for a minimum of 7 months and a maximum of 20 years.

The CSF IgG/albumin ratio was found above the range of normality in all patients, but only 7 patients showed an increase of the quotient $\frac{\text{CSF IgG}}{\text{serum IgG}} : \frac{\text{CSF albumin}}{\text{serum albumin}}$, as a sign of direct synthesis of IgG within the central nervous system. These abnormalities were not related to sex, age, duration or type of leprosy.

Since specific techniques were not available for detection of antibody towards leprosy or other previous or concurrent diseases, in the present study we apply enzyme-linked immuno-sorbent assay (ELISA) to research CSF antibodies against *M. leprae* and their relation to those in serum.

II/124(T) SYPHILIS SEROLOGY IN LEPROSY PATIENTS IN ZAMBIA

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It is generally accepted that there is a higher than normal biological false positive rate in the non-specific reagin tests for syphilis among leprosy patients. In addition syphilis has been found to be more common among leprosy patients in several reported studies, although none from Africa. Zambia has a higher than normal prevalence of syphilis, and the RPR test has been considered to be both sensitive and specific. In a pilot study using serum from 50 randomly selected patients from Liteta Leprosarium, Zambia, RPR, TPHA and FTA-ABS tests were carried out which indicated that 34% of these patients were strongly suspected of having or having had syphilis. There were no false positive RPR tests.

II/125(T) REACTION OF CHARACTERISTIC PHENOLIC GLYCOLIPIDS ISOLATED FROM *M. LEPRAE, M. VACCAE* BCG AND H_{37}RA WITH SERA FROM PATIENTS WITH LEPROMATOUS LEPROSY AND TUBERCULOSIS

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We have studied the immunological reactivity of characteristic phenolic glycolipids isolated from *M. leprae, M. vaccae*, BCG and H_{37}Ra with individual as well as pooled sera from normal healthy human beings and from patients with lepromatous leprosy and tuberculosis, using enzyme-linked immunosorbent assay (ELISA). *M. leprae* was obtained from human biopsy, and *M. vaccae*, BCG and H_{37}Ra were grown in Middlebrook's medium. The phenolic glycolipids were isolated by extraction of bacteria or *M. leprae* infected tissue with chloroform methanol mixture (2:1, V/V) followed by silicic acid chromatography and then purified by preparative TLC. The phenolic glycolipids were characterised by ^{1}H NMR. Appropriate dilutions of different sera were reacted with the phenolic glycolipids coated on to polyvinyl chloride plates and ELISA was done using Protein A-HRPO conjugate.

Under these conditions, with phenolic glycolipids from *M. leprae* and *M. vaccae*, the individual sera from lepromatous leprosy and tuberculosis patients gave very similar scatter in absorption values and with phenolic glycolipids from BCG and H_{37}Ra, the individual sera from tuberculosis patients gave higher scatter in absorption values than the sera from lepromatous leprosy patients.

II/126(T) FURTHER DATA SUGGESTING A CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT IN IMMUNOPATHOLOGY OF LEPROSY

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Cerebrospinal fluid (CSF) and serum albumin, IgG, IgA, and IgM of 17 patients affected with lepromatous (7), tuberculoid (7) and borderline (3) leprosy were examined by means of radiol immunodiffusion. Serum albumin was abnormally low in most patients, while IgG, IgA and IgM were abnormally high in most patients. The blood-brain barrier, when examined by means of the CSF albumin/serum albumin $\times 10^3$ ratio, was shown to be normal in almost all patients. CSF IgG was higher than normal in 82% of subjects, and IgA was similarly altered. IgM was not detectable in the CSF by this method. The IgG/albumin ratio and the IgA/albumin ratio were found constantly increased in the CSF of all patients but one for the IgA. The local production indices were higher than normal in nine patients for the IgG (53%) and in 15 patients for the IgA (88%) as a sign of local synthesis of IgG and IgA within the CNS.

Furthermore, the isoelectric focussing of the CSF samples in a pH range 3.5-9.5 showed numerous oligoclonal bands in the area of migration of the immunoglobulins.

These data, suggesting a local production of immunoglobulins within the CNS of patients with the three forms of leprosy, may give an explanation of what we have already demonstrated about the presence of clinical signs of CNS lesion in the 24% of patients with leprosy. It is too early to argue which kind of alterations leprosy may induce in the CNS; nevertheless, it is important to stress that the CNS is involved in an immunopathological process in the same manner as that which has been suggested for the peripheral nervous system.

II/127(T) A STUDY ON CELL-MEDIATED IMMUNE RESPONSE IN LEPROSY

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Cell-mediated immune response was studied in 70 leprosy patients whose leprosy was confirmed clinically, histologically and bateriologically and in 40 control cases using a battery of *in vivo* and *in vitro* tests. Leprosy cases were grouped and classified into TT, BT, BL and LL types (Ridley and Jopling, 1966). Cellular immunity was studied by using recall antigens PPD, DNCB and Candida for *in vivo* tests and E-rosette test and lymphocyte transformation test (LTT) for *in vitro* study.

Cell-mediated immunity was found to be significantly depressed in all the cases of leprosy. In follow-up (after treatment) cases, highly significant improvement in immune status was observed with *in vitro* tests although *in vivo* tests do not show significant correlations.

II/128(T) EVALUATION OF AN *M. LEPRAE* ELISA

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We developed a sensitive assay for detecting small amounts of *M. leprae* antibody, as might be present in subclinical or paucibacillary leprosy. Sonicated, irraiated *M. leprae* was passively absorbed to polystyrene microtiter plates (125ug protein/well). Serum dilutions were assayed by indirect ELISA using antihuman IgG alkaline phosphatase conjugate. A titer ≥ 1:2000 was designated positive since 95% of sera from healthy Thai (10) and US (10) adults had titers < 1:2000. In each assay, serum from a healthy US-born baby had titers ≤1:100. All active LL patients (11/11) were seropositive; titers ranged from 1:3000 - 1:870,000 ((median 1:22,000). For other leprosy patients, the seropositivity rates and median titers were: LL, inactive 95% (18/19), 1:10,000; BL+BB 83% (15/18), 1:5,000; BT+TT, 60% (37/54), 1:4,000. Healthy household contacts had median titers of 1:1,000 and 29% (22/77) were seropositive. Tuberculosis patients were also seropositive (5/6); titers ranged from 1:300-1:91,000 with a median of 1:5,000. LL sera cross-reacted with sonicates of 7 other mycobacterial species. This ELISA is very sensitive, but not specific for leprosy or for *M. leprae* antigens. This *M. leprae* ELISA could be used for screening monoclonal antibodies. Combined with more specific assays, the ELISA may be clinically useful as well.

II/129(T) COMPLEMENT ACTIVATION IN LEPROSY

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Recently, serum complement activation in leprosy patients has been an important subject of study, since the development of some of the pathological lesions in lepromatous patients with ENL is reported to be related to it.Altered complement component profile, raised C_3d and Ba levels in serum in the lepromatous patients suggest that there is significant activation of the complement cascade in the lepromatous patients and the activation process may thus take place via both the classical pathway and alternative pathway. In the present study,attempts were made to find out whether the bacterial proteins played any role in complement activation. PEG precipitate obtained from leprosy serum by precipitating with polyethylene glycol (PEG) was found to be significantly anti-complementary. The supernatnant obtained after PEG precipitation was also tested and it exhibited anti-complementary activity. But the former was observed to be much more anti-complementary than the latter on total protein content basis. It is possible that soluble mycobacterial proteins may also contribute to the activation of complement system in the affected individuals.

II/130(T) DETECTION OF ANTIBODIES AGAINST ARABINOMANNANS IN PATIENTS WITH LEPROSY OR TUBERCULOSIS BY AN ENZYME IMMUNOASSAY

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Arabinomannans constitute an abundant antigenic material of the mycobacterial cell wall.Detection of antibodies against these components may serve as a tool for the diagnosis of leprosy. With this aim in view,arabinomannans have been purified from *M. smegmatis* which are cross-reactive with *M. leprae*. Using the pure arabinomannan as the test antigen in an ELISA system, the reactivity of the sera from normal human subjects (40), lepromatous leprosy (LL, 20 cases) and tuberculosis patients (40) was tested at a dilution of 1:100. The man titers of LL patients sera were significantly higher than either tuberculosis patients or normals.This test may be of use for the detection of cases of leprosy.

II/131(T) ANTIGENICITY OF ICRC STRAINS AND ITS RELATION TO A POSSIBLE *M. LEPRAE* SPECIFIC ANTIGEN.

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The ICRC strain C-44 was chosen for the preparation of an antileprosy vaccine on the basis of high concordance of Mitsuda reactivity between lepromin and ICRC in both LL & TT patients. Administration of the C-44 vaccine to lepromatous patients showed that all the patients tested were ICRC- in positive but only 60% converted to lepromin positivity. Of these converted LL patients, a few exhibited reversal reaction within 4 months with bacterial clearance. Two years later, one patient reverted to Mitsuda negativity and developed new lesions with BI 5+. A culture isolate obtained from new lesion - strain C-75-was compared with the vaccine strain C-44-as whole bacillary preparations.

We used LMI in a mouse splenocyte system sensitised with strain C-44 and strain C-75, and also human blood samples, to study cross reactivity. The results showed that both react with lepromin (A) but do not show cross-reactivity against each other. Human individuals sensitised with C-44 show no reaction with strain C-75. The results are unusual in the context of the origin of strain C-75 from 'persister' *M. leprae* and strongly indicate that the ICRC strains express *M. leprae* specific antigens. The striking implication is that *M. leprae* with different antigen determinants may exist and could be detected by LMI system. The ICRC strains with *M. leprae* specificity are thus distinct from other cultivable mycobacteria.

II/132(T) IMMUNOLOGICAL PROFILE IN LEPROSY AND ITS REACTION

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Humoral and cell-mediated immunity was studied in 72 cases of different types of leprosy and 20 normal healthy controls. IgG and IgM levels were found in significantly higher amounts in all cases of leprosy and during reaction (E N L type), while IgA levels were raised only in borderline lepromatous leprosy (BL), lepromatous leprosy (LL) and lepromatous leprosy with ENL reaction. The levels of all immunoglobulins were decreased significantly after the reaction had subsided. The significant low counts of total T cells and high counts of B cells were noticed in B L, L L and L L with ENL reaction (during and after reaction).

II/133(T) SIGNIFICANCE OF BLOOD GROUP ANTIBODY TITRE IN THE STUDY OF LEPROSY, TUBERCULOSIS AND OTHER CHRONIC DISEASES COMPARED WITH ANIMALS

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179 blood samples were estimated for blood group antibody titre through serial dilutions of 36 cases of leprosy, 4 leprosy contacts, 32 tuberculosis, 23 filariasis, 1 tuberculoma, 4 rabbits, 2 guinea pigs and 4 albino mice were compared with 73 normals. To get "O" group distribution, an indirect method of a single rabbit's cells against human serum was used throughout the study.

Data for the classification of leprosy, LL & BL towards lower titre, and TT & BT towards higher titre in all the groups are highly significant.

When this is compared with normals as "A" levels are low - LL and BL, as "B" levels are high - TT and BT, as "AB" levels are in average - BB and as "O" levels are distributed in all levels any type of leprosy can occur. In filarias,"O" is low, "A" is high and a slight increase of "B" & "AB" is significant. In tuberculosis, there is an average increase of "O","A", "B" and a significant increase of "AB" observed.

Either there is one gap, equal or reverse ratios of "A" & "B" among "AB" groups found in the said disease, unlike in normals and animals, shows adjacent increased ratio from "A" towards "B". All the investigated animals were "AB" groups, but the ratios were below the human lowest levels.

Blood group antibody titre to be used as a parameter in detecting subclinical phase of the above said diseases, in classifying leprosy, in the study of leprosy pathogenicity, and the possibility of blood group antigen antibody pre-determining the diseases are discussed.

II/134(T) LONGITUDINAL STUDIES OF CIRCULATING IMMUNE COMPLEXES IN LEPROSY

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Association between immune complexes and ENL was demonstrated by many approaches but results were conflicting. Longitudinal studies of immune complexes in ENL were made in 23 patients with ENL. Clq binding test, conglutinin binding test and plasma C3d quantitation were made at two month intervals for 6-24 months. Ten lepromatous leprosy without ENL and six tuberculoid leprosy served as controls. Association between increased Clq binding test and the episode of ENL was observed in 11 out of 23 patients studied. Association between conglutinin binding titers and ENL was observed in five out of 14 ENL patients. Increased plasma C3d was found associated with ENL in ten out of 18 patients studied. ENL is definitely associated with the process of immune complex formation but absence of such association in many patients needs explanation. Similar studies at weekly intervals with better control are now being undertaken.

SESSION III

TREATMENT (A)

Chairman: Bechelli, L.M.

Rapporteur: Adiga, R.B.

TUESDAY, 21ST FEBRUARY, 1984

Auditorium 08.30–12.00

Abstracts

A* : 135-153

TREATMENT (B)

Chairman: Grosset, J.

Rapporteur: Abreu, A.

TUESDAY, 21ST FEBRUARY, 1984

Auditorium 13.00-16.30

Abstracts

A* : 154-171
P* : 172-197
T* : 198-206

*A : accepted for reading
*P : for poster presentation.
*T : for title reading.

III/135(A) CURRENT STATUS OF THE THELEP PROGRAMME

L. Levy, J.Grosset, S.K. Noordeen and H. Sansarricq
Hebrew University-Hadassah Medical School, Jerusalem, Israel

Since the Mexico Congress, the THELEP programme has made gratifying progress towards its goal of improved chemotherapy for leprosy control. Important information has resulted from surveys of the prevalence of dapsone resistance. In several countries, the prevalence of secondary resistance approaches 10 per 100 patients at risk. The prevalence of primary dapsone resistance has been found in areas of two countries to be greater than 30 per 100. In fact, dapsone resistance appears to be universal, and no further surveys are required.

Research designed to yield better treatment by existing drugs has been undertaken in the form of clinical and field trials of combined drug regimens.New information can be acquired only slowly. However, the generally poor compliance of patients with self-administered treatment has been demonstrated conclusively, leading THELEP to propose combined regimens based on the intermittent, fully supervisable administration of drugs.

Finally, the possibilities for developing useful new drugs based on compounds already known to be active against *M. leprae* or *M. tuberculosis* have been explored, with generally disappointing results. Therefore THELEP has embarked on an intensified programme of research into the basic physiology of *M. leprae*.

III/136(A) CLOFAZIMINE (LAMPRENE; B663) IN THE TREATMENT OF LEPROSY IN HONG KONG: A REVIEW OF 400 PATIENTS - 1966–1983

Norman R.
Medical and Health Department, Lee Gardens, Hong Kong.

Clofazimine was first used in the treatment of leprosy in Hong Kong in 1966 and during the past 17 years, 400 patients have received this drug, either for the treatment of the bacillary infection or for the control of adverse immunological reactions. From 1966-1970, it was used in selected patients together with dapsone, but from 1970 onwards, it was given with dapsone to multi-bacillary cases from the outset and also to selected paucibacillary cases, particularly if they were in reaction on presentation.From 1980, clofazimine has been used with dapsone and rifampicin in a triple drug regimen as recommended by WHO. A few patients with intolerance to dapsone (mainly manifested as dermatitis) have had monotherapy with clofazimine. Whether used alone, or with dapsone, or with dapsone and rifampicin, there have been virtually no significant adverse effects attributable to this drug, and although skin and lesional pigmentation have been obvious in many cases, this has not interfered with the acceptance and enthusiasm of patients for clofazimine except in a few cases. On clinical and bacteriological grounds, no evidence of clofazimine resistance has come to light so far.Since the first use of clofazimine for selected cases in 1966 and its routine use for new multibacillary cases from 1970, there have been some cases of dapsone resistance, diagnosed mainly on clinical and bacteriological grounds; this problem is not increasing and - on present evidence - poses no threat to the progress of leprosy control in the colony. From a retrospective examination of the records of previously treated cases and of those recently and currently on clofazimine, there is no evidence that any case has relapsed during the study period of 17 years.In this group of 400 patients in Hong Kong, it may be concluded that this drug has been (1) outstandingly successful in the treatment of the bacterial infection and the control of reactions, (2) well tolerated and accepted by the vast majority of patients and (3) singularly devoid of side-effects.

III/137(A) A RETROSPECTIVE SURVEY OF THE TOLERABILITY OF CLOFAZIMINE IN PATIENTS WITH BACILLIFEROUS LEPROSY

M. Zimmerli -Ning and W.Vischer.
Ciba-Geigy Limited, Basle, Switzerland

Because of dapsone-resistance and the expected wider use of clofazimine, more data on its tolerability were needed. To this end we undertook the present retrospective survey with the co-operation of ILEP in 1980/1981 by means of paired questionnaires on side effects. Data on 2034 patients with and 4261 patients without ENL reactions were obtained from 31 institutions. The dosage was 10 mg or less per day in 82% of patients. The duration of treatment varied between 6 months to 6 years.

Skin discolouration/pigmentation was almost uniformly observed and dose related in lighter skinned patients. Ichthyosis and pruritis were seen in 10-20% and 1% respectively.Conjunctival pigmentation occurred in from 0.4% to 19.5% with increasing dosage.Corneal pigmentation was much lower. Impaired vision, some with night-blindness, occurred only in patients with ocular pigmentation, in less than 1% of the total.No patient discontinued clofazimine because of ocular effects. Abdominal pain and diarrhoea occurred in 1% on 300 mg or less weekly and in 3-5% on 100 mg daily; diarrhoea occurred in 9% on 300 mg daily for ENL reactions with onset within 4 weeks.

This survey shows that skin and conjunctival pigmentation, abdominal pain and diarrhoea are dosage-related phenomena. Contrary to previous reports, no serious gastrointestinal side-effects have been observed. Thus when used at lower dosage, serious gastrointestinal side-effects can be avoided.

III/138(A) A FOLLOW-UP INVESTIGATION OF THE 'MALTA PROJECT'

W.H. Jopling; M. J.Ridley; E. Bonnici and G. Depasquale
Hospital for Tropical Diseases, London, England

This is a report on a follow-up investigation of 122 multi-bacillary patients from Professor Freerksen's 'Malta Project'. All had received multidrug therapy (MDT) consisting of daily treatment with rifampicin 600 mg and two tablets of Isoprodian,each tablet consisting of 500 mg dapsone, 175 mg prothionamide and 175 mg isoniazid. The majority of patients began MDT in June 1972, the minority subsequently, and length of treatment varied between 5 months and 6 years.

Results: One case of clinical jaundice was recorded, treatment being resumed after 4 months. In the remainder, side effects were mild or absent. On clinical examination no signs of relapse were seen, and 6 skin smears from each patient revealed only granular bacilli in 26 patients, in some cases 10 or more years after beginning MDT. Scanty solid-staining bacilli were found in 9 patients; in 3 there were granular forms in addition, but in 6 the solid-staining forms were the only ones found. The two smears from the dorsa of fingers gave maximal information, for fingers were the only sites containing solid-staining bacilli in 7 patients.

These and other findings, together with their implications, are discussed in the paper.

III/139(A) COMPARATIVE STUDY OF TWO REGIMENS OF COMBINED CHEMOTHERAPY OF ONE YEAR DURATION IN MULTIBACILLARY LEPROSY

Pattyn S.R., Saint Andre P., Ferracci C., Bacquillon G.
Institute Tropische Geneeskunde , Antwerpen, Belgium.

Two groups of multibacillary patients were treated for one year with one of two combined regimens: (A) rifampicin 600 mg twice weekly for 6 months, dapsone 100 mg daily for one year (B) the same with prothionamide 500 mg daily added during the first 6 months.

Follow-up was for 5 and 4.5 years on 15 and 14 patients respectively without any evidence of relapse. Clinical and bacteriological improvement was identical in both groups as were the number of ENL episodes. No toxic effects were observed in this small number of patients. The trial shows that 6 months twice weekly 600 mg rifampicin followed by 6 months dapsone daily, cured MB leprosy without relapse in 29 patients, with a confidence limit of 12%.

As a result of the widespread occurrence of dapsone resistance that became apparent since the initiation of the study, the two drug combination rifampicin-dapsone should be reinforced by the addition of clofazimine and probably ethio– or prothionamide.

III/140(A) EXPERIENCE WITH RIFAMPICIN CONTAINING REGIMENS.

M. Aschhoff, P.P. Irudayaraj and J. Jayakumar
St. Thomas Hospital & Leprosy Centre, Chettupattu, , Tamil Nadu, India

This paper reports our experience of 146 patients in whom six rifampicin (RFMP) containing regimens had been used. The patients have been followed up for varying periods up to six years. All patients received T.Isoprodian (INH 175 mg. + prothionamide 175 mg + dapsone 50mg) and the regimens differed only in the duration/mode of RFMP. Rifampicin was given as single dose (6 patients), daily for 7 days (28 patients), daily for 1-5 months (30 patients), daily for 6-12 months (24 patients), daily for 13-30 months (18 patients), pulsed RFMP for 20-55 months along with inj. acedapsone (40 patients).

In all groups except the last one, there was progressive reduction in the B.I over the years.This was more pronounced in groups receiving RFMP for long periods.However, this could have been due to excessive number of patients with low B.I in these groups. When initial B.I. levels were taken into consideration, it was found that the results were similar in all regi mens. No serious adverse effects and no relapses have been encountered.

III/141(A) MULTIDRUG THERAPY FOR MULTI-BACILLARY CASES IN WARDHA DISTRICT (MAHARASHTRA), INDIA

M.S. Nilakanta Rao and M.V. Yellapurkar.
W.H.O. Consultant to the Government of India.

The W.H.O. in 1976 and the Sushila Nayar Committee in 1978 recommended the use of multiple drugs for multibacillary cases of leprosy. The latter committee selected ten hyperendemic districts in different parts of India for the initial trial.The main objectives were: (1) to interrupt transmission and thus hasten leprosy control and (2) to study operational feasibility and replicability in a large area.

The multidrug regimen project was begun in Wardha District by the Government of India with the active assistance of the State Government, the W.H.O. and the Swedish International Development Authority. Out of 2056 positive cases (distributed in 543 villages and 4 towns) in a population of 920,000,. 1618 were still positive in 1981. These patients were initially screened; and 1509 cases and an additional 158 detected in the early stages of the project, were put on an initial three weeks course of daily rifampicin and dapsone; later, they were given INH, thiacetazone and dapsone daily and pulse rifampicin.This combination was continued for one year with some modifications in some patients. Further treatment is continuing.

During the 18 months from October 1981 to March 1983, 637 new multibacillary cases were detected and were put on combination therapy, as recommended by W.H.O. During this period, a sample survey (and a re-survey in the same population, one year later) was done; and an attempt was made to discover the extent of dapsone resistance.

Detailed results will be presented in this paper.

III/142(A) MULTI DRUG THERAPY IN THE FIELD, PHILADELPHIA LEPROSY HOSPITAL, SALUR

M.N. Casabianca
The Leprosy Mission, New Delhi, India

Though much information is available on MDT organising, it poses a challenge to the field staff due to limited field trials conducted and varied field conditions. Following the Government's instructions, MDT has been started for bacteriologically positive cases which numbered 200, out of 2000 at Salur. An initial period of treatment for 14 days with rifampicin, lamprene and dapsone followed by the WHO recommended regimen is being given.As the programme is first of its kind in India, we had apprehensions to organise it for 200 patients who are dispersed over an area of 1000 sq.km. In the preparatory phase, the patients were screened and selected patients, their families and public were educated about MDT. Contrary to our fear at the beginning, the programme went on so well that it is exciting. The patients took so much interest that each day, they were waiting with tumblers of water to swallow the drugs. 95% of the 200 patients had treatment consecutively for 14 days and later 95% of the patients are taking pulse therapy on the scheduled day. So far, only 3% of them had any complications of which Type-II reaction was the commonest.

III/143(A) MULTIDRUG THERAPY FOR MULTIBACILLARY LEPROSY – EXPERIENCE IN BOMBAY

Ganapati R., Revankar C.R. and Gawade P.B.
Bombay Leprosy Project, Bombay, India

To study the feasibility of supervised administration of triple drugs to multi-bacillary leprosy patients under urban field conditions and to judge the efficacy of currently recommended combinations,a scheme was undertaken in Bombay. 793 active multibacillary cases attending treatment centres in slums, general dispensaries and hospitls were included.

New record systems viz. "pulse therapy book" – maintained in the clinics, "due date card" issued to the patient and "agreement" signed by the patient were introduced to monitor regularity.

During the initial daily rifampicin therapy for 21 days (Indian Association of Leprologists 1982), 377 (87%) out of 435 were regular for supervised administration indicating excellent compliance.

Another group of 429 patients were put on direct pulse therapy (WHO• 1982).

Out of the 793 (both the groups), 536 (68%) were regular for pulse therapy; 13% had to be given domiciliary therapy to maintain regularity.

No significant difference was observed in regularity amongst patients attending centres situated in the slums, general dispensaries and hospitals. Findings of clinical and bacteriological (especially those up to BI 2+) changes will be discussed; and further observations on attendance performance over one and a half years of follow up will be presented.

The study showed that multidrug therapy can be practised under urban conditions with better compliance rate than with dapsone monotherapy.

III/144(A) HEPATOXICITY OF THE DAILY THREE DRUG COMBINATION DAPSONE, RIFAMPICIN AND THIOAMIDE.

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From January 1980 to September 1982, 54 cases of multibacillary leprosy, either new or relapsed cases,were treated daily for two years with 600 mg rifampicin plus 100 mg dapsone, supplemented during the first year with 500 mg thioamide (ethionamide or prothionamide). During the same period, 109 new cases of paucibacillary leprosy were treated daily for six months with rifampicin plus dapsone. A 13% incidence of hepatitis was observed in the multibacillary cases, but none in the paucibacillary cases. Symptoms were jaundice in five cases and nausea plus vomiting, associated with significant increase of transaminase levels in two cases. In five cases, the symptoms appeared during the first two months of therapy and in two later. Hepatitis was not related to viral infection and was not apparently influenced by age, sex, weight or the length of leprosy history. As thioamide was held responsible for hepatitis, it was decided to reduce the daily dose of thioamide to 5 mg/kg for all cases of multibacillary leprosy treated since September 1982.

III/145(A) PRELIMINARY REPORT ON MULTIDRUG THERAPY IN BHUTAN

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The Leprosy Mission, Bhutan

This is a longitudinal study of treatment results under field conditions in an area where dapsone therapy was introduced in the late sixties. In 1979, rifampicin was introduced as an initial one month course, followed by dapsone alone. In October, 1982, MDT according to WHO recommendations was started in 3 selected blocks.

The purpose of this study is to evaluate the rifampicin and dapsone therapy and to compare it with the results of MDT. Evaluation criteria are BI, number, MB rate and child ratio of newly detected cases.

Comparison between the two regimens is based on the results of 1½ years MDT in, 3 blocks compared to the results of conventional treatment in 3 comparable blocks.

Evaluation of rifampicin and dapsone therapy:

BI after two years: Neg. in 50.5%, improved in 26.6%, remained neg. in 16.4%

Stationary or worse in 6.5%

The reservoir of infection in the population is markedly reduced. However, in a few cases dapsone resistance may have developed.

MDT: Exact results are not yet availabrle, but will be known in 8 months. Indications are even now that MDT is an improvement over rifampicin and dapsone.

III/146(A) HEPATOTOXICITY OF THE COMBINATION OF RIFAMPICIN–ETHIONAMIDE IN THE TREATMENT OF MULTIBACILLARY LEPROSY

Groenen G., Pattyn S.R., Janssens L., Bourland J., Saylan T., Davies E., Grillone S., Ferracci C. and the Collaborative study Group for Treatment of Leprosy
Leprosy laboratory, Institute for Tropical Medcine, Antwerpern, Belgium

During treatment of multibacillary leprosy with the combination rifampicin (RMP) 600 mg, ethionamide (ENJ) 500 mg and either dapsone (DDS) or clofazimine (CLO) 100 mg, hepatotoxicity was observed in 4.5% of 596 patients. Hepatitis appeared after 5 to 186 days, with a mean of 93 days and a median of 76 days. Mortality was 26%

In all regimens ETH and DDS or CLO were administered daily. RMP was given either daily or daily during the first 2 weeks or 8 weeks, followed by a once weekly dose. It is concluded that the association RMP–ETH is the toxic component. In some patient groups, there was a high correlation of toxicity with age. Administration of RMP twice a week during 3 months was not accompanied by hepatotoxicity. Future studies should show if reduction of the daily dose of ETH or reduction of the duration of the administration of RMP-ETH might reduce the incidence of hepatotoxicity, while conserving the efficacy.

III/147(A) THE HEPATOXICITY OF COMBINED THERAPY FOR LEPROSY

Chen JK, Wang CM, Xia G, Ji BH
Shanghai Zeng Yi Hospital, China

Eighty-nine leprosy patients, 39 in Hai-an Leprosy Hospital and 50 in Shanghai Zeng Yi Hospital, were treated with combined therapy. The patients of Hai-an were divided into three subgroups: (A) dapsone 100 mg and prothionamide (PTH) 300 mg daily, isopiperazinylrifamycin SV (R-76-1) 300 mg on each of the initial two consecutive days and then once monthly; (B) dapsone 100 mg and PTH 300 mg daily, R-76-1 300 mg on each of the initial 14 days and then 600 mg oncemonthly; (C) PTH 300 or 500 mg daily as monotherapy on initial 90 days and then supplemented with R-76-1 300 mg on two consecutive days every month. The patients in the Shanghai group were treated with dapsone 100 mg and PTH 300 mg daily, rifampicin (RMP) 900 mg PTH 500 mg and Clofazimine (CLO) 300 mg once monthly. Liver damage had been observed in both groups after combined therapy, after one to four months. The incidence rate of liver damage was 56.6% in the Hai-an group and 22% in the Shanghai group. Fatalities due to acute yellow atrophy of liver had been observed in 2 patients, one in each institute, after three or four months treatment. The real cause of the liver damage has not been identified. The possibility is that of PTH. The necessity of testing liver function monthly in the initial 6-month course of combined therapy, particularly in those regimens containing PTH, is stressed.

III/148(A) INTRODUCTION OF PULSE THERAPY IN LEPROSY CONTROL PROGRAMME

P.D. Samson, M.V. Yellapurkar, S.M. Parkhe
The Leprosy Mission, Miraj, India

There is an increasing emergent fear of dapsone resistance among leprosy patients all over the world. The Multi-Drug Therapy overcomes this resistance and prevents transmission of the disease.

The Kawathe Mahankal and Miraj Talukas in Sangli District, Maharashtra State, were selected for Pulse Therapy Programme - The Leprosy Control unit in this area covers a population of 233, 294, scattered in 65 villages and in one Miraj Urban area.

A special one-week training course was arranged for Para-Medical Workers and non-medical supervisors. Ten key indicators were set to assess the operational efficiency during the preparatory period.

As a result, the drug compliance reached over 90%. All leprosy patients were bacteriologically screened and clinically assessed. Deformities were graded according to the WHO classification.

Active cases – 410 paucibacillary and 612 multibacillary – were brough under regular treatment. Drugs were given in the villages under regulai supervision of medical officers. The WHO recommended Pulse Therapy regimen is followed. Compliance by patients ranged from 95% to 97%. The Tiles Test was used to ascertain whether the patient had taken dapsone or not. Side effects were negligible.

III/149(A) TREATMENT OF 5000 PATIENTS WITH RIFAMPICIN AND HANSOLAR. A FIVE-YEAR CUBAN EXPERIENCE

Alfredo Abreu and Zobeida Lovio
Ministerio De Salud Publica, Cuba

The treatment of leprosy in Cuba consists of the controlled administration of rifampicin during the attack phase. The dose administered is 600 mgs. of rifampicin daily for a period of six months for positive patients and three months for negative patients.

During the consolidation phase, treatment of all clinical forms of the disease is carried out with Hansolar – intramuscular 225 mgs. (1.5 ml.) once a month.

This treatment was administered to all patients in both categories of the disease.

The treatment is administered by nursing staff at the primary health unit level, the polyclinic. At the beginning of the treatment in 1977, there was a total of 893 patients with a positive bacteriological index, representing 18.1% of the total prevalence. At the end of 1982, only 273 patients had a positive bacteriological index, representing 4.7% of the total prevalence.

5717 patients representing 98.6% are receiving treatment. Clinical improvement has been reported in 90.4% of the patients. Tables and graphs of incidence, clinical forms, bacteriological studies, clinical evolution, contacts examined and distribution of the disease in the country will be presented.

III/150(A) THE USE OF RIFAMPICIN IN THE REGULAR AND INTERMITTENT POLYTHERAPEUTIC TREATMENT OF LEPROSY PATIENTS

Jean Languillon
Ajaccio, France.

Rifampicin has proved highly bactericidal against *M. leprae* both in mice foot pads as well as in leprosy patients.

Following the appearances of the sulfone-resistance of *M. leprae* polytherapy has become essential, in both paucibacillary and multibacillary cases for an allergi form could be infected by a sulfone resistant *M. leprae*.

We are therefore using a polytherapeutic treatment that combines rifampicin, clofazimine and dapsone. With patients who can be temporarily hospitalised or those who are under regular treatment by our mobile units, we start with an emergency treatment i.e. 1200 mg of rifampicin once a month for 6 months (administered by a muse) + 50 mg of clofazimine every day for 6 months (provided to the patient) and 100 mg of dapsone every day for 6 months (also provided to the patient). The emergency treatment is followed by a consolidation treatment and then a maintenance dosage.

Unfortunately, in Africa, it is difficult to get regular treatment. Patients arriving from various regions in Senegal and in whom the disease was detected at our consultation centre in ILAD, spent several weeks in the urban zone of Dakar, before reaching their own home towns where they could receive regular treatment, and there was absolutely no question of giving them rifampicin for self administration.

With a view to making the leprosy patient non-contagious to his neighbours and family as quickly as possible, we used a single dose of 1500 mg of rifampicin, administered by a doctor; this was followed up by a daily dose - self-administered - of 100mg of dapsone.

The results, similar to those obtained by SHEPARD (1974) LEVY (1976) HOGERZEIL and REES (1975), showed a rapid disintegration of the *M. leprae* eliminated by the upper aero-digestive passages. We would therefore propose the classical treatment for control patients and an epidemiological treatment for patients undergoing irregular treatment.

III/151(A) INTERMITTENT ADMINISTRATION OF DIMOCIPHON RIFADIN, AND CLOFAZIMINE TO LEPROSY PATIENTS

T.S. Gnenuck, N.M.Goloschapov
Leprosy Research Institute, Astrakhan, USSR.

The results of intermittent administration of dimociphon (a new antileprosy drug, synthesized at the Institute of Organic and Physical Chemistry, the USSR Academy of Science) together with rifadin and clofazimine to 97 lepromatous leprosy patients with relapses and clinically proved dapsone-resistance are presented. 32 patients were treated with dimociphon (200 mg) and rifadin (300 mg) every other day; 31 patients were given dimociphon and Lamprene (100 mg) every other day; 34 patients received dimociphon (200 mg) rifadin and Lamprene in the same doses by turns. The therapy lasted 6 months. Drug tolerance was satisfactory; no side-effects were observed; functional state of liver, kidneys and peripheral blood showed no change. Clinical improvement was noted after 4-6 weeks from the beginning of therapy. Clinical, bacteriological and histological assessment of the patients after 6 months of therapy suggests effectiveness of intermittent regimens, which is especially high with administration of all three drugs. Out of 34 patients, 31 showed marked clinical improvement with regression of the histo-pathological changes. Significant decrease in histological (in averagely 50.2%) and bacterioscopic (6,1 times, $P < 0.05$) indices, and only a few ENL reactions (in 2 cases) were noted. The data obtained encourage the recommendation of an intermittent regimen with three drugs for large-scale therapy of leprosy patients who have relapsed or who have dapsone-resistant bacilli.

III/152(A) CLINICAL RESEARCHES OF TRIPTERYGIUM WILFERDII HOOK. F. (TWH) IN THE TREATMENT OF LEPROSY REACTION

Shao KW, Yang LH, Ye GY
Fujian Cooperative Research Group of TWH, Chinese Academy of Medical Sciences, China.

This is to report that TWH and its extracts "741" and "T11" have been used in treating 58 cases of type I leprosy reaction, in which 56 cases proved effective (96.6%); while in treating 303 cases of Type II leprosy reaction, it was effective in 297 cases (98%). After this medicinal herb is taken, the temperature will drop rapidly, the red swelling in the damaged skin and the erythema nodosum will disappear and neuralgia will be relieved. TWH syrup also has a good effect on the inflamed lymph nodes, arthritis, orchitis and iridocyclitis. The thalidomide group treated 113 cases of Type II reaction, among which 109 cases were effective (96.4%). By comparison of the results the two groups achieved in treating Type II leprosy reaction, there is no real difference, in symptomatic effects and erythrocyte sedimentation

rates. TWH syrup has side-effects in 36.2%, mainly symptoms of gastrointestinal irritation. But decrease in leucocytes is seldom found. As compared with the side-effects of 41.1% in the thalidomide group, some striking contrasts remain. Toxic experiments on acute, sub-acute and chronic cases show that the interior of TWH root is slightly toxic; therefore it is quite safe to administer this medicine. Various pharmacological experiments have shown that TWH has the property of disinfection and is thus antiepidemic which has given good results in treating leprosy reaction and has also provided some ethical evidence of its value.

III/153(A) LEPRA'S POLICY AND ACHIEVEMENTS IN MULTIPLE DRUG THERAPY IN MALAWI

N.M. Chitimba, F. Gjalt Boerrigter, B.D. Molesworth and R.J.W. Rees.
Balaka, Malawi

At the request of the Government of Malawi, LEPRA assumed responsibility for Leprosy Control in the Southern Region in 1965 and subsequently in virtually all parts of the Country.

Daily dapsone monotherapy was used until 1975, when Multiple Drug Therapy (M.D.T.) with daily dapsone and daily thiacetazone for all patients with positive skin smears was introduced. In January 1981, M.D.T. using daily dapsone and monthly rifampicin, occasionally in combination with clofazimine, was introduced for all lepromatous(LL, BL and BB) patients. During 1983, the full WHO recommendations for M.D.T. in all forms of leprosy were implemented.

From the 9 years' experience of M.D.T. for patients with multibacillary leprosy, data will be presented on the number of mouse footpad proven or clinically suspected cases of dapsone resistance which have been detected. Although the data are incomplete, the prevalence of dapsone resistance is probably considerably less than in countries where treatment has been based on dapsone monotherapy.

In terms of trained personnel,laboratory facilities, record-keeping and experience of fieldwork,Malawi is now particularly well placed for the detailed study of the immediate and longer term impact of M.D.T. on patients with all types of leprosy.

The methodology of this study will be described.

III/154(A) A CONTRTOLLED TRIAL TO COMPARE THE THERAPEUTIC EFFECTS OF DAPSONE IN COMBINATION WITH DAILY OR ONCE-MONTHLY RIFAMPICIN IN PATIENTS WITH LEPROMATOUS LEPROSY

Diltor V.A. Opromolla, Claudio J.S. Tonello and Raul Negrao Fleury
Hospital Lauro de Souza Lima, Brasil

In 1981, we published the results obtained in 36 patients with the use of the association of rifampicin and dapsone using two regimens for six months. A group of patients was given a daily dose of 450 mg of rifampicin plus a daily dose of 50 mg of dapsone. Another group was treated with a monthly dose of rifampicin of 1.200 mg plus a daily dose of 50 mg of dapsone.

At the end of the trial, both groups presented similar results, clinical, histological and bacteriological.

At the end of this first six month of observation, the patients were periodically examined on an ambulatorial basis, receiving during this period daily doses of 100 mg of dapsone.

After 4 years, the patients were again evaluated; clinical, bacteriological and histological results will be presented and discussed in this paper.

III/155(A) CONTROLLED CLINICAL TRIAL OF TWO REGIMENS IN BACTERIOLOGICALLY POSITIVE CASES OF LEPROSY

Thomas A, Balakrishna A, Nagarajan M, Prabhakar R and Tripathy S.P.
Tuberculosis Research Centre, ICMR, Madras, India

The Tuberculosis Research Centre is undertaking a controlled clinical trial of multidrug regimens in multibacillary lepromatous and near lepromatous leprosy. The patient is eligible for admission to study if he has disease classified as LL or LI histopathologically and the BI is 2.5 or more on Ridley's scale.

Patients are randomly allocated either to regimen (a) dapsone plus clofazimine daily for 60 months, or to regimen (b) with an intensive phase of 4 drugs, rifampicin, isoniazid, dapsone and clofazimine daily for 3 months, followed by dapsone and clofazimine up to 60 months. All drugs are administered orally in a single daily dose.

Interim analysis at 36 months shows that patients on both regimens had improved clinically and bacteriologically. There was, however, no apparent additional benefit derived from the 3 months supplement of rifampicin and isoniazid. The possibility of a benefit becoming manifest during the later periods of follow-up cannot, however, be ruled out.

III/156(A) SHORT-TERM MULTIDRUG REGIMEN OF WHO (OCTOBER 1981) – A REVIEW OF 350 PAUCIBACILLARY PATIENTS

Patricia Rose
Guyana Hansen's Disease Control Programme, George Town, South America

The W.H.O. multiple drug, short-term treatment regimen was introduced in Guyana on the 1st December, 1981 for all newly diagnosed patients. Paucibacillary patients already on treatment with dapsone monotherapy changed on to the new regimen at their first clinic attendance after 1 December.

This paper reviews the clinical progress of approximately 350 paucibacillary patients commencing the new regimen between 1 December 1981 and 31 July 1983, who remain in the country. The patient population is divided into newly diagnosed, previously untreated patients and those previously treated with dapsone monotherapy and grouped according to type of disease (I, TT, BT). Results so far have been very satisfactory with few reactions, few drug side-effects and a low relapse rate.A longer period of surveillance is needed before firm conclusions can be drawn, particularly with regard to relapses in BT patients, but the present rate is quite acceptable.

III/157(A) SHORT COURSE TREATMENT OF TUBERCULOID (TT/BT) LEPROSY PATIENTS

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A prospective study has been undertaken to evaluate the efficacy of short duration treatment in untreated non-lepromatous (TT/BT) patients, Relapse rates in the post-treatment period are being compared in 4 treatment regimens which are: (i) dapsone alone (100 mg daily) for 12 months, (ii) dapsone (100 mg daily) for 12 months + Steroid (betamethasone 10 mg daily) for first one month (iii) dapsone (100 mg daily) for 12 months + rifampicin (600 mg daily) for first 7 days and (iv) DDS (100 mg daily) for 6 months + monthly 600 mg rifampicin for 6 months. Allocation of patients to the first two groups was randomised, while in the other two, it was on continuous basis.

It has been observed that a proportion of patients (about 15%) continue to show activity of the disease, even at the end of 12 months treatment. Data on relapses during the follow up period will be presented and the results discussed.

III/158(A) MANAGEMENT OF PATIENTS WITH NON-LEPROMATOUS LEPROSY – THE KARIGIRI EXPERIENCE

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Patients with non-lepromatous leprosy fall into three categories as regards their treatment. The first are patients who register for treatment and take their treatment regularly. The second group consists of irregular patients who default from treatment. The third group consists of patients who refuse to come for treatment and remain unregistered. This paper reviews three separate studies which dealt with groups of patients from each of the three categories. The first study was on 2,027 non-lepromatous patients released from control (RFC). These patients had dapsone monotherapy for a minimum period of 4½ years. 1,701 of these patients were followed-up and examined for evidence of relapse. 51 patients relapsed, giving a relapse rate of 3% or 9.7 per 1000 person years of risk.

The second study consisted of 442 defaulters with non-lepromatous leprosy, of whom 421 were followed up and examined for evidence of relapse. These patients had a significantly shorter duration of treatment and more irregular treatment than the patients in the RFC study. 10 patients relapsed giving a relapse rate of 2.4% or 4.6 per 1000 person years of risk.

The third study consisted of 88 patients with non-lepromatous leprosy who refused to take treatment. Depending on the criteria used, the leprosy in between 40-75% of the patients, healed spontaneously without any treatment.

The implication of the findings of these studies in relation to the recommendations of the World Health Organization (1982) on short-term chemotherapy of patients with non-lepromatous (paucibacillary) leprosy are discussed. Operational guidelines for the management of these patients are also suggested.

III/159(A) PRIMARY AND ACQUIRED RESISTANCE OF DAPSONE AND RIFAMPICIN OF *M. LEPRAE* IN MARTINIQUE AND GUADELOUPE

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Between January 1980 and December, 1982, from a total of 700,000 inhabitants in Martinique and Guadeloupe, 74 new cases of multibacillary leprosy have been registered and 59 relapse cases occurred among a thousand multibacillary cases already tested for more than 5 years. For each of them,

a skin bioposy was performed for mouse footpad inoculation and dapsone and rifampicin sensitivity testing. At present, drug sensitivity results are available for 17 strains isolated from new cases and for 37 isolated from relapsed cases. Among the former, only 5 were fully sensitive to dapsone, 9 were resistant to 0.0001% dapsone and 3 resistant to 0.001% dapsone. None was resistant to 0.01% dapsone or rifampicin. Among the latter, only 2 were fully sensitive to dapsone, 2 were resistant to 0.0001% dapsone, 12 resistant to 0.001% dapsone and 21 to 0.01% dapsone. Six of the strains with the highest degree of resistance to dapsone were also resistant to rifampicin. All six strains were isolated from patients who had received irregular and prolonged courses of rifampicin alone. The alarming prevalence of drug resistance in Martinique and Guadeloupe underlines the need for applying strictly combined drug regimens.

III/160(A) EFFECT OF SHORT-TERM SUPPLEMENTARY TREATMENT ON THE OVERALL RELAPSE RATE AND THE INCIDENCE OF DAPSONE-RESISTANT LEPROSY IN LEPROMATOUS PATIENTS

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In 1976, a clinical trial was initiated at ALERT, Addis Ababa to study the effect of a one year supplementary treatment on the incidence of dapsone-resistant leprosy in lepromatous patients already on dapsone monotherapy. 750 patients on dapsone therapy were each randomly assigned to one of four groups and followed for six years.The first group served as a control group, the second received thiacetazone daily for 12 months, the third received thiacetazone daily for 12 months plus rifampicin daily during months one and seven, and the fourth received rifampicin daily during months one and seven but no thiacetazone.

The thiacetazone treatment had no significant effect on either the overall relapse rate or the incidence of dapsone-resistant leprosy. The rifampicin treatment, on the other hand did significantly lower the relapse rate and no case of dapsone resistance was detected.

III/161(A) (CLOFAZIMINE, B 663, LAMPRENE) MONOTHERAPY OF DAPSONE-RESISTANT LEPROSY

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In the Eversley Childs Sanitarium, Cebu, a study of the occurrence of relapses was begun in 1975. Dapsone-resistance was established by inoculatin of acid-fast bacilli into footpads of mice fed with concentration of 0.0001%, 0.001%, and 0.01% dapsone in the diet. From 1975-1979, of 36 relapses, sequentially admitted, 24 were proven dapsone-resistant by mouse footpad inoculation; 12 were relapses due to dapsone-sensitive organisms. Both groups of patients were placed on clofazimine monotherapy; at a dose of 200 mg., three times weekly.

The clinical, bacteriologic, and histologic changes with clofazimine monotherapy after 4-8 years of treatment; occurrence of ENL, and side-effects of the drug, will be presented and discussed.

III/162(A) THE EFFECTIVENESS OF DAPSONE IN PATIENTS WITH PRIMARY DAPSONE-RESISTANT LEPROSY

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Between 1971 and 1982, over 180 new, previously untreated multibacillary leprosy patients admitted to the National Hansen's Centre at Carville, have had mouse footpad drug sensitivity studies on bacilli isolated from them. Twenty-seven of these were found to be infected with primary dapsone-resistant *M. leprae* since their bacilli grew to varying degrees in mice fed 0.0001% or more dapsone in their diet. Prior to this, all bacilli tested from such patients had been sensitive to this level of dapsone. Over half of these cases were initially treated with dapsone monotherapy and with but few exceptions their response was completely normal as measured by all the usual criteria. This indicates that dapsone continues to be useful in the majority of U.S. cases where evidence of primary dapsone resistance is found on mouse footpad studies. However, these results should not be considered evidence in favour of the further use of dapsone monotherapy. Rather, they support, the continued use of dapsone in combination drug regimens such as those proposed by the WHO Study Group on Chemotherapy of Leprosy for Control Programs, even in areas with a high incidence of primary dapsone resistance.

III/163(A) DAPSONE-RESISTANT INFECTION AMONG LEPROSY PATIENTS IN POPULATION OF GUDIYATHAM TALUK

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The first population based survey of dapsone-resistant infection in a leprosy-endemic rural area was done in Gudiyatham Taluk, the leprosy control zone of the Schieffelin Leprosy Research and Training Centre, Karigiri, South India. Dapsone monotherapy had been used from 1955 up to the end of the survey period in 1981. Of the total population of about 450000, with about 7000 patients under treatment for some form of leprosy,all 1580 patients with LL or BL leprosy were listed for the survey. 1224 could be fully studied. 142 mouse footpad tests for dapsone-resistant *M. leprae* were performed. Detailed statistical analysis of the data has been undertaken. The results will be presented.

Data 1) comparing the 1960s and 1970s for patients' response to dapsone monotherapy;
2) indicating the course of LL and BL patients after the attainment of smear negativity;
3) indicating the current status of lepromatous patients, treated with dapsone monotherapy for 20 years – will also be presented.

III/164(A) THE PROBLEM OF DAPSONE–RESISTANT LEPROSY IN THE PHILIPPINES

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Segregation of infectious patients is no longer in practice as a control measure against leprosy. No protective anti-leprosy vaccine is yet available, partly because *M. leprae* continues to be uncultivable *in vitro*. Leprosy is currently controlled only by case-finding plus chemotherapy, so that chemotherapy in leprosy has two main objectives: (1) to cure the patients and (2) to interrupt the transmission of the disease by "sterilizing" infectious patients as rapidly as possible with bactericidal drugs.

Dapsone monotherapy has been used for the cure and control of leprosy all over the world for more than 30 years. The very serious problems posed by the increasing emergence of secondary dapsone resistance among lepromatous patients, treated with dapsone monotherapy and among those whom such cases may subsequently infect with primary dapsone-resistant leprosy are now widely recognized.

This report is a study of the actual prevalence inthe Philippines of (a) secondary dapsone-resistant leprosy among relapsed lepromatous patients previously treated with dapsone, and (b) primary dapsone-resistant leprosy among new and untreated lepromatous patients, as determined by mouse footpad inoculation tests for various degrees of resistance to dapsone. Various aspects of this serious problem are discussed.

III/165(A) PRIMARY DAPSONE-RESISTANT TUBERCULOID LEPROSY

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Primary dapsone-resistant tuberculoid leprosy can be diagnosed with confidence, if a patient known to be taking dapsone in adequate dosage and regularity fails to improve and has progressive active leprosy at a time when effective treatment should have controlled the disease. Care must be taken to avoid confusion with reversal reaction. In Dhoolpet Leprosy Research Centre, search for such cases has been carried out since 1979. All patients with tuberculoid (BT and TT) leprosy failing to show the normal pattern of clinical improvment when treated with dapsone have been regularly assessed, including clinical examination, serial biopsies of active skin lesions, and urinalysis for dapsone. A total of 15 cases have been detected where the causes of failure of treatment was almost certainly primary dapsone-resistant leprosy; this represents about 1 per cent of newly diagnosed cases of tuberculoid leprosy attending the centre. The significance of these results will be discussed.

III/166(A) PARALLEL DAPSONE–AND RIFAMPICIN–RESISTANCE

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It has been a general experience in this Institute that compared to new untreated lepromatous cases, cases with secondary dapsone-resistance were more refractory to treatment with rifampicin. Based on this observation, a study was planned to investigate the patients with suspected dapsone-resistant strains and screen them for rifampicin resistance using the mouse footpad model. It was found that *M. leprae* obtained from five multibacillary leprosy patients who had irregular monotherapy with dapsone for varying periods, three strains were found to be resistant to dapsone. Subsquently these dapsone resistant strains were also found to be resistant to rifampicin. Primary rifampicin resistance was thus confirmed in secondary dapsone resistant cases.

III/167(A) PRIMARY DAPSONE-RESISTANT LEPROSY IN THE REPUBLIC OF KOREA

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As the number of lepromatous patients with acquired dapsone-resistant leprosy increases, the likelihood that they will become the source of infection of new cases showing primary dapsone resistance, also increases. The occurrence of primary dapsone resistance leprosy in this country has been investigated since 1979 and so far 24 patients with active and previously untreated lepromatous leprosy were subjected to skin biopsy before initiation of chemotherapy. The organisms from each specimen were inoculated into the footpads of mice, and the susceptibility to dapsone was measured. *M. Leprae* obtained from 18 patients were sensitive to dapsone while 6 patients were resistant to dapsone. Of six primary dapsone-resistant cases, two showed a high degree of resistance, one moderate resistance and three low resistance. Since the survey has not covered the entire area, one could not estimate the prevalence of primary dapsone resistance in the country. However, the results obtained show the presence of primary dapsone-resistant leprosy in the Republic of Korea.

III/168(A) PLASMA EXCHANGE IN SEVERE ENL.

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Though the pathogenesis of erythema nodosum leprosum is not fully understood, it is generally accepted that immune complexes are implicated in its onset. Plasma exchange has been proposed as an efficient therapy for a variety of immunological diseases, including immune complex diseases, such as lupus erythematosus.

In four patients with severe, recurrent ENL, resistant to conventional therapy, we performed plasma exchanges. In some instances, the removal of plasma, followed by replacement with albumin and gamma-globulin solutions, was effective. In other instances, the patient was improved only when fresh frozen plasma was used as the replacement fluid. In some cases, plain plasma infusions improved the ENL. Overall, transfusional therapy induced a dramatic improvement in severely ill patients.

This uncontrolled study of plasma exchange in ENL indicates that this procedure can be useful in selected cases. Its mode of action is unknown. Plasma exchange alters in a complex manner the network of humoral and cellular immunoregulatory interactions.

III/169(A) RESULTS OF OUTPATIENT TREATMENT OF NEURITIS IN BORDERLINE LEPROSY USING A STANDARDISED STEROID REGIMEN

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A total of 45 patients with borderline leprosy, who first attended Dhoolpet Leprosy Research Centre during 1982, received outpatient corticosteroid treatment for neuritis associated with evidence of recent nerve damage. The prescribed dosage and duration of treatment was much the same in all cases; a typical course consisted of prednisolone 30 mg daily for 1 month, then reducing the daily dosage stepwise by 5 mg per month, so that the total course lasts 6 months. Patients usually attended the centre monthly; complications of the treatment were minimal. Thirty-three of the patients were available for reassessment 9 - 18 months later, when their neurological status was re-evaluated. There was marked improvement in most cases. The results indicate that standard corticosteroid treatment is safe and effective in the outpatient treatment of neuritis in borderline leprosy.

III/170(A) IMMUNOTHERAPY OF LEPROSY WITH A MIXTURE OF *M. LEPRAE* AND BCG

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A mixture of 6×10^8 purified, heat-killed *M. leprae* and variable amounts of BCG has been used to treat 577 patients with active and inactive LL, BL and Mitsuda-negative indeterminate leprosy, as well as Mitsuda-negative contacts. Clinical, histopathological and immunological criteria were used to evaluate the response to immunotherapy. Clinical changes were observed in 57% of the active LL and 76% of active BL cases after 8 to 10 injections, as well as in all indeterminate cases after 3 of 4 injections; skin test conversion varied from 38% in the active BL-LL group to greater than 95% in the indeterminate patients and contacts. In a series of 60 patients evaluated by an international group of histopathologists, 90% of the patients with an initial diagnosis of LL and 83% of the BL group showed reversal reactions of variable intensity, sufficient to permit their re-classification on the Ridley-Jopling criteria, to BB in the majority of cases. Secondary effects have been mild and readily controlled by small doses of corticosteroids.

These results, which demonstrate the efficacy of immunotherapy in low-resistance forms of leprosy, will be discussed in terms of their relevance to the control of leprosy, with particular reference to the problems of drug resistance and "persisters".

III/171(A) MULTIDRUG CHEMOTHERAPY TRIAL IN LEPROSY USING CLOFAZIMINE, DAPSONE AND PULSED RIFAMPICIN

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In september 1981, awakening to the increasing problem of primary and secondary dapsone resistance following low dosage and irregular monotherapy, a multidrug regimen was set up in a typical rural setting of 1,68,478, population at the Emmaus-Swiss Leprosy Project at Palamaner, A.P., using (1) Rifampicin 1500 mg in pulsed supervised monthly intervals; (2) Clofazimine 300 mg/weekly unsupervised; (3) Dapsone 600 mg/weekly unsupervised.

This trial was limited to 101 positive cases who in spite of 3-5 year's treatment with 75% regularity showed (1) an increase in BI and clinical deterioration; (2) no decrease in a persistently high BI; and (3) fresh cases with BI of over 2+.

The trial was conducted at field level, with simple investigations for liver and kidney dysfunction.

The most outstanding feature after initiation of treatment was (1) a rapid change towards negativity in the less than 2+ group, (2) the absence of severe ENL and neuritic episodes, (3) the rapid clinical improvement and (4) no pathological effect in 2 pregnant women. However, 5 cases not responding were proved in all instances to be irregular in drug intake. There are no serious complications up to date. The two year period ends in August 1983.

III/172(P) REVERSION OF DOWNHILL COURSE OF ACTIVE LEPROMATOUS LEPROSY BY COMBINED IMMUNO-CHEMOTHERAPY : REPEATED FRESH BLOOD TRANSFUSIONS AND MINIMAL DOSE OF CLOFAZIMINE IN THE MANAGEMENT OF SEVERE FORMS OF LEPROMATOUS LEPROSY WITH ERYTHEMA NODOSUM LEPROSUM.

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With the ongoing lepromatous process, the bacillary load increases, immunologic paresis becomes more generalized and the disease spectrum shifts to the LL form, which could be reversed by human foetal thymic grafts. These patients often suffer from severe repeated ENL, leading to various deformities and blindness. They often become cortisone dependent and some develop dapsone resistance. Viable allogeneic blood lymphocyte infusions showed dramatic clinical, histological, bacteriological and immunological improvement. However, infusions of trasnsfer factor were proved to be useless. Also, infusions of mitomycin C blocked allogenic blood lymphocytes were ineffective. But repeated fresh blood transfusions were proved to be very effective. In this communication, we shall present our recent experience in the management of 13 patients, suffering from severe ENL, with combined immunochemotherapy (total 3 to 10 units of fresh blood transfusions within 3 to 10 weeks and minimal dose of either rifampicin or clofazimine). Repeated fresh blood transfusions along with 100 mg. clofazimine every alternate day for one month was a more effective method than treating with fresh blood transfusions alone, because the schedule of combined therapy could manage those 'hopeless' cases very effectively, who could not be easily controlled by immunotherapy alone.

III/173(P) THE ROLE OF PYRAZINAMIDE AS A PART OF COMBINATION THERAPY IN MULTIBACILLARY TYPE OF LEPROSY

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Leprosy bacilli in the human host exist in different places, both intracellularly and extracellularly. They may remain dormant in various sites and can cause relapse. Pyrazinamide as part of combination therapy has been found to be bactericidal against *M. tuberculosis* particularly in closed cavities and intracellular bacilli. This has been found to be of great value in reducing relapses in tuberculosis if it is added to various regimens, particularly at the beginning of therapy. Though this drug has not been found to be of much value against *M. leprae* in animals, its role as a part of various drug combinations in human host is not known. The effect of pyrazinamide on the persisting bacilli in borderline lepromatous and lepromatous leprosy patients is being tried in the present studies.

The various drug regimens being tried are:

i) Rifampicin plus pyrazinamide plus dapsone
ii) Clofazimine plus pyrazinamide plus dapsone

iii) Isoniazid plus thiacetazone plus pyrazinamide plus dapsone
iv) Pyrazinamide plus dapsone.

Three other regimens act as control of the above regimens and do not contain pyrazinamide. The patients are being followed up at regular intervals clinically, bacteriologically by smears and bacterial counts per gram of tissue, biochemically and by mouse footpad inoculation. The detailed results will be presented and discussed.

III/174(P) EVALUATION OF THE ANTI-LEPROSY ACTION OF DESOXY-FRUCTOSE SEROTONIN IN MAN.

C. Farracci, P. Saint Andre and S. Pattyn.

Earlier clinical observations illustrated the antileprosy action of desoxyfructose serotonin (DFS). Unpublished observations on mice (R. J.W. Rees) demonstrated that the product has purely bacteriostatic action. The activity of DFS was evaluated by inoculation of mice with cutaneous biopsies from patients who had been treated. Biopsies taken after 15 months were positive in mice, as were those taken after periods of 3, 7 and 10 months, after stopping the treatment that had been given for 14 to 16 months. The purely bacteriostatic action of DFS in man was thus confirmed.

III/175(P) COMPARISON OF THREE REGIMENS IN THE TREATMENT OF PAUCIBACILLARY LEPROSY.

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After clinical, bacteriological, neurological and histopathological examination, paucibacillary leprosy patients were randomized to be treated by one of the following 3 regimens : X dapsone 100 mg daily, 3 years. Y: rifampicin 900 mg once a week, 12 doses. Z: rifampicin 900 mg once a week, 8 doses. Full evaluation of the patients was done at 9, 18 and 30 months or more after the start of treatment. There were no important differences in the regression of the lesions, nor in the reactions. The results will be discussed in detail.

III/176(P) SHORT TERM TREATMENT OF PAUCIBACILLARY LEPROSY IN ANJOUAN (COMORES)

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Short term treatment of paucibacillary leprosy was introduced on the Island of Anjouan in 1980. This treatmetnt consists of the controlled daily administration of 600 mg of rifampicin. All the diagnoses, with the exception of a very few cases, were confirmed by cutaneous biopsies and progress was evaluated two years later, by means of another biopsy. More than 700 patients were placed on treatment. Neurological clinical results, changes in the deformities and the histopathological results after two years of treatment are presented and discussed in the paper.

III/177(P) EARLY RESULTS OF A MULTICENTERED TRIAL OF SHORT COURSE TREATMENT OF PAUCIBACILLARY LEPROSY

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In several countries (Zaire, Rwanda, Burundi), paucibacillary patients were randomized to receive one of two treatment regimens: A: 9 weekly doses of 900 mg rifampicin (RMP), B: a single dose of 1500 mg rifampicin followed by one year of dapsone. The diagnosis of every case was confirmed by histopathological examination. All RMP administrations were supervised; dapsone was not. Results of the clinical and histopathologic evaluation at 2 years after the start of treatment will be presented and compared with a non-randomized but similarly diagnosed and evaluated group of patients treated in the Islamic Republic of Comores with 10 weekly doses of 600 mg rifampicin.

III/178(P) CHEMOTHERAPY TRIAL WITH A TRIPLE-DRUG REGIMEN, INCLUDING ONCE-MONTHLY (1200 mg) RIFAMPICIN PLUS DAILY DAPSONE (100 mg) AND CLOFAZIMINE (50 mg), IN PATIENTS WITH MULTIBACILLARY TYPES OF LEPROSY.

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Thirty patients with multibacillary types of leprosy (20 LL, 6 LI & 4 BL) were treated for 6 months with a triple-drug regimen, comprising 1200 mg rifampicin given in a single dose once monthly, lamprene (clofazimine) 50 mg daily and dapsone 100 mg daily. The patients comprised 23 males and 7 females, ranging in age from 25-50 years.

Moderate to marked clinical improvement was observed in 28 patients. The MI averages of the skin smears either reached or came near to zero in 20 of the 30 patients, following six months' treatment. Average decreases in the bacteriologic indices (BI) of the skin smears and nose blow smears were 1.9 and 2.1 (Ridley's scale) respectively.

Lamprene-induced reversible brownish pigmentation was observed in all 30 patients, while two patients suffered from the "flu" syndrome. Reversible increase in blood urea (to 67.0 mg %) was reported in one patient at the end of 6 months' treatment. No patient had ENL reactions, anuria, oliguria, thrombocytopenia or anaphylactic shock.

The triple-drug regimen used in this trial proved effective, resonably safe and fairly economical for treating patients with multibacillary leprosy.

III/179(P) THE PRELIMINARY RESULTS OF THE SURVEY OF PRIMARY DAPSONE RESISTANCE AMONG MULTI-BACILLARY LEPROSY PATIENTS.

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The study includes Shanghai Municipality, Hai-an County and Su-Zhou Prefecture of Jiangsu Province. Leprosy control programme has been conducted for more than 20 years in these areas, and dapsone monotherapy has been given to the great majority of patients. Up to the end of February 1983, 15 untreated multibacillary leprosy had been found. Four out of 9 patients who completed the dapsone susceptibility test by mouse footpad technique were resistant to dapsone. Among them, 3 strains were low-grade and 1 strain was intermediate-grade of resistance. Since one of the resistant patients was BB type, it indicated that primary resistance might occur in any type of leprosy. The preliminary result suggested that primary resistance (like secondary resistance) is a widespread phenomenon and combined therapy should be urgently introduced for leprosy. Since most resistant patients showed low-grade resistance, dapsone is still an effective component in combined regimens for untreated leprosy.

III/180(P) DAILY COMBINED THERAPY IN MULTIBACILLARY LEPROSY - REPORT ON EFFICACY AND SIDE EFFECTS

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Daily administration of three anti-bacillary drugs is one of the best available regimens for the treatment of multibacillary leprosy.

35 patients are at present treated with rifampicin (600 mg daily), prothionamide (375 mg daily) and a bacteriostatic drug, dapsone 100 mg daily (18 pts.) or clofazimine (17 pts).

Clinical, biological and bacteriological examinations have been performed regularly.

The results of this treatment regimen are as follows:

- Cutaneous lesions slowly improve.
- Nerve lesions remain unchanged or improve. One case of ENL with acute neuritis has been observed.
- Reactional states are rare: only one case of reversal reaction has been seen, without nerve involvement. 10 patients had presented ENL reactions before the administration of this treatment; among them, 5 suffered from new episodes, 3 mild and 2 severe. Among the 25 patients who had not had ENL before treatment, only 2 suffered from mild ENL

The bacteriological examination showed that the morphological index fell to near zero under a month. The bacillary index fell from a mean of 2.80 at the beginning of therapy to 2.14 after 6 months, 1.90 after 1 year and 1.41 after 21 months. It was noted that patients with ENL had a slower decrease of the bacterial load than patients without ENL.

Some side effects were observed: one case of haemolytic anemia, probably due to rifampicin; 5 cases of gastro-intestinal disturbance, which in 3 cases were the initial symptoms of an acute toxic hepatitis. These 3 hepatitis patients ran a benign course, after the interruption of the therapy. When the liver function returned to normal, the treatment could be restarted, with the exception of prothionamide. Hepatic toxicity is attributed to prothionamide, or to the association prothionamide-rifampicin.

It is concluded that this therapeutic regimen is an efficient one. But it requires a close supervision because of the frequency of side-effects.

III/181(P) PRIMARY DAPSONE-RESISTANT LEPROSY IN SAN FRANCISCO

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Attempts were made to assess the dapsone sensitivity of all *M. leprae* strains from multibacilliferous, previously untreated patients presenting to the United States Public Health Service Hospital in San Francisco from 1978

to 1981. For this purpose, 5×10^3 *M. leprae* obtained from skin biopsies of 54 appropriate patients were inoculated into both hind feet of Balb/C mice, and the mice were continuously fed diets containing no dapsone, 0.0001% dapsone, 0.001% dapsone, and 0.01% dapsone. Fifty-three (98%) of these strains were fully sensitive to dapsone, i.e. *M. leprae* by 6 months or more multiplied to $> 2 \times 10^5$ /footpad (generally $> 10^6$) while bacterial counts from mice treated with all three levels of dapsone were $< 3 \times 10^4$/footpad (generally $< 10^4$). One patient's *M. leprae* were resistant to 0.0001% but not to higher dietary dapsone concentrations; control mouse footpad yielded 9.9×10^5 *M. leprae* footpad, while 0.0001% dapsone and 0.001% resulted in 2.8×10^5 and $< 4.3 \times 10^3$ *M. leprae*/footpad respectively. On five separate occasions, mouse plasma dapsone concentrations from groups of these dapsone-treated mice were analysed by high-pressure liquid chromatography and this confirmed the reliability of the levels of dietary dapsone utilized in these studies.

At least in some locales, primary dapsone resistance remains an unusual phenomenon.

III/182(P) MULTIDRUG THERAPY FOR PAUCIBACILLARY LEPROSY–EXPERIENCE IN BOMBAY

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Short-term multidrug therapy for paucibacillary leprosy (WHO 1982) was instituted to study the feasibility under urban field conditions in Bombay and also to judge the efficacy of therapy. 1057 active paucibacillary cases (smear negative) were included. The regularity was monitored by using "pulse therapy book" maintained in the clinics and "due date card" issued to the patient. Domiciliary supervised treatment had to be practised in irregular cases. Both rifampicin and dapsone were stopped after 6 months in 498 patients and followed up.

Out of 498 cases, 455 (91%) were regular for supervised pulse therapy indicating a better compliance rate.

On stopping treatment, 231 (46%) patients improved markedly (group-A), 202 (41%) were active though signs of regression were noticeable (group-B) and 65 (13%) became inactive (group-C). Tuberculoid patients showed significantly higher regression rate than those with borderline tuberculoid leprosy.

Out of 423 patients available for follow-up, 36% of group-A became inactive and 22% of group-B continued to show regression.

Histopathological findings of 83 cases on stoppage of treatment will be presented.

This study indicated that such therapy could be practised under supervision by field workers. Multidrug therapy in paucibacillary leprosy cases not only increases compliance rate but also hastens clinical regression.

III/183(P) LONG TERM RESULTS OF THE CONTINUOUS TREATMENT OF 2000 LEPROMATOUS HANSENIAN PATIENTS FROM 1.10.50 to 30.12.72

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The continuous study of 2000 lepromatous patients from 1950-1972 (therefore with a minimum follow-up period of 10 years) has enabled us to determine the recurrences and reversal reactions following either monotherapy with dapsone, TBI, Ethionamide, Sulfamethoxypyridazine or polychemotherapy.

The following were observed:

- influence of ENL on the time of negativity and the recurrences and reversal reactions.
- regularity or irregularity of the treatment.

It is interesting to note that 78 cases, who had been subjected to monotherapy with dapsone and who were placed under observation without treatment after 4 years of stable negativity, presented 17.5% recurrences in LL in '82. These recurrences follow a GAUSS curve between the 5th and 10th year, with a peak at 8 years. After that period the recurrences are unpredictable. 4% of reversal reactions, all bacteriologically negative have also been observed.

The study of resistance has been conducted in two manners.

1) either by the monthly evaluation of the decline of the morphological index during 3 months of hospitalization of the patient put on trial medication, under strict control.
2) or by inoculation of lepromatous material into the mouse footpads.

III/184(P) TREATMENT OF LEPROSY WITH CLOFAZIMINE– REVIEW OF 46 CASES IN 15 YEARS (1968-1983)

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This study shows the results of treatment with clofazimine of 46 patients with leprosy in Juiz de Fora-MG, most of them lepromatous. They were followed up with periodical clinical and laboratory tests for 15 years.

Although clofazimine was used mostly in patients suspected of having dapsone-resistance, it was also used in patients in reaction due to immune complexes. Doses of as low as 100 mg a day caused hyperpigmentation in 4 patients, ichthyosis in 8 patients, gastrointestinal disturbance in 2 patients and sexual impotence in one patient. Only 3 patients had to stop treatment because of these symptoms.

Most of the patients started treatment with dapsone but had to be changed to clofazimine because of one of the reasons showed above.

This study showed the efficacy of clofazimine in the treatment of leprosy, and the attenuation of the Hansenic reaction.

III/185(P) COMBINED THERAPY OF LEPROSY PATIENTS WITH SULPHONE RIFADIN AND PROTHIONAMIDE.

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The effectiveness of daily and intermittent administration of rifampicin and prothionamide together with sulphone (50% solution of sulphetrone at a dose of 3.5 ml twice a week) was compared. One group of patients received rifampicin 500 mg and prothionamide 500 mg daily; another group was given rifampicin 300 mg on the first and fourth day and prothionamide 500 mg on the second and fifth day of the week. A total of 22 patients with lepromatous leprosy, among whom there were newly diagnosed, and relapsed patients and those with delayed progress and active bacterioscopically positive manifestations, were observed. In 6 months, 15 patients under daily treatment showed definite clinical progress, the BI fell 2.7 times (solid mycobacteria) and 1.5 times (fragmented mycobacteria). The average decrease in histological index was 37%. Seven patients under intermittent therapy showed, along with clinical improvement, more marked decrease in number of solid and fragmented mycobacteria (by 10 and 7 times, respectively). The histological index decreased on average by 39.5%. The results of our trial indicated that both regimens of combined administration of the three drugs were highly effective, especially in cases of bacilliferous leprosy. In active leprosy, the intermittent administration of rifampicin and prothionamide is recommended as a more convenient, sparing and economical method, particularly for the treatment of elderly patients and those with intercurrent diseases.

III/186(P) NEW ANTILEPROSY DRUGS WITH IMMUNE STIMULATING ACTIVITY

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Sulphone-resistant leprosy is occurring with increasing frequency and makes the search for new antileprosy drugs urgent. Sulfapyrimidine derivatives have a mechanism of action different from that of sulphones. Firstly, sulfapyrimidine enhances both humoral and cell-mediated immunity (increase in total lymphocytes, absolute and relative numbers of T-cells with rise in blast transformation of lymphocytes by 2-3 times). Unlike dapsone, diuciphon shows T-cell-stimulating activity three times greater than the activity of the immune modulator, levamisol. Diuciphon is highly effective in the treatment of patients with sulphone-resistant leprosy. The sulfapyrimidines are 3-4 times less toxic than dapsone; they cause no side effects characteristic of the sulphones: hypochromic anemia, toxic hepatitis, ENL. During 10 years, we observed 81 patients with lepromatous leprosy treated with diuciphon and 65 control patients given standard antileprosy therapy. 3 patients from the study group with previous diagnosis of LLs showed the appearance of tuberculoid elements with positivation of the lepromin test in two patients. Histological study showed the signs of upgrading transformation with the appearance of lymphocytic infiltration and epithelioid cells in lepromatous granulomas in 12 cases. No similar findings were noted in the control patients after 30 years of observation. Out of 44 patients treated with diuciphon and discharged for ambulatory treatment, 9 cases were previously considered as resistatnt to sulphones.

III/187(P) TOXICITY OF ETHIONAMIDE AND RIFAMPICIN GIVEN IN MULTIDRUG THERAPY

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The W.H.O. Study Group on the Chemotherapy of Leprosy for Control Programmes (1982) has recommended that ethionamide or prothionamide should be used as the third drug in the treatment of multibacillary leprosy in those patients who find clofazimine unacceptable. There are, however, few published reports on the toxicity of the thioamides which, save as prothionamide in combination with isoniazid and dapsone (Isoprodian), have been little used hitherto in leprosy treatment. An account will be presented of ethionamide toxicity encountered in England among leprosy patients receiving rifampicin (usually monthly) plus daily

ethionamide with or without daily dapsone, including 3 cases (10%) of ethionamide-induced jaundice. These results will be compared with similar data now being generated elsewhere, and their significance for multidrug therapy discussed.

The rare and mild toxicity to monthly rifampicin which has been encountered will also be described.

III/188(P) RELAPSES AND RELAPSE CONTROL AFTER DISCONTINUATION OF TREATMENT

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Even with LL-cases, life-long dapsone monotherapy can be replaced by short-term combination therapy.

Criteria are required for determining the timing of release from treatment It is the decrease in the total number of bacteria which is decisive, and not the bacteriological "positivity" or "negativity" of the smear.

Based on personal experience with about 250 patients, the author exposes

- the bacteriological findings requiring continuation or allowing discontinuation of treatment;
- the frequency of taking and examining smears in order to get a clear idea of the bacteria present in the tissue and their decrease;
- the good correlation between clinical and bacteriological healing;
- that the non-occurrence of relapses is the most important criterion in the evaluation of anti-leprosy drugs.

A therapy permitting 10% or more relapses after discontinuation must be considered clinically and epidemiologically inadequate.

Only forms of therapy should be used whose efficacy in preventing relapses has been proven.

III/189(P) EXPERIENCE ON INTENSIVE PHASE OF MULTIDRUG THERAPY PROGRAMME IN FIELD CONDITIONS

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All bacilliferous leprosy patients are included in the combined therapy programme. A detailed plan of action is worked out, assigning drug delivery points. The work in each sector is done at a time.

After excluding the patients suffering from chronic illness, 458 patients were given combined therapy. As many as 98.3% completed treatment uninterruptedly for 14 days, and 1.7% patients discontinued treatment for various reasons. 3.7% patients developed reaction of different degrees, 0.4% patients acute neuritis and 0.2% acute deformity. Clinical improvement is noted in the majority of patients. New patients voluntarily reporting are dealt with simultaneously.

The intensive phase of Multidrug therapy programme in our Control Unit has been carried out successfully without any drug toxicity or major complications. A small fraction of the patients showed reactions no more than usual. It is undoubtedly felt that combined therapy in the field can be advocated successfully, after screening the patients thoroughly.

III/190(P) THE LEPROSY ERADICATION PROGRAMME IN PARAGUAY WITH THE COMBINATION RIFAMPICIN-ISOPRODIAN

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A leprosy eradication programme is being developed in Paraguay, using a combination of rifampicin and isoprodian (INH-PTH-DAPSONE) which proves to be effective and has a good tolerance, as has already been observed in the Malta Project.

The period of observation varies from one month to 46 (forty six) months and includes 781 (seven hundred and eighty- one) patients. The conditions of the programme are the same as those prevalent in this field, using the Madrid classification.

The clinico-bacteriological control was carried out monthly, carefully observing the ethical requirements of the country.

The patients were grouped according to sex, age, whether they had previous monotherapy treatment or not, as well as other data of interest.

The side effects of the drugs, like hepatitis, renal problems, anemia and gastric disturbances which have been carefully registered are not very significant.

The ENL symptoms observed do not differ much from those normally expected in the treatment of lepromatous cases and they generally responded well to thalidomide and other anti-inflammatory drugs. The frequency of neuritis did not exceed the level usually observed in monotherapy.

To date, no relapses have been observed during post treatment control.

The combined treatment with rifampicin and isoprodian in Paraguay is heartening because a sufficiently rapid clinico-bacteriological improvement has been obtained, without involving too much effort either for the patient or the programme staff.

III/191(P) CLINICAL TRIALS OF COMBINED CHEMOTHERAPY IN UNTREATED AND PROVEN SECONDARY DAPSONE RESISTANT CASES OF LEPROSY IN THAILAND

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Joint Chemotherapy Trials in untreated and proven secondary dapsone-resistant cases of leprosy have been conducted in Korea, Philippines and Thailand, with the assistance of the Sasakawa Memorial Health Foundation of Japan. The duration of the trial is 2 years. Follow-up will be made for a further 3 years. In Thailand, selected 60 cases of untreated lepromatous cases were randomized into two groups, the first of which receiving rifampicin 1200 mg as single initial dose and dapsone 100 mg daily indefinitely, while the second group was given rifampicin 600 mg daily for four weeks with dapsone 100 mg daily indefinitely.

The other 60 treated cases of lepromatous leprosy, proved as secondary dapsone resistance by footpad inoculation, were also randomized into two groups for combined chemotherapeutic regimens. The first group of 30 cases was placed on 600 mg daily of rifampicin for 4 weeks with clofazimine 100 mg every other day indefinitely, while the second group received rifampicin 600 mg daily for 2 weeks and clofazimine 100 mg every other day indefinitely.

The trials are aimed not only to select the most suitable regimens as to be judged by anti-leprosy efficacy and drug safety, but also to determine their field practicability and economic feasibility, prior to being used for mass-treatment.

The methods used are similar to the standard THELEP programme. The findings of the trial will be presented and discussed.

III/192(P) BCG-SCARIFICATION FOR IMMUNOSTIMULATION OF PATIENTS WITH LEPROMATOUS LEPROSY

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Six patients with LL and one with BL were treated from 1 to 2.5 years with combination of dapsone (50 mg/day), clofazimine (100 mg/day) and rifampicin (450-600 mg/day). Since May 1983, we gave ritampicin i.v. by intusion because oral administration produces an enzyme induction against its metabolites and therefore it is not very effective. As the patients did not show a satisfactory improvement, we performed BCG-scarifications (Immun BCG Pasteur F) for immunostimulation as we do with patients with malignant-melanoma. The scarifications produce exudative reactions and after 10 to 14 days, they develop lupoid granuloma. With this immunostimulation, the patients develop E.N.L. at a higher rate than non-scarified patients, but this complication can be treated with thalidomide. We suggest this regimen to be more effective than chemotherapy alone.

III/193(P) ASSESSMENT AND IMPROVEMENT OF PATIENT COMPLIANCE TO DAPSONE BY USE OF A CONTINUAL MONITORING PROGRAMME IN AN OUTPATIENT HANSEN'S DISEASE CLINIC

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A compliance monitoring programme was initiated in our clinic to assess and improve the compliance of Hansen's Disease (HD) patients receiving dapsone. Thirty-six adult patients receiving dapsone were monitored over an eighteen-month period. Compliance was assessed by a modification of the colorimetric procedure of Ellard *et al* for determination of the urinary dapsone-to-creatinine ratio (D/C). The accuracy of the compliance standards was confirmed prospectively in 10 patients. The determination of time since the last dose was assessed on 9 occasions in 7 patients, using the mean Std D/C from the compliance controls (CC). A paired T-test demonstrated no significant difference ($p > 0.10$) between actual 42.6 ± 31.2 hrs.) and predicted (42.4 ± 29.7 hrs.) time since last dose. An initial assessment of compliance over a 6-month period showed 48% of the patients were found to be non-compliant (i.e. outside of the 99% confidence inter-

val of CC). After a 6-month period of continual monitoring and compliance education, a second assessment of compliance showed that only 22.7% of the clinic population was non-compliant. These results demonstrate that this method can be accurately applied to an out-patient HD clinic and that patient compliance can be improved by a continual compliance monitoring programme.

III/194(P) PROGRAMME OF LEPROSYAND ITS TREATMENT WITH MULTI-DRUGS IN REPUBLICA DOMINICANA

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The authors make a resume of the programme of leprosy in the Dominican Republic where they present the 6,400 cases discovered in 17 years of programme and analyze the results of the 1st year of therapy with multidrugs given to about 4000 active paucibacillary cases: rifampicin 600 mgs and clofazimine 300 mg supervised each month, and DDS 600 mgs each week; and, in the multibacillary cases the same scheme to which we added 300 mgs of clofazimine each week.

III/195(P) MULTIDRUG REGIMEN IN LEPROSY CONTROL PROGRAMME REPORT OF ACTIVITIES IN GANJAM DISTRICT (ORISSA)

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The drug combination used was rifampicin 600 mg. clofazimine 100 mg and dapsone 100 mg daily for 14 days intensive supervised therapy, followed by once a month (Pulse) supervised dose of rifampicine 600 mg., clofazimine 300 mg and dapsone 100 mg for 2 years and clofazimine 100 mg on alternate days with dapsone 100 mg daily unsupervised for 2 years. Out of the total of 5327 multi-bacillary cases present in the district, 3677 cases (68.93%) were selected for multi-drug therapy. Out of 1650 who were not selected, 462 (28%) were those who have left the villages to earn their livelihood, 198 (12%) cases were rejected by the Medical Officers as they were not medically fit to receive the multi-drug therapy due to various reasons 198 (12% were being treated otherwise either at Medical Colleges, or R.L.T.I. or privately. 951 (25.86%) cases were added up to the project during the intensive phase.Out of these 951, 573 (60.25%) cases were old cases who had earlier refused to take treatment or were absent from the villages. 378 (39.75%) were newly detected cases who have reported voluntarily to the Clinic points, during the intensive phase. Out of the total of 4628 cases, 4268 (92.22%) cases took treatment during the phase regularly. The rest 360 (7.78%) patients stopped the treatment for various reasons. 33 (9.11%) dropped out due to complications. 246 (68.33%) left the area to earn their livelihood. 81 (22.5%) refused to continue the treatment in spite of the best efforts of field staff. 173 (3.73%) cases developed complications. Out of this 45 (26.01%) cases were E.N.L. reactions. 2 cases developed jaundice, 12 cases gastritis, 9 cases severe anaemia. Rest + 105 cases complained of neuralgia and general weakness. Out of 173, only 33 cases dropped out due to complications, the rest 140 cases continued the treatment with supportive treatment for complications. Clinical and bacteriological follow-up of the cases on M.D.T. at 3 months interval is being done.

III/196(P) STUDY OF THE BIOLOGICAL AND CLINICAL TOLERANCE OF DAILY POLYCHEMOTHERAPY FOR 58 LEPROSY PATIENTS

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From January 1982 to June 1983, 58 leprosy patients were treated with the combination of 2 to 3 drugs daily. They were followed up every month clinically and biologically at the beginning of treatment, and then once every three months.

Among the 34 patients with lepromatous leprosy, 18 were given three drugs (rifampicin, prothionamide and dapsone) and 4 were given rifampicin, prothionamide and clofazimine.

Among 24 patients with tuberculoid leprosy, 16 were given three drugs (rifampicin,prothionamide and dapsone).

12 patients complained of gastrointestinal disorders; in 11 cases it was related to prothionamide, which had to be discontinued in 8 cases.

Among the 40 patients treated with rifampicin and prothionamide, 7 had hepatitis proven by an increase of transaminase on one occasion (6 cases), or by a spontaneously resolving hepatitis with jaundice (1 case).

The high frequency of clinical and biological disturbances following this drug combination requires close follow-up of the patients, as well as control of the regular drug intake.

III/197(P) INVESTIGATIONS OF THE REGULARITY WITH WHICH PATIENTS SELF-ADMINISTER ETHIONAMIDE, PROTHIONAMIDE AND THIACETAZONE USING ISONIAZID-MARKED FORMULATIONS

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In the multi-drug treatment of lepromatous leprosy, it is recommended that if clofazimine cannot be tolerated, it should be replaced by either ethionamide or prothionamide. It was expected that the compliance of these two thioamides might be unsatisfactory, since when they were used in the treatment of tuberculosis at daily doses of from 500 to 1,000 mg, gastro-intestinal side-effects were quite common. There has, however, been much less experience of their use at the lower daily doses (250 - 375 mg) recommended for leprosy.

The results of two compliance studies, carried out among out-patients in Hyderabad using specially formulated tablets and capsules of ethionamide prothionamade or thiacetazone containing 6 mg amounts of isoniazid as an innocuous marker, will be reported. In the first study, patients were prescribed 3-month courses of daily treatment with100 mg dapsone together with 125 or 250 mg doses of either ethionamide or prothionamide in randomized sequences. In the second study, patients were given consecutive 3-month courses daily dapsone plus thiacetazone, the drugs being given either separately or combined as a single capsule.The regularity with which the drugs were taken was assessed by means of simple urine tests for isoniazid and dapsone metabolites.

III/198(T) SECONDARY DAPSONE RESISTANCE

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Secondary dapsone resistance has been reported from various centers in India, but such cases have not been recorded from the eastern part of the country. An attempt was made to identify the existence of *prima facie* cases of secondary dapsone resistance in and around Varanasi. A total of 26 were selected from among 732 multibacillary patients that were being treated in the University Hospital. They had been taking treatment with dapsone for prolonged periods of time.

After conducting the therapeutic trial for a period of six months giving dapsone with a close clinical and bacteriological examination during the period, two cases out of 26 relapsed showing signs of secondary dapsone resistance. It was further confirmed by showing marked clinical and bacteriological improvement by administration of multi-drug therapy with clofazimine and rifampicin.

III/199(T) EFFECT OF LEVAMISOL ON LEPROMIN REACTIVITY IN CASES OF BORDERLINE AND LEPROMATOUS LEPROSY

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A study was conducted on 30 cases which included 10 lepromatous, 3 borderline lepromatous, 11 borderline borderline and 6 borderline tuberculoid.

Lepromin test was done with lepromin – A and the Mitsuda reaction was read at 3 weeks and 4 weeks. Patients were put on 100 mg dapsone daily in addition to levamisol 150 mg. once a day on three consecutive days respectively every fortnight for three months. After three months therapy, the lepromin test was repeated.

Levamisol had no significant effect on the lepromin reaction in lepromatous leprosy and borderline lepromatous leprosy. It however, significantly increased the lepromin reactivity in borderline/borderline cases.

III/200(T) EFFECT OF PROBENECID ON SERUM RIFAMPICIN LEVELS

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Serum rifampicin levels were determined by a microbiological assay using *Staphylococcus aureus* in 22 cases of leprosy after administering the drug with and without probenecid. Most of the patients showed higher serum rifampicin levels when probenecid was given along with rifampicin. Six patients showed statistically significant increase in the serum levels of the drug, when given in the dose of 300 mg along with 1 g. of probenecid one hour before breakfast and these levels were comparable with those obtained following administration of 450 mg of rifampicin alone two hours after breakfast. Thus administration of probenecid preceding rifampicin may be employed to reduce the cost of drug as well as hepatotoxicity in patients requiring rifampicin for long periods.

III/201(T) A STUDY ON THE EFFECT OF THE TREATMENT OF PATIENTS IN A LEPROSARIUM AND IN LEPROSY CLINICS

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The purpose of the present study is to analyse and to discuss the effect of the treatment for leprosy patients in a leprosarium and in leprosy clinics.

In the national leprosarium Nagashima Aiseien, 70 patients died between 1980 and 1982 and 60 cases were selected for the study. Out of the 60, lepromatous cases were 34 (male 25 and female 9). Of the male lepromatous patients, eight cases had become negative in slit-smear examination for acid-fast bacilli long before death and nine were frequently positive, till the end of life. Eight were continuously positive till the last examination. Of the females, the results were one, six and two cases respectively. In the leprosaruim about 30% of lepromatous cases remained bacteriologically positive.

JALMA (Japan Leprosy Mission for Asia) opened a clinic in Ghatampur village of Kanpur district, U.P. State, India at the beginning of 1966. The effect of treatment for the lepromatous patients living in this area was obtained in the clinic and compared with the above mentioned results from the leprosarium.

III/202(T) WATER RETENTION WITH THALIDOMIDE ADMINISTRATION IN LEPROSY

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20 patients suffering from lepromatous or borderline leprosy with chronic recurring ENL reactions were treated with thalidomide. Although acute reactions subsided within a short time, due to the rebound phenomena and recurrence of reaction, thalidomide was continued in small doses for several months. The common side effects observed were bilateral oedema of the feet, with considerable increase in weight, bradycardia and occasional extra-systoles. The majority of these patients showed a rise in eosinophils. Neither the retention of fluid, nor the bradycardia warranted withdrawal of the drug. The possible mechanisms of water retention in the use of thalidomide are discussed.

III/203(T) ACUTE DAPSONE POISONING

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Dapsone poisoning is either accidental or suicidal, but in young children it is always accidental due to negligence of parents. Irritability of the central nervous system is the most common presentation. Methaemoglobinaemia and hemolytic anaemia are also not uncommon. Of the 4 cases presented in the Philadelphia Leprosy Hospital at Salur, two had methaemoglobinaemia, two had extrapyramidal disturbances and all 4 had increased irritability of the central nervous system. Death occurred in one of the four children, due to pneumonia and pre-existing conditions. Details of the clinical presentation of acute dapsone poisoning in children and its management are discussed.

III/204(T) A CASE OF MODERATE JAUNDICE AND POSITIVE AUSTRALIA ANTIGEN IN SEVERE ENL, RESPONDED DRAMATICALLY TO STEROID

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A BL leprosy patient, seen at a hospital with high fever, jaundice, and skin rashes with superficial ulceration for one month, was treated as sepsis without improvement and transferred for investigation. He looked weak, toxic and had moderate jaundice. He had numerous, small, tender nodules with superficial ulceration, neuritis, orchitis, and multiple arthritis which was compatible with severe ENL. The total bilirubin was 7.56 mg%, with direct bilirubin of 5.4 mg%, SGPT 167 IU, SGOT 350 IU and alkaline phosphatase 8.5 BL units. Thalidomide was chosen for treatment in the presence of positive Australia antigen. Slight improvement after few days of treatment, therefore, prednisolone was given to replace thalidomide. His severe ENL, jaundice and general condition improved dramatically, whereas the Australia antigen remained positive.

This is a case of leprosy with jaundice caused by severe ENL and misdiagnosed as sepsis. The other causes of jaundice and ENL which will be discussed are ruled out. Both his jaundice and ENL responded dramatically to a steroid. Therefore ENL should be considered as one of the differential diagnoses of jaundice in leprosy patients. Presence of Australia antigenemia is not a contraindication to the use of steroid.

III/205(T) LIPOCLASTIC ENZYME IDENTICAL TO POTENT PANCREATIC LIPASE IS THE CURE FOR LEPROSY AND TUBERCULOSIS PATIENTS

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INTRODUCTION:

(A) POTENT PANCREAS: is immune to leprosy and tuberculosis and affords immunity to mankind. Potency rests in the normal "Lipoinsulin Reflex" phase, that is, with high lipase insulin is less and vice versa. Developmentally, insulin functions from sixth month, high lipase from birth and later with gradual waning of lipase and increase of insulin, the relation is established by four years. High lipase of early life cures children from the diseases, shows the Ghon's foci and accounts for healing of 180 infants, in Lubeck's tragedy, who were fed in massive doses thrice by first ten days of life with active, virulent cultures of H37RV strain of bacilli.

(B) IMPOTENT PANCREAS: is also immune to leprosyand tuberculosis, but the deranged LIR with diminishing lipase, renders people susceptible to the disease. The low lipase causes (1) lowering of blood lipase, (2) upset of fat metabolism, (3) hyperinsulinism with breakdown of fat to fatty acid and glycerol, (4) accumulation of glycerol, (5) steatosis and (6) steatorrhoea. The accumulated glycerol travels to the blood to be changed to glucose and form a vicious cycle of "Glycerol coming and glucose forming" media for *M. leprae* and *M. tuberculosis* and the predisposing cause in the etiology. These observations are confirmatively proved by injecting a lipoclastic enzyme prepared in identical activity and PH value of a potent pancreas to adult T1, T2, TB, B1, BL, L1, L2, L3, ...leprosy and to tuberclosis patients in proper doses. The patients show quick clinical response, healing with bacteriological negativity by 2/3 months. On inflitration, highly +ve patches with 100/200 *M. leprae* per field become-ve by 4 to 72 hours, and mice footpad experiments confirm negativity. EXPERIMENTS SHOWING LIR IN POTENT PANCREAS: (1) Test Tube (2) Electrocautery of Islet and assaying insulin absence with high lipase in the ducts of a dog (3) Tying of the duct and assaying insulin activity.

EXPERIMENTS SHOWING DERANGED LIR IN AN IMPOTENT PANCREAS. (1) Lower blood-serum lipase levels than in potent pancreas (2) undigested fat in stool with steatorrhoea and high glycerol (3) Hyperglycemia resulting from travel of glycerol to blood from onset proves the formation of the vicious cycle, the media and the predisposing cause in the etiology and subsequent entry of *M. leprae* and *M. tuberculosis*, the exciting causes.

CONCLUSION:

Lipoclastic enzyme treatment should be declared as the treatment.

III/206(T) THE DAPSONE SYNDROME

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Dapsone given in daily doses of 50 to 100 mg. can occasonally give rise to a special complex qf symptoms.

Two cases of borderline leprosy, who developed adverse cutaneous and systemic reaction following dapsone therapy, at SLR & T Centre, Karigiri, are presented. Jaundice, fever, generalised morbilliform rash appeared in the sixth week of treatment with dapsone.The rash ended in a generlised dermatitis, associated with generalised lymphadenopathy, liver enlargement and in one splenomegaly and was followed by extensive desquamation.

Complete blood cell and WBC differential counts showed extreme lymphocytosis and at typical lymphocytes, changes similar to that seen in viral infections, particularly 'Infectious mononucleosis'.

Although the full syndrome is rare, it is important to recognize its individual components, because of the implications for subsequent treatment.

The dapsone syndrome may be misinterpreted, because of the similarity to viral infections or leukaemias, may sometimes resemble Lepra Reaction, particularly in multibacillary leprosy.

SESSION IV

MICROBIOLOGY

Chairman: Nakamura, M.

Rapporteur: Pattyn, S.R.

WEDNESDAY, 22ND FEBRUARY, 1984

Auditorium 08.30–12.00

Abstracts

A* : 207-228
P* : 229-243
T* : 244-250

*A : accepted for reading
*P : for poster presentation.
*T : for title reading.

IV/207(A) PURIFICATION OF *M. LEPRAE* FROM INFECTED ARMADILLO TISSUES

Philip Draper, Celia Lowe and R.J.W. Rees
National Institute of Medical Research, London, England

M. leprae grown in the nine-banded armadillo must usually be purified before use. Techniques used to isolate subcellular organelles are applicable, beginning with homogenization and including differential and density-gradient centrifugation. Since one important application of the purified bacteria is immunological, antigenic components of the bacteria must not be damaged by the isolation methods or by host components released from the tissue. Additionally, an ideal purification system should give quantitative yields of bacteria, free from contamination of host origin. Such an ideal system has not yet been devised; available methods involve compromise between the various requirements.

The method currently used by the IMMLEP programme has been developed after a long series of trials, with testing of the products by collaborators in the programme at each stage. It gives quantitative yields from heavily infected tissues. Antigenic determinants are believed to be undamaged but some contamination by tightly bound host components persists. The method involves homogenizatin at high pH, removal of host DNA, purification in a Percoll density gradient and partition in an aqueous 2-phase system. The suspension may be kept uncontaminated and the viability of the *M. leprae* may be preserved if necessary.

IV/208(A) A NOVEL PURIFICATION OF *M. LEPRAE* AND OTHER HOST-GROWN MYCOBACTERIA

John H. Hanks
The Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland, U.S.A.

Armadillo livers yield only 1/100th the bacterial concentration required for direct assays of ATP. Purification must eliminate more than 100 multiples of host components. The current 20-30 step methods were not acceptable because of potential contamination and extraction of metabolic pools. We have devised a three-step (one centrifugation) procedure that decontaminates and yields *M. leprae* of greter purity than is required.

STEPS: (1) Host-cell debris is lysed in 0.5N NaOH, which clears 86% of the original OD.

(2) Angle centrifugation of the homogenates in 30% Percoll concentrates the bacteria and accompanying tissue miscelles into a B-band (bacterial band) resting on 55% Percoll.

(3) The NaOH, tissue miscelles, etc.are eliminated from the B-bands by filtration on 0.45u Millipore membranes.

COMMENT: The alkali lysis of host components has been routine since 1956, requiring that host-grown mycobacteria be separated from only 14% of the junk in crude homogenates. The remarkable efficiency of Percoll is due to the plastic-coated colloidal silica forming spontaneous density gradients, which sort particles on the basis of density. Differential centrifugation is not appropriate for separating bacteria from pycnoticlly equivalent Percoll and host debris. The efficiency of filtration is 33-fold greater than that obtainable by centrifugation.

IV/209(A) A UNIQUE FORM OF GLUTAMIC ACID DECARBOXYLASE IN *M. LEPRAE*

E.B. Harris and K. Prabhakaran
USPHS, National Hansen's Disease Center, Carville, USA

It is not clearly understood why *M. leprae* has an unusual affinity for peripheral nerves. In this study , the bacilli were purified from the spleen or the lymphnodes of experimentally-infected armadillos. Host-tissue enzymes were inactivated by washing the bacteria with dilute alkali. The organisms decarboxylated ^{14}C-glutamic acid, releasing $^{14}CO_2$. The enzyme was pyridoxal phosphate-dependent and was inhibited by hydroxylamine, suggesting that it is true amino-acid decarboxylase. The glutamic acid decarboxylase (GAD) of the bacilli was inactiyated at higher temperatures, indicating its enzymatic nature. The optimum temperature was 37°C; at lower temperatures, the enzyme was inhibited 50% at 30°C and 75% at 25° C. The activity was four times higher at pH 4.5 than at pH 6.8, showing that it is of microbial origin and not derived from the host tissue. Unlike that in other bacteria, the *M. leprae* GAD was a particular enzyme. It was inhibited by excess substrate and substrate-analogs and was stimulated by alpha-ketoglutarate and glutarate. The activity was suppressed by added glutathione and by AET (aminoethylisothiouronium bromide), but was stimulated by DTNB (dithiobis-2-nitrobenzoic acid) Bacteria from heavily infected armadillo liver were sometimes contaminated with bile pigmets and had little GAD activity. Glutamate is the most abundant amino-acid in nerve tissue. The decarboxylation product GABA is an inhibitory neurotransmitter. Moreover, gluatamate could serve as an energy-source for the bacilli. The data offer a possible explantion for the neural affinity of *M. leprae*.

IV/210(A) ENZYMES IN *M. LEPRAE* AND OTHER MYCOBACTERIA STUDIED IN CROSSED IMMUNOELECTROPHORESIS AND POLYACRYLAMIDE GEL ELECTROPHORESIS

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Certain enzymes are highly preserved during evolution and therefore found in a wide variety of bacterial species. Structural comparison of such enzymes isolated from different species may provide important information about the polygenetic relation between bacteria. We therefore started to search for enzyme activity in immunologically defined components of *M. leprae* and other mycobacteria in an attempt to elucidate the taxonomic position of *M. leprae*. Freshly prepared sonicates of mycobacteria were run in crossed immunoelectrophoresis and polyacrylamide gel electrophoresis and the unstained gels were used for detection of enzyme activity. To detect catalase activity, the washed gels were incubated in .005% H_2O_2, washed briefly, and stained in a freshly prepared solution containing .01% ferricyanide and ferric chloride. Catalase activity was seen as clear yellow bands against a dark blue-green background.

Catalase activity could not be detected in *M. leprae* but was easily demonstrated in several other species using this technique. Superoxide dismutase activity was detected by a nitroblue tetrazolium method according to Beauchamp and Fridovich 1971. Enzyme activity was seen as clear almost colourless zones against a blue background. The bands were sometimes weak and difficult to demonstrate.

When enzyme activity was present, this technique allowed a precise localization of the activity to one of the precipitate lines in the crossed immunoelectrophoresis pattern. Attempts will be made to expand this approach to include additional enzymes.

IV/211(A) RESPIRATORY ENZYME ACTIVITY OF *M. LEPRAE*

Tatsuo Mori, Yasuyo Miyata, Kenji Kohsaka and Masanao Makino
Research Institute for Microbial Diseases, Amagasaki, Japan

M. leprae was collected from nude mice footpad leproma. Ficoll solutions were overlayed in nitrocellulose tube 30% 2ml, 27% 5 ml, 24% 5ml, 21% 5 ml, 18% 5 ml, 15% 5 ml, 12% 5ml and 6.5 ml of leproma tissue homogenate which was prepared by filtration through absorbent cotton from grind suspension made in a mortar were also put on it. These tubes were centrifuged in swinging bucket at 27,000 rpm for 1 hour. Fractions 1 to 4 were diluted with distilled water and Ficoll solution was washed by centrifugation. Precipitate was homogenized with 4% NaOH and diluted 8 times and centrifuged for 10 minutes at 10,000 rpm. The preciptate was washed with pH 7.2 phosphate buffer saline by centrifugation. This bacillary fraction was almost free from tissue contaminants. Oxido-reductive difference spectrum of cytochromes was measured. Cytochrome c (550 mμ) was not found but cytochrome b_1 (560 mμ) was seen as the cytochromes of *M. lepraemurium,* but cytochrome a_2 (630 mμ) was not clear. Q_{O_2} of endogenous respiration in *M. leprae* was very small 1 μl/mg, hr compared to that of *M. lepraemurium* 4 μl/mg, hr. This endogenous respiration was not inhibited by diethyl dithiocarbamate which is an inhibitor of diphenol oxidase.

IV/212(A) FACTORS INFLUENCING THE METABOLIC ACTIVITY OF *M. LEPRAE IN VITRO*

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The fundamental "conditions" required for maintaining actively metabolizing *M. leprae* are unknown. Experiments aimed to define these requirements are now possible with large numbers of bacilli derived from armadillo tissue. Using microculture techniques, the influence of a variety of environmental factors was studied. The metabolism of *M. leprae* was monitored by the incorporation of radio-tracers such as ^{3}H-thymidine (1 μCi/well, 70 Ci/mole), Carrier-free ^{32}p (3 μCi/well, 285 Ci/mg), ^{14}C-amino acids (0.1 μCi/well, 50 mCi/mole) into the mycobacteria. Infected armadillo tissue was aliquoted, programme frozen to -50°C and stored at -70°C. One million bacilli extracted from frozen tissue were suspended in 200 μl of RPMI-1640 enriched with 10% fetal calf serum. The microplates were incubated at 37° in 5% Co_2 atmosphere. Prior to harvesting, cultures were screened for contaminants and treated with 4% w/v NaOH. The suspensions were filtered using 0.45 μ membranes and processed for liquid sci-

ntillation counting. The results showed the radioactivity was (a) higher with "live" bacteria as opposed to controls, (b) proportional to the number of bacteria in the inoculum, and (c) a strain-to-strain variation in its ability to incorporate thymidine. The implications and observations of cultures maintained at lowered temperatures and oxygen content environments will be discussed.

IV/213(A) PURINE METABOLISM IN *M. LEPRAE*

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M. leprae organisms generally incorporated purines more rapidly than pyrimidines into nucleic acids from incubation medium. Purine synthesis *de novo* took place at a very slow rate, suggesting a preference of the organism for preformed purines. In cell-free extracts of leprosy bacilli, enzymes for scavenging and interconversion of purines were detected. The results are discussed in relation to devising culture media for *M. leprae*, and developing drug-screens. In an attempt to show whether these results reflect the metabolism of *M. leprae*, or the metabolism of a mycobacterium growing *in vivo*, preliminary results of experiments on purine metabolism of *M. microti*, grown *in vivo* and *in vitro*, are presented.

IV/214(A) IDENTIFICATION AND ANALYSIS OF MYCOBACTERIAL LIPIDS IN SKIN TISSUES OF LEPROSY PATIENTS

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It has been possible to detect characteristic mycobacterial lipids in skin biopsies of leprosy patients. Extraction procedure of Bligh and Dyer (1959) modified by Kates (1972) and Card (1973), when applied to analysis of these lipids could detect Mycoside (phenolic glycolipid) and Phenol phthiocerol dimycocerosate (PDIM) in tissues weighing as little as 100 mg. Thin layer chromatography and high performance thin layer chromatography techniques were applied to identify these lipids. Few reference mycobacteria and corynebacterium (PW 8) were included for identification of the nature of lipids. Strongly UV-absorbing derivatives of mycolic acids such as dinitro-benzyl-dinitrobenzoyl derivatives were prepared for analysing mycolic acids present in biopsies. This work is still in progress. The significance of this study lies in the fact that characteristic lipids could be detected even in leprosy biopsies in which *M. leprae* may be present in small numbers. It might be possible that these lipids are those derived from *M. leprae*, once present in large numbers in skin and perhaps degraded now by chemotherapy.

IV/215(A) BIOCHEMICAL STUDY OF THE PERIBACILLARY SUBSTANCE OF *M. LEPRAE*

Yukiko Fukunishi, George P. Kearney, John D. Whiting, Jr., Gerald P. Walsh, H. Binford, Wayne M. Meyers and Frank B. Johnson
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A peribacillary substance in the form of small spherical droplets has been observed in phagolysosomes in freeze-etched specimens of tissues from *M. leprae*-infected humans, nude mice, armadillos and mangabey monkeys. There is a corresponding electron transparent zone around the leprosy bacilli in ultra-thin sections. These findings suggest that lipids constitute a major portion of the peribacillary substance.

Biochemical studies were made of lepromas obtained from a nine-banded armadillo infected with *M. leprae* obtained from a mangabey monkey *Cercocebus atys* with naturally acquired leprosy. The leproma was extracted with a chloroform-methanol mixture. The extracted material was analysed by: high performance liquid chromatography in the normal phase, reversed phase, and gel-permeation mode; gas liquid chromatography UV/Vis spectrophotometry, infrared spectroscopy, and mass spectroscopy.

The peribacillary substance contained a mycoside A-like phenolic glycolipid (PGL I) similar to that reported by Hunter and Brennan in *M. leprae*-infected liver and spleen. The core molecule and carbohydrate component were similar; however, the fatty acid moieties had a lower carbon number and lacked the characteristic methyl branching. Possible relations of variations in the fatty acids to the origin of starting materials and procedures will be discussed.

IV/216(A) PHENOLIC GLYCOLIPID ANTIGENS AS A TOOL OF SERODIAGNOSIS OF LEPROSY

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In 1980, Brennan *et al.* found a novel *M. leprae*-specific antigen. Hunter *et al.* demonstrated that the antigen is a phenolic glycolipid with methylated trisaccharide and phthiocerol dimycocerosate. Recently, one of the authors (T.F.) synthesized the saccharides which have the same of comparable antigenicity.

We are now developing new techniques for serodiagnosis of leprosy and infection of leprosy bacilli, by using both native and synthetic antigens.

In the presentation, the sensitivities and specificities of the new methods will be considered, and the possibility of using the techniques in the field of leprosy control will be discussed.

IV/217(A) EFFECT OF LONG-TIME CONTACT OF DAPSONE WITH MYCOBACTERIA AND NOCARDIA ON SOME BASIC METABOLIC PROCESSES

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In order to obtain data regarding the long-time effect of dapsone on the metabolism of mycobacteria and Nocardia, cultures were performed on dapsone containing solid growth medium (DSGM)and without dapsone as well (solid growth medium, SGM). A marked inhibition of the following processes was obtained:

1. enzyme induction (histamine: NADP+ oxidoreductase in *M. smegmatis* SN 46; histidine ammonia lyase in *M. smegmatis* SN 2; urease);
2. ammonia uptake;
3. Glucose oxidation (strong inhibition); xylose and mannose oxidation (slight inhibition).

Contrarily, enzymatic activities were found to be higher for:

4. monooxygenase (catechol oxidation in *Noc. lutea*);
5. asparaginase.

Activities remained unchanged for:

6. rhamnose, arabinose, galactose, mannitol and sorbitol oxidation.

In addition, experiments were carried out in order to:
(a) protect the cells against dapsone action during growth. To reach this goal, folic acid (FA), p-amino-benzoic acid (PABA), methionine (met), serine (ser) and thymine (thy) were incorporated into the DSGM and enzymatic activities measured. Only PABA and 'met' were able to achieve a protection as well as enzyme induction, ammonia uptake or glucose oxidation were concerned;
(b) to make the damage caused by dapsone reversible; compounds mentioned under(a) were added to bacteria grown on DSGM, incubated and the enzymatic activities measured. Neither FA nor PABA or the other compounds were able to achieve a reversion of the damaged metabolic steps

However, metabolic activities were fully restored if the bacteria grown on DSGM were inoculated on fresh SGM. Consequently, in order to keep some metabolic steps inhibited, cells must be in a steady contact with the drug.

The results will be discussed regarding the sulfonamide-like activity of dapsone; deviations from the sulfonamide-theory will be mentioned as well.

V/218(A) LEPROSY-DERIVED CORYNEBACTERIA, *M. LEPRAE* AND RELATED ORGANISMS: A COMPARISON OF THEIR CELL ENVELOPE ARCHITECTURE BY ULTRASTRUCTURAL AND CYTOCHEMICAL METHODS

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Cell envelope architecture of three strains of Leprosy-Derived Corynebacteria (LDC) named Kim, FPSA and 43 LL were compared with the members of the *Corynebacterium-Mycobacterium-Nocardia* (CMN) group as well as with other related organisms *(M. flavum* and *Lactobacillus acidophilus)*. The ultrastructure of *M. leprae* was also compared with above organisms. Cytochemical studies were performed at the ultrastructural level after-staining with silver proteinate, acidic phosphotungstic and ruthenium red colourations which revealed different polysaccharide components. These studies showed that none of the LDC strains resemble the member of the CMN group including *Corynebacterium pseudo-tuberculosis*. Moreover the above LDC strains had different ultrastructures and varied in their cytochemical pattern among themselves. *M. leprae* on the other hand, had a typical mycobacterial ultrastructure and gave a cytochemical response common to other members of the CMN group.

IV/219(A) EFFECT OF PYRIDINE EXTRACTION ON THE ACID FASTNESS OF *M. LEPRAE*: ITS POSSIBLE MECHANISM

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Pyridine extractability of acid-fastness of *M. leprae* was initially described as its specific character and was thought to be due to phospholipids. This was later refuted by some workers and was linked to ageing process of mycobacteria. In a study conducted in our laboratory, it has been found that besides *M. leprae*, *M. vaccae* and *M. phlei* also lose their acid-fastness

when extracted with pyridine for 2 hours at room temperature. However, other mycobacteria including *M. tuberculosis* do not lose their acid-fastness under similar experimental conditions. In the present study, *M. vaccae* and *M. tuberculosis* have been taken as model organisms to understand the mechanism of this loss of acid-fastness by pyridine. The cultures of *M. vaccae* and *M. tuberculosis* were extracted by pyridine for 2 hours at room temperature and the extracted lipids were then fractionated using florisil column chromatography. These fractionated lipids were separated by thin-layer chromatography and their patterns were compared. It has been found that pyridine extracts not only phospholipids but neutral lipids and glycolipids as well. However, thin-layer chromatograms revealed the differences between the extractable lipid pattern of these two species. Detailed findings will be presented and the role of the different lipids including mycolic acids in the acid-fastness extractable by pyridine *M. leprae* and other mycobacterial species will be discussed.

IV/220(A) TAXONOMIC STUDIES OF MYCOBACTERIA BELONGING TO THE *"M. LUFU"* GROUP

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Slow-growing environmental mycobacteria, sensitive to dapsone (MIC between 0.06 and 0.03 mg/l), were isolated in Zaire. Some of them, isolated from the LUFU river, were temporarily named *"M. lufu"*. Further investigations (chemotaxonomic and genetic studies) permitted the classification of 14 strains in three homogenous groups, different from the species of mycobacteria recognised at present.

The name *M. lufui* should be proposed for the new group containing the organism studied as a model for drug evaluation against *M. leprae*.

Analysis of other dapsone sensitive strains (from the other new groups), might create new possibilities for studies of the action of dapsone and related compounds.

IV/221(A) RAPID RADIOMETRIC *IN VITRO* ASSAY FOR THE EVALUATION OF ANTILEPROSY DRUGS AND THE DIAGNOSIS OF DAPSONE RESISTANCE

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In recent years, our laboratory has developed *in vitro* assay for the evaluation of *M. leprae* viability. *M. leprae* resident human/murine macrophage cultures maintained for 3 and 2 weeks respectively and continuously pulsed with 3H thymidine show incorporation of the radiolabel as compared to paired cultures with heat-killed bacilli. (1) Dapsone showed significant inhibition of 3H thymidine incorporation at levels ≥ 3 ng per ml. *M. leprae* from 21 lepromatous patients clinically suspected of dapsone resistance showed a high degree of concordance for sensitivity and resistance when compared in the radiometric assay and in mouse footpad done independently at Central JALMA Institute, Agra, and National Institute for Medical Research, Mill Hill, London. (2) Rifampicin showed exquisite inhibition in 31 human and one armadillo - derived *M. leprae* strains. Inhibition was observable consistently from 3 ng onwards. The *in vitro* sensitivity for this drug is several fold less than that observed in the mouse footpad model. (3) Clofazimine supplied by Dr. Conalty, Medical Research Council of Ireland, showed inhibition even at 48 hours exposure in cultures, whereas the analogues (B 3648, B 3640, B 3713, B 3691) were effective at a longer time period of 72 hours.

IV/222(A) APPLICATION OF ATP ASSAY TO PATIENT CARE IN LEPROSY

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The inability to cultivate *M. leprae in vitro* has been a major bottleneck in leprosy research, especially in evaluating the effects of therapy on viability of organisms. The mouse footpad method is time-consuming and expensive. Because of ubiquitous distribution and metabolic importance of adenosine triphosphate (ATP), it is considered as an indicator of viability of *M. leprae*. In randomly selected leprosy cases, treated as well as untreated, ATP assay results agreed well with mouse footpad data on the status of M. leprae from these patients, especially in identifying drug-resistant cases. An international collaborative programme is under way in which previously untreated leprosy patients are being monitored at periodic intervals during therapy to determine the efficacy of anti-leprosy treatment on their bacterial populations. The results of the first group of 20 patients show that the ATP assay findings correlate well with mouse footpad results, in identifying drug-resistant cases within 2-3 months after initiating therapy. The only difference is that the ATP results are obtained instantaneously (2hours), while with the mouse footpad technique, it took 10-12 months to obtain the same results, and that ATP assay technique is much cheaper to adopt widely in endemic areas.

IV/223(A) *IN VITRO* GROWN *M. LEPRAE* – CULTIVABLE BACTERIA WITH CONDITIONED PHENOTYPIC EXPRESSION

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The efforts to cultivate acid-fast bacteria from nodules of leprosy patients have shown multiplication of *M. leprae* repeatedly in special conditioned medium. Such isolated *in vitro*-grown acid-fast bacilli show several characteristic features of M. leprae during 3-4 passages, each passage into fresh medium being at an interval of about 2 months. After this, the characters get lost; but are regained, if such isolates are then passaged through mice. The characters identified as typical of *M. leprae*, are pyridine extractable acid-fast staining, uptake of labelled DOPA, specific inter-action with macrophages from lepromatous leprosy patients leading to altered membrane functions, reduced protein synthesis, as well as induction of specific nerve damage in mice along with characteristic growth in the mouse footpad. Isolation of drug-resistant leprosy bacilli from patients and demonstration of such resistance both *in vitro* and *in vivo* has also been possible. Thus *M. leprae* are cultivable, but behave as conditioned phenotype *in vitro*.

IV/224(A) CULTIVATION OF *MYCOBACTERIUM X* FROM *M. LEPRAE* INFECTED TISSUES AND OF *M. LEPRAEMURIUM* IN A PROPANE TETRADECANE LIQUID MEDIUM

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The medium contained in 1 litre distilled water KH_2PO_4 7g, Na_2HPO_4 0.5 g, $(NH_4)_2SO_4$ 2g, $MgSO_4$ 0.1 g, yeast extract 0.1 g and ferric ammonium citrate 20 mg. The pH was 5.8. To each of the 50 ml tubes containing 15 ml medium, 0.1 ml tetradecane was added. Partially purified, NaOH-treated suspension of *M. leprae* was prepared from the livers of *M. leprae*-infected armadillos. *M. lepraemurium* suspensions were prepared from subcutaneous lepromata of mice. The media were inoculated so as to obtian 10^5 per ml of *M. leprae* or *M. lepraemurium* cells respectively in the media. The inoculated media were bubbled aseptically for 10 seconds with propane gas. Cultures were incubated at 32°C.

Growth developed as a whitish veil in 4 to 12 weeks at the interface of tetradecane floating on the surface of the medium. The veil increased in volume with time and developed into a disc like shape, containing masses of strongly acid-fast bacilli. Counting of cells was done in the cultures diluted with acetone (1:1 v/v) to emulsify tetradecane in the medium. A slow growth was counted in the tetradecane medium. The growth rate and yield were considerably higher in the propane-tetradecane media. Subcultures grow in the propane-tetradecane media, but not on Lowenstein or in Dubos media. Cultures obtained from *M. leprae*-infected animals (designated as *Mycobacterium X*) produced the disease typical of *M. leprae* in the footpads of mice. Cultures obtained from murine lepromata produced the characteristic murine leprosy when injected subcutaneously into mice.

IV/225(A) THE EPIDEMIOLOGICAL SIGNIFICANCE OF THE OCCURRENCE OF *M. LEPRAE*-LIKE MICROORGANISMS IN THE ENVIRONMENT

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To clarify the epidemiological significance of the occurrence of *M. leprae*-like microorganisms in the environment, samples of water, soil and vegetation in former and recent leprosy regions have been examined. A total of 565 samples collected in Norway, Ivory Coast, Purtugal, Peru, India, Spain and USA (Louisiana) has been processed up to the moment, inoculated in mice footpads and examined for acid-fast bacilli after 6, 9, 12, 18 and 24 months. Positive samples (25 to 55% of the samples) were tested for "non-cultivability" in conventional media for mycobacteria and then inoculated in sphagnum nutritive substrate, where *M. leprae* has been shown to be able to multiply. When growth occurred, inoculations into arrmadillos and nude mice together with biochemical tests (Dopa oxidase and pyridine extraction) were performed. A great part of these mycobacteria showed the same biological and biochemical properties as *M. leprae*. The production of antibodies against *M. leprae* antigen 7 in armadillos, infected with these mycobacteria, has also been observed. The epidemiological importance of this possible environmental source of *M. leprae* is discussed.

IV/226(A) BIOLOGICAL PROPERTIES OF LEPROSY-DERIVED CORYNEBACTERIA

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Leprosy-derived corynebacteria (LDC), non acid-fast gram-positive bacteria, are frequently isolated, in addition to *M. leprae* (ML), from cutaneous lesions, blood and bone marrow of leprosy patients. LDC can be shown in patient tissue sections and smears by use of certain staining

techniques. They can be grown axenically. LDC are immunologically related more closely to ML than the reference corynebacteria, as shown by double diffusion tests. By crossed immunoelectrophoresis with intermediate gel, several cytoplasm components of LDC were shown to crossreact with those of mycobacteria. Indeed, a strong crossreactivity of LDC antigen M and ML antigen 7 (a major antigenic component of lepromin) has been assessed. This immunological kinship might be the basis of a pathogenic cooperation between LDC and ML. Such a hypothesis was tested by following the proliferation of ML in the footpads of mice previously injected/or not with a small number of viable LDC. By the 3rd month, the number of ML in LDC-injected foot pads greatly exceeded that in footpads receiving saline. The reason for the enhanced growth kinetics (an effect which is restricted to the site of injection) has not been established. The reverse effect was observed upon repeated local injections of large amounts of inactivated LDC : no proliferation of ML took place. LDC preparations (whole-cell homogenates, walls and cytoplasm) were used for cutaneous tests in leprosy patients. In tuberculoid cases, a good correlation between lepromin and LDC antigens was observed in both Fernandez and Mitsuda reactions. In lepromatous leprosy, the number of responders to LDC antigens was higher than that to lepromin.

In conclusion, the frequent presence within leprosy lesions of LDC with constant morphological and biochemical (cf. the accompanying abstract by C. Cocito *et al).* traits is suggestive of a possible participation of LDC to the development of the disease (isolation of this kind of organisms from healthy persons has been so far unsuccessful). A facilitation of *M. leprae* proliferation has been experimentally reproduced by local LDC injection. The strong crossreactivity of major ML and LDC antigens might account for the pathogenic cooperation between these 2 kinds of microorganisms.

IV/227(A) INGESTION OF *M. LEPRAE* FAILS TO STIMULATE PHAGOCYTE METABOLIC BURST ACTIVITY

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The mechanism by which obligate intracellular pathogens such as *M. leprae* escapes destruction following ingestion by phagocytic cells remains unclear. Following phagocytosis of microorganisms,phagocytic cells produce reactive oxygen intermediates during the "metabolic burst". Earlier work had shown that *M. leprae* was ingested by murine macrophages (MØ), but that phagocytosis of the organism failed to stimulate MØ postphagocytic metabolism as measured by chemiluminescence, hexosemonophosphate shunt activity and reduction of nitroblue tetrazolium. We now report that the ingestion of irradiated *M. leprae* by MØ from BALB/C mice also failed to stimulate the production of superoxide anion (0_2), and oxygen intermediate thought to be important in bacterial killing. BALB/C MØ responded normally to control stimuli. MØ challenged with viable BCG, released significant amounts of 0^-_2 that was enhanced by opsonization with normal human serum. 0^-_2 assays were also performed with human blood neutrophils (PMN) and monocytes. *M. leprae* failed to stimulate 0^-_2 release by either cell type even when opsonized. Human PMNs and monocytes challenged with viable BCG exhibited significant 0^-_2 productin that was enhanced when the organism was opsonized. These studies indicate that *M. leprae* fails to stimulate both murine MØ and human PMN and monocyte post-phagocytic metabolism and that this may be an important mechanism by which *M. leprae escapes Phagocyte microbicidal activity.*

IV/228(A) CHARACTERIZATION OF THE ANTIGENIC STRUCTURE OF M. LEPRAE AND RELATED MYCOBACTERIA

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Detailed knowledge of the antigenic composition of *M. leprae* is a prerequisite for studies of humoral and cellular immune responses in leprosy, and as basis for purification of individual immunogenic components from the bacillus.

Model studies will be described with an emphasis on crossed immunoelectrophoresis (CIE) of *M. leprae* and related mycobacteria. The technique offers precise demonstration and identification of individual immunogenic constituents of mycobacteria in native form, as they occur in sonicates of bacilli and culture fluids. A new technique will be described for characterization of the specificity of monoclonal antibodies, produced by hybridoma technology at the level of reactivity with a single component defined by CIE. The combined use of immunological and biochemical techniques will be described, based on studies of the reactivity of monospecific antimycobacterial antisera in CIE, compared with various techniques of electrophoresis and immunoblotting. Combined with various staining techniques, these offer a system of high precision and resolving power for charaterization of the immunogenic constituents of mycobacteria.

IV/229(P) POLYACRYLAMIDE GEL TECHNIQUES FOR ISOENZYME CHARACTERIZATION OF MYCOBACTERIA : THEIR RELEVANCE IN TAXONOMY AND IDENTIFICATION

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The development of reproducible electrophoretic techniques with high resolving power has resulted in an upsurge of interest in metabolism of different tissue and *in vitro* grown parasites and also in their biochemical systematics. The techniques for separation of the lactic dehydrogenase (LDH) and esterase isoenzymes of mycobacteria have been standardised, and various influencing factors as well as reproducibility has been established at our laboratory. LDH and esterase isoenzyme patterns of various representative mycobacterial species, namely *M. tuberculosis,* B.C.G., *M. kansasii, M. scrofulaceum,* different Skinsnes' isolates from leprosy lesions, *M. gordonae, M. avium, M. gastri, M. smegmatis, M. phlei, M. lepraemurium,* strains and species described to be closely related to *M. leprae (M vaccae,* ICRC bacillus, *M. strains w),* normal human sera, extracts of *M. leprae*-infected nodules and normal human skins have been studied. It was found that all the mycobacterial species tested showed characteristic isoenzyme patterns. The relevance of these findings in the identification and taxonomy of mycobacteria, specially those species difficult to grow, and also their metabolic importance, wil be presented and discussed.

IV/230(P) BIOCHEMICAL PROPERTIES OF LEPROSY-DERIVED CORYNEBACTERIA

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A collection of 25 leprosy-derived corynebacteria (LDC) (non-acid-fast bacteria isolated from human leprosy lesions) from the J. Delville's Collection (Brussels) has been analysed. This group of organisms proved highly homogeneous, according to biochemical criteria. Base composition of the isolates was, on the average, of 56% GC (corynebacteria have 50 to 60% GC), and mycobacteria 67 to 69%. A high degree of homology was revealed by hybridization studies with LDC-DNA; instead, a negligible homology between the DNA of LDC and reference corynebacteria was found. The structure of LDC peptidoglycan has been unravelled : it contains the tetrapeptide L-Ala-D-Gly-(L)-mDAP-(L)-D-Ala (mDAP = mesodiaminopimelic ac.), and partly glycolylated muramic acid (a feature lacking in reference corynebacteria). The LDC peripheral polysaccharide consists of arabinogalactomannan with lateral chains of mannose and arabinose : its structure, thus, differs from that of both mycobacteria and corynebacteria. To this polymer, corynomycolic acids with 24 to 36 carbons and 0 to 4 double bonds (another peculiar property of this kind of bacteria) are linked. Crossed immunoelectrophoretic analysis has shown that 17 out of 20 antigenic components of LDC cytoplasm crossreacted among them. Some of these antigens also crossreacted with mycobacterial components. The complex M of LDC cytoplasm, a major thermostable immunogen of LDC, strongly crossreacted with antigen 7 of *M. leprae,* a major component of lepromin.

In conclusion, LDC represent a unique and homogeneous group of microorganisms within genus Corynebacterium s.s. (human pathogens). They have distinct traits differing from those of reference corynebacteria, and are immunologically more closely related to *M. leprae* than to known corynebacteria.

IV/231(P) BIOCHEMICAL CHARACTERISTICS OF *M. LEPRAEMURIUM* PRO-PAGATED IN CELL-FREE LIQUID MEDIUM

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From the results of amidase activity of *M. lepraemurium* (Mlm) grown on Ogawa solid medium, *Mlm* has been classified in a group that includes *M. avium.* The present paper reports the results concerning extraction of the cord factor from *in vitro Mlm,* polypeptide analysis by SDS-polyacrylamide gel eletrophoresis and a trial of extraction of plasmids from SM^r as well as INH^r *Mlm,* which were established in liquid culture system. For propagation of Mlm, NDLAS (US-J. Meeting 1982) and ND-11 liquid culture medium were used.

The results obtained indicated that a cord factor extracted from *in vitro Mlm* was identical to that from *in vivo Mlm* previously reported by Goren *et al.* (1979), and that polypeptides of *in vitro Mlm* were quite similar to those of *M. avium.* It was difficult to extract polypeptides from *in vivo Mlm.* Regarding plasmids, no reproducible results were obtained so far.

IV/232(P) GROWTH FEATURES OF *M. LEPRAEMURIUM* IN CELL-FREE LIQUID MEDIUM

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In order to evaluate the culture medium for growth of *M. lepraemurium (Mlm)*, morphological observation along with the growth of bacilli was carried out. For this purpose, a slide culture method is useful, and scanning electron microscopy was employed. Three following culture media were tested: (1) ND--5 (1975) (2) NDLAS (1982) and (3) ND-11 medium. The ND-11 medium is composed with Dubos base containing asparagin, supplemented by egg yolk, alpha-ketoglutarate, hemin, l-cysteine, and albumin.

The results obtained demonstrated that the growth of Mlm took place by binary fission with elongation, and that the best yield of Mlm was found in ND-11 medium which contains no calf serum.

Accordingly, it could be suggested that the growth of *Mlm* might be extremely sensitive to a natural inhibitor in animal serum. Therefore, it could be speculated that this fact might convey an important suggestion to the study of the cultivation of *M. leprae*.

IV/233(P) A CLINICAL ASSESSMENT OF FLUORESCENT STAINING PROCEDURE FOR MEASURING THE VIABILITY OF *M. LEPRAE*

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A fluorescent staining procedure using fluorescein diacetate (FDA) and ethidium bromide (EB) has been shown to measure accurately the viability of saprophytic mycobacterial cells. Viable cells stain green due to the presence of intracellular acetylesterase which hydrolyses non-fluorescent FDA to fluorescent fluroescein and an intact cell membrane which permits enzymatically generated fluorescein to be accumulated and EB to be excluded from the live cells. Dead cells stain red since FB readily penetrates cells which lack an intact cell membrane, thereby allowing EB to intercalate between DNA bases. The purpose of this research is to determine whether the staining method accurately measures the viability of *M. leprae* and, as a result, serve as a clinical tool for monitoring the efficacy of chemotherapy in lepromatous (LL) and borderline lepromatous (BL) leprosy patients.

Clinical data obtained at the Leonard Wood Memorial's research facility in Cebu, Philippines, suggest that the staining method is indicating the viability of *M. leprae*. A significantly lower percentage of green-stained *M. leprae* was detected in the tissues of 24-month treated LL patients (8%) as compared to 3-month treated (35%) or untreated patients (58%). A high percentage (90%+) of green-stained M. leprae was detected in infected mouse footpads.

IV/234(P) GROWTH OF *M. LEPRAE* IN SPHAGNUM MOSS EXTRACT: MULTIPLICATION RATES AND NUTRITIVE REQUIREMENTS

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Epidemiological evaluation of the former leprosy endemic in Norway revealed a significantly higher occurrence of leprosy, when a close contact (drinking water, working in) of the population with sphagnum moss vegetation could be reported. Other experiments have stated, that the grey layer of sphagnum mosses contains nutritive substances, which allow the growth of a variety of pathogenic and saprophytic mycobacteria. The extract of the grey layer of sphagnum vegetation prepared by homogenisation, autoclaving and filtration (pore size 0,2μ) contains 20 amino acids, a variety of carbohydrates and steroids and has been used as a cultivation medium for *M. leprae*. Growth occurred within one month when human and armadillo-derived *M. leprae* were used, and reached maximal growth rates in three months-increase from 10^4 to 10^6/ml. During the growth of *M. leprae* lysine, 3-methylhistidine and histidine have been utilized, while gamma-aminobutyric acid, glutamine and asparagine were only utilized in part. The uptake of steroids has also been observed. The cultures of *M. leprae* in sphagnum extract remain non-cultivable in conventional media for mycobacteria, while the typical pathogenicity in footpads of nude mice is observed.

IV/235(P) ON THE DIFFERENTIATION BETWEEN DRUG-SENSITIVE AND RESISTANT MYCOBACTERIAL STRAINS BY MASS FINGERPRINTS OF SINGLE CELLS

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The laser microprobe mass analyzer LAMMA opens up the possibility of producing mass fingerprints of single bacterial cells. In a first investigation, it could be demonstrated that these finger-prints are characteristic for different strains. Computer-aided statistical methods allow the sophisticated evaluation of such fingerprints for the detection of minute differences as they appear between various mycobacterial strains of the same species or between drug-resistant and drug-sensitive strains. However, these differences are only reliable if the bacteria are prepared and analysed under identical conditions. For a differentiation procedure, typically one hundred single cells of each sample are mass analysed. On the basis of the statistically significant differences as obtained from a comparison of each mass of the averaged finger prints of each sample, a nonlinear map is established demonstrating the degree of similarity between the various samples in a 2-dimensional plot. Results on a number of cultivable strains of some mycobacterial species and from isolated *M. leprae* are presented.

IV/236(P) DETECTION OF IMPAIRMENT *OF MYCOBACTERIA* BY SINGLE CELL MASS ANALYSIS OF INTRACELLULAR CATION CONCENTRATIONS

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The laser microprobe mass analysis LAMMA, a new micro-analytical technique, which is based on the laser-induced ionization and subsequent mass spectrometric analysis of very small volumes($\approx 1/\mu m^3$) is a promising method in microbiology and bacteriology by supplying information on single bacterial cells. At present, however, statements on the molecular level can be made only on the basis of mass fingerprints, because (due to yet unknown fragmentation mechanisms involved in the laser-sample interaction) it is not possible to identify reliably peaks other than those of some elements. These include the cations sodium, potassium, magnesium, and calcium, which are well known for their regulatory role in cell function. As the sodium-potassium ratio is a particularly sensitive indicator of cell viability, the principal intention behind the application of single cell mass analysis to the measurement of the sodium-potassium ratio (or absolute content) is the utilization of this method in leprosy research (e.g. therapy development). It should be of great advantage that all information can be obtained from a very limited number of bacteria. To these criteria belong conclusions regarding the mechanism of action of external factors which can be deduced from calculations of distribution patterns for these elements within a cell population (a few hundred cells).

IV/237(P) GROWTH OF *M. LEPRAE* IN A REDOX SYSTEM

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Mycobacteria recovered from human lepromatous nodules and presumably *M. leprae*, have been grown in a medium that ensured a minimal oxygen tension at initiation of growth, and an increasing availability of oxygen as bacillary growth increased, requiring marginal increments in oxygen tension. This physico-chemical environment was achieved by the addition of strong biological reductants in the medium, and a combination of partial vacuum and alkaline pyrogallol in the culture vessel. In addition, n-tetradecane, a straight-chain hydrocarbon, and lipids like cholesterol and lecithin, all three substances mixed in the aqueous medium as liposomes, were added and found to be useful. Menadione, or Vitamin K_3, added to the medium considerably improved growth efficiency. Growth occurred initially as non-acid fast coccoids and bacilli that gradually changed to acid-fast bacilli and globi, and cell-wall deficient, spherical L-form elements. Appearance of growth in any form was perceptible within 1 to 2 weeks and optimal growth as acid-fast bacilli took upto 3 months. Both the acid-fast and the non-acid fast bacilli could not be grown in conventional media, but the non-acid fast coccoids could be readily isolated from these cultures in a specially enriched liquid medium. The problem of harvesting of the growth free of lipid-hydrocarbon substances has still not been solved, as also an optimum oxidation-reduction potential. The growth is transferable.

IV/238(P) MACROPHAGE-MYCOBACTERIA INTERACTIONS: A COMPARATIVE ULTRASTRUCTURAL STUDY OF *M. LEPRAE*, AND OTHER PATHOGENIC AND NON PATHOGENIC MYCOBACTERIA AFTER PHAGOCYTOSIS BY MOUSE BONE-MARROW-DERIVED MACROPHAGES

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Interactions between mouse bone-marrow-derived macrophages and *M. leprae* purified from experimentally infected armadillo, were studied under the electron microscope. The results were also compared with other phagocytosed pathogenic (*M. avium* and *M. tuberculosis* H_{37} Rv) and non-pathogenic mycobacteria (*M. tuberculosis* H_{37} Ra and *M. aurum*). Infected macrophages were studied, using bacteriological control and varied techniques of electron microscopy during several weeks, in order to compare the ultrastructural appearance of the bacteria, their fate and multiplication. The occurrence of phagosome-lysosome fusion was also quantified, using cytochemical methods and careful analysis of the electron micrographs.

IV/239(P) NATURAL RESISTANCE TO BCG AND *M. LEPRAEMURIUM* IS EXPRESSED BY MACROPHAGES AND LINKED TO H_2O_2 METABOLISM

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Antimycobacterial effects of peritoneal macrophages, spontaneous release of hydrogen peroxide (H_2O_2) and superoxide anion (O^-_2), levels of Superoxide Dismutase (SOD) and Glutathion peroxidase (GPO) of spleen macrophages from normal, BCG and *M. lepraemurium* (Mlm)-infected strains of mice, known to be naturally resistant (NR) or naturally susceptible (NS) to BCG and Mlm, were evaluated. Present evidence shows that *in vitro* metabolism of BCG phagocytosed by peritoneal resident macrophages from normal mice was constantly inhibited as measured by an *in vitro* isotopic incorporation assay. Moreover, using the same macrophage/BCG ratio, calculated inhibition indices were always higher in NR strains (C3H mice) compared with NS strains (C57B1/6 and Swiss mice). A significant increase of spontaneous H_2O_2 production, but not O^-2, was observed in spleen macrophages from BCG or Mlm infected NR strains C3H, A/Jax, and CD2 mice) but no such increase occurred in NS strains (C57B1/6, Balb/c and Swiss mice). Increase of H_2O_2 production was always associated with a significant rise of SOD and GPO levels after mycobacterial infection, in spleen macrophages. Similarly, *in vitro* phorbol myristate acetate (PMA) induced H_2O_2 production, but not O^-2, was further increased with exogenous SOD and reduced with diethyldithio-carbamate (DDTC), a known SOD inhibitor. These results strongly suggest a possible linkage between mycobacterial-induced TOI metabolism in macrophages and natural resistance to BCG and Mlm infection in mice

IV/240(P) DEVELOPMENT OF AN *IN VITRO* TEST FOR THE ASSESSMENT OF VIABILITY AND METABOLISM OF INTRACELLULAR MYCOBACTERIA

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The aim of the study was to develop a procedure whereby the growth and metabolic activity of mycobacteria resident in human monocyte-derived macrophages can be measured with higher sensitivity and consistency. A number of radioactive precursors measuring different metabolic pathways were studied. These include ^{14} C-acetate, ^{3} H-thymidine, ^{3} H-uracil, ^{3} H-leucine and ^{14} C-glucose. ^{14} C-acetate was found to be incorporated more rapidly and in higher amounts as compared to other labels by two cultivable mycobacteria. *M. w* and *M. vaccae* used as model bacteria in this system. The experimental system enables distinction to be made between killed and live mycobacteria, and measures with fair accuracy a small number of viable mycobacteria. Since ^{14} C-acetate is incorporated by the bacteria as well as the host cell, an experimental procedure was devised to obtain a differential response. The system may be useful to evaluate the influence of lymphokines, drugs and other agents on the growth of intracellular mycobacteria.

IV/241(P) CULTIVATION OF *M. LEPRAE* AND *M. LEPRAEMURIUM*

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A peculiar yeast-like microorganism, isolated from leprous lesions, was discovered to produce a growth-promoting factor for *M. leprae*. This organism, for producing the growth factor, required iodine compounds and morphologically showed a wide range of biophase (fungal to bacterial) according to the composition of the medium.

From mass culture of this organism, an oil substance stimulating the growth of *M. leprae* was extracted and purified using organic solvents.

When inoculating *M. leprae* on the special solid medium, chemically defined and with the added emulsified factor, and incubating for 10 days in 35-36° C, growth of acid-fast bacilli was observed as light yellow R type colony. Successive cultivation of the bacilli was possible only on the special medium used but not on media for general mycobacterial species.

The same growth-promoting factor was effective also on *M. lepraemurium*. In this case however, the basal medium was a little different. Nutritionally, *M. leprae* was arabinose tartrate type and *M. lepraemurium* was xylose-citrate type. Identification studies on the cultivated bacilli are now proceeding. The growth factor would be supplied to world researchers, on request.

IV/242(P) NADH-METHAEMOGLOBIN REDUCTASE AMONG LEPROSY PATIENTS

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The activity of NADH-methaemoglobin reductase (NADHMR) was investigated in blood samples of 183 adult leprosy patients who were ingesting a daily dose of 100 mg dapsone, as well as in blood samples of 137 healthy soldiers. The mean age was 52 years (s.d.= 16.36) for the leprosy patients and 19 years (s.d.= 0.94) for the healthy subjects.

The mean NADHMR activity exhibited by the leprosy patients did not differ from that observed among the healthy individuals. However, the variance of the former was significantly higher than that observed among the healthy subjects. The greater variability of NADHMR activity detected among the leprosy patients seems to be due mostly to their lower hemoglobin levels. Age and dapsone blood-level play a less important role for influencing the NADHMR activity.

As expected, the methemoglobin level was, on the average, significantly higher among the leprosy patients (7.03%; s.d. = 3.83%) as compared to the healthy individuals (5.47%; s.d. = 3.67%). Nevertheless and curiously enough, the methemoglobin level was not correlated with the NADHMR activity nor with the dapsone blood-level.

IV/243(P) NUMERICAL TAXONOMY OF LEPROSY-DERIVED ACID-FAST CULTURES

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Twenty selected biochemical characteristics and sensitivities to ten chemotherapeutic agents of 30 leprosy-derived acid-fast cultures will be compared with similar determinations for nine strains of *M. scrofulaceum* and four strains each of *M. avium* and *M. intracellulare*. Additionally, results will be presented of electron microscopic observations of the reactions of these mycobacterial strains with immuno-peroxidase antibody preparations from human lepromatous leprosy and from rabbits immunized with *M. leprae* which have been absorbed with other suitable mycobacterial strains to remove cross reacting antibodies. The results will be computer analyzed (numerical taxonomy). The similarities for each and every of the above mycobacterial strains will be clustered acccording to similarities and dissimilarities, and dendrograms will be utilized to demonstrate the results.

The results of monoclonal antibody from *M. leprae* reacting with the computer selected strains of similarity, as well as DNA-DNA reassociation with armadillo derived *M. leprae* will be presented as available.

IV/244(P) ELECTRON TRANSPORT-LINKED RESPIRATION IN CULTIVATED *M. LEPRAEMURIUM*

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M. lepraemurium considered as non-cultivable since its discovery in 1903, can now be cultivated *in vitro*. The mycobacterium was grown on Ogawa egg-yolk medium and the respiratory components were investigated. The whole cells of both Hawaiian and Kumato strains of *M. lepraemurium* contained flavins, cytochromes of the *a*, *b*, and *o* type. The cell-free extracts catalysed the oxidation of NADH, succinate and ascorbate. Although NADH oxidation was markedly inhibited by rotenone, amytal and atebrine, these inhibitors had no effect on succinate oxidation. Oxidation of NADH and succinate was completely inhibited by antimycin-A or cyanide. The NADH-reduced minus oxidised spectrum of cell-tree extracts was completely inhibited by flavoprotein inhibitors. When cell-free preparations were incubated with antimycin-A, the addition of NADH or succinate caused the reduction of cytochromes *b* but cytochrome *a* remained in the oxidised state. The effects of inhibitors on NADH and succinate oxidation as well as on electron transfer reactions indicated that respiration in cultivated *M. lepraemurium* is mediated through the electron transport chain.

IV/245(T) COLLECTION METHOD OF *M. LERPAE* FROM INFECTED ARMIDALLO LIVER

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Collection method of *M. leprae* is an important subject in studying leprosy. Many researchers have tried to collect purified leprosy bacilli, but a successful result has not been reported. A simple and efficient collection method of *M. leprae* from infected armadillo liver, without using any enzyme, has been developed in our laboratory. Armadillo liver was homogenized with twice its volume of distilled water. The homogenate was filtered through 4 layers of gauze. Percoll gradient technique was carried out as follows. The liver homogenates were laid on top of the percoll solution with decreasing 10% concentration starting from 100% and decreasing to 40%, and were centrifuged for one hour at 100,000 x g. After centrifugation, pure leprosy bacilli free from tissue contaminant were found accumulated in the middle zone of the percoll gradient as checked by the Ziehl-Neelsen and Ziehl-Nile blue staining. The yield was 46.7% of leprosy bacilli from the liver homogenate. Enzymatic test to check for tissue contaminants in the bacterial fraction was not carried out, because the AMPase activity of the liver homogenate was very low.

IV/246(T) ADAPTATION OF *M. LEPRAE* AND *M. LEPRAEMURIUM* IN TISSUE CULTURE CELLS AND PATHOGENICITY OF *M. LEPRAEMURIUM* IN MICE

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M. lepraemurium grow well in tissue culture cells A31. They also produce rough colonies of Ogawa's egg yolk medium as described by Ogawa *et al.* *M. lepraemurium* passaged for more than 10 years on Ogawa's medium produced smooth colonies. However, the bacilli from smooth colonies lost their pathogenicity for mice (attenuated bacilli). These attenuated *M. lepraemurium* were difficult to grow well in tissue culture cells. After a long incubation time in tissue culture cells, these bacilli were well adapted to cells and their pathogencity for CBA mice was restored.

M. leprae from nude mice were inoculated into tissue culture cells with a view to encouraging adaptation, and slow-growing acid-fast bacilli in these cells were obtained. Identification of these bacilli has not yet been made.

It may be that the CBA mouse is a low responder and that the C57BL/6 mouse has a high cellular immunity against *M. lepraemurium* infection. On interferon induction, we demonstrated that CBA was low and C57BL/6 was high, and the attenuated *M. lepraemurium* was a higher inducer than virulent *M. lepraemurium*. The relation between pathogenicty and interferon production will be discussed.

IV/247(T) *M. LEPRAEMURIUM* AND *M. LEPRAE* IN CULTURED MACROPHAGES OF MICE

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We have studied for two decades experimental murine salmonellosis. In this system, live vaccine was effective in preventing death from the challenge infection. Peritoneal macrophages of mice immunized with live vaccine inhibited intracellular growth of the pathogen *in vitro*. On the contrary, growth of the bacteria within 3 days was observed in normal macrophage. Glycogen-induced macrophages (CBA) were cultured with Waymouth medium containing 20% horse serum in TD-15 culture to be fixed with 4 pieces (9×12 mm) of cover glass in the bottom. At 0, 1, 2 and 3 weeks after phagocytosis the cover glass was removed, and the specimen was fixed with methanol and stained with Ziehl Neelsen and Giemsa. *M. Lepraemurium* (Hawaiian Strain) was growth in macrophages after 3-4 weeks of initial infection. The growth pattern of *M. Lepraemurium* resembled closely that of globi of *M. leprae*. Proliferation of the bacteria was observed in macrophages not only of susceptible strain (CBA) but all of relatively resistant strain (C57BL/6). *M. leprae* was obtained from an outpatient of Kitasato University Hospital. The nodule was homogenized and frozen in 50% glycerin at–80 C until use. *M. leprae* grew in cells very slowly and proliferation was not clearly observed until 4-5 weeks after infection.

IV/248(T) ATTEMPTS AT CULTIVATING *"M. LEPRAE"* IN HUMAN PLASMA

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In three experiments, we inoculated cutaneous serosity from leprosy patients suffering from borderline or lepromatous leprosy into human plasma taken from healthy and lepromin negative persons. The tubes of the experiments were kept at a temperature (36° C)and periodical examinations of its contents were made, during three months. At the end of the process, we found an abundant growth of an acid-fast and Gram-positive organism whose morphoiogy was very similar to that of *M. leprae*, i.e. rods, isolated and grouped cocci and globi.

IV/249(T) PURIFICATION OF *M. LEPRAE*

Endo, Hiroko and Nakayama, Tetsu
National Institute for Leprosy Research,Tokyo, Japan

IMMLEP selected Protocol 1/79 for purifying *M. leprae* from infected armadillo tissues. However, this method still contained difficult problems.We are now engaged in the purification research independent of IMMLEP Protocol, based on our own views.

The leprosy bacilli, derived from infected armadillo liver, always adhered to the amorphous, filmy background substance. Removal of this substance without damage to the bacilli was extremely difficult by the usual methods.

At the Mexico Congress, we reported about LAFB (large acid-fast bodies found in leprosy material). Adopting the working hypothesis that amorphous, filmy substance might be the stretched capsular material of LAFB ("Sporangium"), we tried to discover suitable enzymes in fungi for digesting this substance. Trehalase, Keratanase, cellulase and chitinase were chosen after many attempts.

After treatment with these enzymes, the bacilli and the other substances (tissue debris and fungal components) were separated in the special aqueous 2-phase system.

Counter-current distribution would be applied for separating the naturally contaminated microorganisms.

IV/250(T) ANALYSIS OF THE SUBCELLULAR PROTEINS AND LOCALISATION OF THE ANTIGENS OF *M.VACCAE* J28

V. Sritharan, Manjula Sritharan, A.K. Sharma and P. Suryanarayana Murthy
Dept. of Biochemistry, University College of Medical Sciences, New Delhi

Studies have been undertaken on the analysis of sub-cellular localisation of proteins of *M.vaccae* with particular emphasis to their cross-reactivity with leprosy serum. *M. vaccae* J28 was grown on Youmans and Karlson's medium. Cells were grown for 10 days. Cell wall and membrane fractions were obtained by subjecting the cells to ultrasonic disintegration and by differential centrifugation. Proteins from the culture filtrate as well as from cell wall and membrane fractions (after solubilization with urea) were separated by DEAE Cellulose and gradient polyacrylamide gel (5-20%) electrophoresis. Culture filtrate showed 6 protein fractions. 28 fractions could be detected from the solubilized membrane fraction by electrophoresis. Immunodifussions studies using serum from untreated LL cases revealed one precipitin line from the culture filtrate and more than one cross-reacting component in the membrane and cell wall fractions. The results will be discussed.

SESSION V

SURGERY AND REHABILITATION

Chairman: Fritschi, E.P.

Rapporteur: Bourrel, P.

WEDNESDAY, 22ND FEBRUARY, 1984

Commission Hall 'H' 08.30–10.00

Abstracts

A* : 251-266
P* : 267-281
T* : 282-284

*A : accepted for reading
*P : for poster presentation.
*T : for title reading.

V/251(A) PLANNING FOR DISABILITY PREVENTION IN A LEPROSY CONTROL PROGRAMME

Jean M. Watson
The Leprosy Mission, Kingston Surrey, England

It is primarily in the clinic situation that disability can be prevented in leprosy patients. By the time that a patient reaches hospital, nerve damage, ulcers or other problems may well be established. A major problem in clinic situations is shortage of time. In areas of sparse population, where a mobile-clinic system of travelling "experts" is impracticable, time shortage is compounded by lack of expertise in leprosy problems on the part of general-purpose medical workers. As a result of experience gained in disability prevention in Africa, the author suggests that disabilty could be more effectively minimised in many areas by the following means:

1. Better planning and evaluation-the selection of objectives that are both limited in number and measurable in effect, based on patients' needs and available resources, and measurement of progress towards these.

2. Better hospital back-up of clinic staff: In planning, teaching and evaluating disability prevention in the clinic situation; In encouraging the habit of efficient self-care in hospitalised patients; In designing and supplying effective and acceptable protective devices–in many instances, over a wider area than at present as part of a regional plan.

V/252(A) ROLE OF REHABILITATION SURGERY AT RURAL LEPROSY VILLAGE

Nilofer Bhagat and Atul Shah
Tata Department of Plastic Surgery, J.J. Hospital, Bombay, India

The rehabilitation of leprosy patients does not end by providing them with food, clothes, shelter and a job. In fact, it is just the begining of the long

term plan for their care. Because almost all of them are deformed, have anesthetic limbs and develop innumerable problems at intervals where surgery can only help them. To understand their actual difficulties, surgeons must perform surgery in villages where clusters of leprosy patients collect, rather than at specialised institutes which are miles away and often disregard rural environmental and field conditions.

This paper deals with an experimental regular rehabilitation service, provided for a cluster of 450 leprosy patients in Sindhrot Village, Baroda Taluka, Gujarat, with consultations of more than 1000 patients per month as out-patients.

The experience, results, difficulties and pitfalls in surgery at specialised institutes compared with a rural rehabilitation surgical service, and the financial implications of providing such service are presented.

V/253(A) NEUROPHYSIOLOGICAL CORRELATES OF PERIPHERAL NEURAL DEFICITS IN LEPROSY AND THEIR CLINICAL SIGNIFICANCE

P.K. Oommen, H. Srinivasan and C, Rajakumar
Central Leprosy Teaching and Research Institute, Chengalpattu, India

Eighty-three sites served by the ulnarnerve in 42 hands of 21 leprosy patients were examined in detail for perception of constant touch, moving touch, vibration of low frequency and high frequency, pain and heat as well as discrimination of two static points and two moving points.

Out of the eight modalities tested, up to 3 were affected in 50% of the nerves, and 7 to 8 modalities were affected in only 5 nerves, indicating that in leprosy, the nerve become damaged in stages. Thermoception was affected in 57% of the nerves, nociception in 48%, high frequency vibroception in 43%, low frequency vibroception in 24%, perception of moving touch in 14% and perception of static touch in 7%. However, two-point discrimination, static or moving, was affected in almost all cases. The results of perception tests point to preferential involvement of non-myelinated fibres, and the results of discrimination tests suggest a great reduction in the myelinated fibre population also. No association was found between the loss of different modalities indicating their neurophysiological independence and a random pattern of involvement of Schwann cells.

No significant difference was found between the two test sites, pulp of little finger and hypothenar eminence, regarding the degree of neural deficit or the results of perception tests. However, two point discrimination was affected significantly more often in the pulp of the little finger. It appears that static or moving two point discrimination test used over the pulp of the little finger will be the most sensitive single test for recognizing damage to the ulnar nerve at an early stage.

V/254(A) BAROGRAPHIC TECHNIQUE FOR ASSESSING FOOT PRESSURES IN LEPROSY PATIENTS

K.M. Patil, T.S. Babu, P.K. Oommen and H. Srinivasan
Biomedical Engineering Division, Indian Institute of Technology, Madras, India

This paper describes a barographic technique for measurement of pressures in leprosy patients. The barograph consists of a thick glass plate illuminated at its edges by fluorescent light. The top surface of the glass plate is covered by a thin opaque white plastic sheet, upon which the subject stands. Greater pressure levels cause more intimate contact between the plastic and the glass which results in the breakdown of total internal reflections within the glass. When viewed from a 45° inclined mirror, placed below the glass plate, the areas of contact of the foot can be seen with light intensity related to the applied pressure. The resulting image recorded photographically is scanned for pressure intensity patterns using a microdensitometer. The pressure intensities are calibrated, using known weights over specified areas.

For normal subjects, the results show that, during standing, the pressure indifferent parts of the sole of the foot appear to be uniformly distributed. In leprosy patients, when there is an abnormality in the foot, the pressure distribution is not uniform giving rise to high pressure zones. Barographic study confirms that the scars are discrete sites of very high pressure of the order of 90-110 N/cm^2 (130-160 lbs/in^2). This technique appears to be very suitable for studying the effects of structural and functional changes in the foot. This will help us to identify potentially vulnerable feet of leprosy patients and take adequate action to prevent further damage.

V/255(A) STRATEGY AND TACTICS IN LEPROSY SURGERY:

P. Bourrel
Institut de Medicine Tropicale - le Pharo, Marseille, France

The medical treatment of neuritis is not always successful, and often paralyses and mainly permanent sensory loss of the extremities occur, the cause of infection and mutilations, which compel patients to repeated dressings for many years, before the "indispensable" amputations. However, nerve trunks are subjected to "internal compression" due to inflammation into the sheath, which has become inextensible, and to "external compression" of the hypertrophic neuritis in the osteofibrous tunnels. Surgical external and internal decompression of these nerve trunks is relatively easy, but it must be carried out "at the right time", when the medical treatment and corticoids have failed: in the hyperalgesic neuritis, before pain disappears, owing to death of the nerve-in progressive neuritis, after 6 to 8 weeks for the neuritis of tuberculoid leprosy, after 6 to 8 months for lepromatous neuritis. Therefore, it is interesting to discover early signs of nervous lesions by simple and rapid investigastions.

When non-specialist surgeons are working, close to treatment centers for leprosy, they must be able to perform these "decompressions" either in their department, or in the hospital for leprosy patients, so that the highest number of patients could be treated and in order to avoid the occurrence of mutilations. In the case of permanent paralyses, this problem is not urgent, and it is possible to wait for several weeks. It must be possible either to direct these patients to a specialized center, or to gather them for the temporary visit of a surgeon experienced in reconstructive surgery.

V/256(A) RECENT MEDICAL OR MEDICO-SURGICAL DECOMPRESSION OF HANSENIAN NEURITIS (CHOICE OF THERAPY)

A. Carayon

Decompression of medical choice: association of corticoids with an antihansenian and anti-inflammatory drug B663 at a dose of 300mg in the long-term treatment of reversal reactions. Association with DDS in L – ENL neuritis. Mention is made in the paper of the biological bases of the action of B663 and also the penetration into the nerve in a wax formulation.

Therapeutic basis: a comparison of 2 series of studies — (i) until 1977– On 685 cases of neuritis treated with DDS and anti-inflammatory drugs, 361 cases of recent neuritis were subject to close observation. (ii) 1978-1982: 258 cases of recent neuritis were under observation on a total of 380 neuritis cases treated with B663+ corticoids.

(a) *Comparisons carried out on neurological results - not assessed*
1st series – (101 L, 260 non-L) without data evaluation

2nd series – (97 ENL, 159 R.R., 2 non-reactional) evaluated by a physiotherapist.

– Proportion of painful phenomenon

1st series Pain on elongation - compression - hyperalgesia	(Marneffe)	32%	30
2nd series		10%	7

(b) *Complications of tne LL-ENL Neuritis*
1st series (101) abcess 9+ extra-epineural thickening
2nd series 97+ None

(c) *Treatment of neuritis in reversal reaction*
– Medical treatment alone
1st series : DDS+ Corticoids – 1 case (infant) of rapid recovery.
2nd series : B 663 + corticoids – 19 cases of recovery by the 8th day

N.B. 2 cases treated with rifampicin resulted in sudden worsening and the tests were stopoped.

– proportion of caseous complications
– 1st series : 43 cases observed (cold abscess) 16.5%
– 2nd Series : 13 cases studied – (3 showed the beginning of necrosis and 10 had abscesses only) 9%
– Prevention of relapses of R.R. after too short a period of treatment.
12 with DDS – 100 mg
2 with B663 at 50 and 100 mg
0 with B663 at 200 mg

Associated Surgical Decompression: The pathalogical bases are discussed in the paper.
– 3 types of neurolysis are associated with extra-neural decompression including the systematic treatment for the ulnar nerve (epicondylectomy)
– general indications for neuritis

Reversal reactions: early detection: only medical treatment
– if there is delay and hypertrophy – surgery should be associated.

LL–ENL simultaneous medico-surgical treatment: neurolysis after 3 weeks in 90% of cases

N.LL. non reactional (resistance) cases: medical treatment

Complicated neuritis
R.R. Necroses: early excision of the fibres necrotic.
AdvancedENL: the appropriate complicated neurolysis. Rare indication (intractable pain).

V/257(A) NEURITIS IN HANSEN DISEASE: RESULTS OF TWO HUNDRED NEUROLYSIS

F. Chaise
Hospital Saint-Louis, Paris, France

Two hundred leprous nerves were reviewed 6 months to 13 years after neurolysis (80 ulnar nerves, 50 median nerves, 32 popliteal nerves, 36 posterior tibialis, 2 radialis). Overall results are as follows:

Short-term benefit: pain relief is rapid, constant and durable, rendering analgesic medication unnecessary,

Medium-term benefit: motor and sensory recoveries were seen in 60%;

Long-term benefit: few recurrence have been observed in the operated nerves.

The parameters of prognosis value: to improve results, four factors should be taken into account – the length of time before operating. At present, we use a standard protocol for surgery, after 10 days of using large doses of oral steroids and antibacterial agents, the neurolysis is performed; – the operative technique: We have already noted that the operative procedure should allow sufficient decompression without inducing ischemia longitudinal and segmentary epineurectomy – immunopathological form : the course of the neuritis appears to be much more severe in the tuberculoid form, whereas the lepromatous form can benefit from surgery much later-the nerve trunk: the severity of compression syndrome. According to our results, the current indications for decompressive surgery are as follows:

acute painful hypertrophic neuritis (paralytic and non-paralytic);

recent painful neuritis which progresses in spite of medical treatment;

distal neurotrophic changes;

painful neuritis of longstanding duration, in this case we hope only for analgesic effect;

the foot ulcerations.

V/258(A) THE DEFORMED FOOT–SURGICAL RECONSTRUCTION TO REDUCE ULCERATION AND DISABILITY

Grace Warren and Trevor Smith,
McKean Rehabilitation Instiute, Chiangmai, Thailand

Deformity of the foot may predispose to recurrent ulceration in spite of good care and special footwear. The surgical reconstruction of the foot to reduce the risks of ulceration has resulted in a greatly reduced incidence of ulceration and the need for special footwear, thus decreasing rehabilitation and rejection.

The main methods: First, Wedge Osteotomies to realign the basic configuration of the foot, especially to correct inversion. Adequate bone healing does occur with prolonged immobilisation.

Second, the transfer of weight from a badly scarred side to an area of healthier skin, whilst ensuring minimum reduction in the total weight-bearing area. This may be achieved by trimming bony irregularities that cause ulceration from within the foot and may be supplemented by tendon transfers. These procedures have helped many patients to remain ulcer-free even though walking without shoes in the house and using simple footwear available in the local market.

V/259(A) MODERN PODOLOGY APPLIED TO LEPROSY FOOT

Bourzgui Kh., Rollier R., Rollier B., Braun, S.
National Leprosy Service, Ain-Choch Hospital
Casablance, Morocco.

These techniques are used mainly when the general line of the foot placement is conserved and regained, after reducing the deformities by surgery.

1 – The basic principle is the serially well-defined shoe-making apparatus.

2 – In order to reduce the ground space, one uses necessary and sufficient elements for neutralising any abnormal pressure whatsoever. The correction of barometric stato-dynamic anomalies of the fore-foot is controlled by well-codified laws; here comes the introduction of toe orthèses which are a victory of the modern pedicure.

3 – The authors make a critical study of thermo-plastics (polythylene sponges) which form part of comments on the plastic material used in traditional podology as well as those which are newly introduced.

These techniques are efficient and elegant and diminish in particular, the use of plasters and of shoes of extravagant forms. The economic factors are analysed.

V/260(A) EVALUATION OF SURGICAL RECONSTRUCTTION OF THE LEPROSY HAND FOLLOWING TRIPLE NERVE PALSY

G.D. Sunderaraj
Christian Medical College, Vellore, India

Simultaneous paralysis of the ulnar, median and radial nerves in Hansen's Disease is seen about 1% of hands with nerve paralysis. 40 such cases were treated between 1955 and 1976; 35 have been followed up. Two hands presented with a high radial, median and ulnar palsy and allowed no scope for reconstruction. The other 33 cases which underwent two stage reconstructive surgery are presented here.

The first stage reconstruction involves restoration of active wrist, finger and thumb extension, and the muscles ideally suited for these transfers would be the Pronator teres, Flexor carpi radialis and Palmaris longus respectively. A restoration of more than Grade III muscle power was achieved in 90%, 96%, and 100% of these individual transfers. An arthrodesis of the wrist is not recommended, when suitable muscles are available for active transfer. The second stage reconstruction attempts to restore finger intrinsic function and thumb opposition; under these circumstances, the sublimi provide ideal motor tendons for both these transfers with satisfactory restoration of function in 90% and 83% respectively.

Only 18 hands needed all 5 tendon transfers to be performed. The others needed fewer tendon transfers. Ten of the 18 hands which underwent all 5 tendon transfers showed consistently excellent or good results in all five procedures.

V/261(A) LONG DURATION CLAW HAND DEFORMITIES IN HANSEN'S DISEASE – A REVIEW OF VARIOUS OPERATIVE RESULTS

George A. Anderson
Hand & Leprosy Reconstructive Surgery Unit, Christian Medical College Hospital, Vellore, India

Various operative procedures have been developed and followed for correction of hands in Hansen's patients for over three decdes at this Hospital. Based on their successful outcome with regard to correction in early deformities, the same procedures were adopted on hands with deformities of long duration. The results of these operations performed on 136 deformed hands over a ten-year period (1971-1980) on deformities of over five years' duration is reviewed. Approximately 45% of these hands had recurrence of deformitty. Better results were obtained in hands where flexor muscle transfer was used. Unsatisfactory results followed in spite of prolonged pre-operative and post-operative physiotherapeutic care. Besides faulty operative technique in a few cases, obvious in the immediate post-operative period, recurrence of deformity was also found to ensue where re-education of transferred muscle was not brought under conscious control by the patient, as evident in the late post-operative period and follow-ups.

Activities of daily living and occupational orientation using corrective splinting on hands long deformed prior to surgery, better choice of surgical procedures appropriate to individual cases and a renewed campaign for early introduction to the idea of surgical rehabilitation from the outset of treatment is suggested.

V/262(A) MULTIPLE SUBLIMII MOTOR FOR OPPONENS AND LUMBRICAL REPLACEMENT – ONE STAGE CORRECTION OF LEPROUS CLAW HAND

Atul Shah
Tata Department of Plastic Surgery, J.J. Hospital, Bombay, India

One stage correction of total claw deformity of leprosy is desirable, particularly in India where there is a high percentage of deformed patients waiting for surgery. This not only conserves scarce resources but also improves the ability of patient to resume his occupation as soon as possible. The patient is psychologically 'not waiting' for another operation as well, as even a minor unsatisfactory result of the first stage procedure in a multistage reconstruction programme may make him anxious about the eventual outcome, thereby increasing his reluctance for further interventions. The one-stage correction by this method allows the working of thumb and fingers in uniformity, and reeducation is easier. The thumb can be opposed to the fingers, and the fingers can be flexed for pinch and grasp against the newly-obtained thumb opposition.

Multiple sublimii motor technique entails the use of the flexor sublimis of the ring finger for opponens plasty; sublimii of the index and the little finger are looped at the metacarpophalangeal joint and sutured to themselves for the lumbrical replacement; sublimis of middle finger is split into two; one slip is looped for the middle finger and the other for the ring finger. Thus one-stage correction of total claw hand is achieved. The operative technique, results and complications of this new one-stage procedure for correction of total claw hand in leprosy are presented.

V/263(A) THE BENEFICIAL EFFECTS OF TEMPORALIS MUSCLE TRANSFER

E.C. Tjepkema
Dutch Leprosy Rehabilitation Association, Addis Ababa, Ethiopia

Patients who had Temporalis Muscle Transfer (TMT) for correction of lagophthalmos were evaluated. The main aim of the study was to assess to what extent regular automatic blink was restored. Preliminary results show that a habit of regular automatic blink, rarely if ever, is seen post-operatively. The beneficial effects of the TMT seem to be a better approximation of the eyelids, resulting in less exposed area of the eyeball and restoration of tear drainage from the eyeball.

Eye protection primarily depends on the presence of protective sensation of the eyeball. Patients with lagophthalmos and preserved sensation rarely develop eye complications, because the eyes of these patients are protected (Bell's phonomenon).

The beneficial effects of the TMT seem to be of a "static" nature and do not depend upon active eye-closure. Our experience is that it is not possible to teach the patient to use the temporalis muscle regularly.

Previously described techniques might be further developed to provide a simpler alternative procedure.

V/264(A) EVALUATION OF THE "LASSO" OF ZANCOLLI IN THE LEPROUS CLAW HAND – ABOUT 48 CASES

P. Boucher and C. Oberlin
Instiute of Lepriolegie Aippliques, Dakar

48 cases of "lasso operation" from 2 different series are presented (a series of 22 operations was performed by Dr. Boucher; a series of 26 cases by Dr. Oberlin.)

41 cases with a follow-up of more than 6 months were reviewed by the authors. Post-operative function was evaluated according to disappearance of metacarpo-phalangeal hyperextension and quality of metacarpo-phalangeal flexion with fingers extended. Clinical cases show the limits of this type of intervention:

- supple claw hand according to the Bouvier test: utilization of one tendon flexor superficialis for 2 fingers,
- still claw hand with deficit of extension between 10 and 60° : utilization of one tendon for one finger.

It must be noted that no diminution of the stiffness of the interphalangeal joint has been observed, when there was pre-operative stiffness, even minimal.

The authors insist on the simplicity of this technique, and the quality of results without reeducation.

V/265(A) ECONOMICAL RECONSTRUCTIVE SURGERY OF HANDS AFTER FAILURE OF OPPONENS REPLACEMENT OF THUMB OR/AND MANY-TAILED LUMBRICAL REPLACEMENT

August Beine
Sivananda Rehabilitation Centre, Hyderabad, India

During the past 10 years, patients for surgical repair after reconstructive procedures, opponens replacement of thumb, EFMT, sublimis transfer or palmaris longus transfer had failed, showed good results after re-operation, when the transferred (old) motor tendon was functioning and insufficient action of the distal tendon transfer was replaced attaching an additional tendon (free graft) to the original transferred motor tendon, using 'sutureless suture technique'. The technique connecting the grafted tail to the (old) motor tendon and fixing it with itself is described and its use is shown in 8 procedures (5 patients under recent observation).

The technique is recommended as repair, when simple re-tightening in case of insufficient result fails. In suitable cases, this restoring procedure permits avoidance of premature arthrodesis of thumb MP-joint as well as unnecessary extravagance' of using an additional motor for completion of the above mentioned reconstructive procedures.

V/266(A) SURGICAL TREATMENT OF NASAL DEFORMITIES OF LEPROSY

V. Pandya, Narendra J. and Anita Noshir H.
Bombay, India

Of all the stigmata of leprosy a depressed nose is perhaps the most distressing at all.

We present a retrospective review of 86 parients who were treated surgically for nasal leprosy deformities at the Tata Department of Plastic Survey, J.J.Group of Hospitals,Bombay. There were 72 males and 14 females and the age varied from 18 to 60 years. All patients had received medical treatment for the disease.

The procedures commonly used were a post-nasal inlay of split skin graft, a bone graft, a silicone rubber implant, a nasolabial forehead or a tubed arm flap or an external prosthesis.The need for an improved facial appearance was the commonest presenting complaint.

The follow-up period varied from 3 months to 15 years. In the post-operative evaluations, the results were graded as good, fair and poor – based on subjective comments of the patients as well as the objective observations made by the surgeons.

The post-nasal skin graft inlay was the most frequent procedure, and it seemed best suited for these repairs in developing countries, where the patients often present late with major deformities. For minor and early nasal deformities, the insertion of a bone graft or a silicone rubber implant is recommended.

V/267(P) RIGID "ROLLER" SOLE FOOTWEAR

Sten J. Stenstrom, H Payne and J. Muliyil
Community Health Department, Christian Medical College, Vellore, India

The Poster will show and comment on:

1. The 2 types of rigid sole footwear, one with "rocking" and the other with "rolling" bottom, described by Dr. Paul Brand to distribute the weight-bearing for reducing the risk of ulcer formation. We prefer the "rolling" type, since it gives a safer feeling at the push-off phase of the gait and can be made less high, with less risk of spraining the ankles. However, the weight-bearing might be less perfectly distributed, the reason for which is still to be studied.

2. Diagrams of the Brand "roller" type, the development of our modification and how the heel lifting capacity is calculated.

3. The different stages of the manufacturing of our modification: (A); the patients's measurement taken directly onto the standard wooden sole, (B); the wood cut to shape and the microcellular rubber and tyre stuck on, (C); the upper fitted over the foot and stapled to the sole.The whole process is simple and quick.

4. The wooden sole that can be moulded to relieve pressure on persistent ulcer sites or vulnerable scars.

5. The ground surface excavated to accommodate unevenness in the ground.

6. The following-up of the patients revealing that chronic ulcers show improvement and recurrent ulcers are prevented.

V/268(P) LEPROSY ULCER TREATMENT:

Kuryan George, J. Muliyil and Sten J. Stenstrom
Community Health Department,Christian Medical College, Vellore, India

The Poster will show two methods of dressing ulcers in leprosy patients and their results.

1. In case of uncomplicated superficial and deep ulcers, zinc oxide adhesive tape is directly applied. Though in the present study adhesive tape from Molnlyoke Company, Sweden and Johnson & Johnson, India was used, any similar tapes could be used.

2. In the case of complicated and infected ulcers, wet gauge sponges are applied and covered with Kraft paper, so as to keep the dressing moist. This aids easy removal of slough and encourages early formation of healthy granulation tissue.

Both the above types of dressings are easy to apply and require no technical skill.Healing is accelerated, and their use reduces the need for antibiotics.

It is stressed that even after healing, special care must be given to keep the plantar scar resilient and soft.

V/269(P) A STUDY OF FIRST PLANTAR ULCERS ON HEADS OF METATARSALS ONLY

Sahu Jayadev
Gandhi Memorial Leprosy Foundation, India

312 leprosy patients with plantar ulcers were screened at GMLF Control Unit, Chilakalapalli, India. 230 had multiple ulcers who are omitted in the analysis. The remaining 82 cases having a single ulcer on MT heads only have been analysed in this study. The study reveals that 52 cases had a plantar ulcer on the head of the 1st MT; 6 cases on the head of the 2nd MT; 6 cases on the head of the 3rd MT; 7 cases on the head of the 4th MT and 11 cases developed an ulcer on the head of the 5th MT.

The full text of the Paper includes a Table showing the number of cases in the various groups; %; sites of ulcers; type of foot (normal; in-toeing; flat; out-toeing; drop foot) and walking gait.Five diagrams depict the line of Walking Roll by various types of feet and the style of walking.The author

discusses the formation of the first plantar ulcer over the heads of the MT, in relation to the type of feet and walking gait and suggests foot care and preventive measures to be taken to avoid plantar ulcers on anaesthetic feet and advocates use of microcellular rubber footwear.

V/270(P) RESULTS OF THE TREATMENT OF 126 PATIENTS OF NEURITIS OF THE TIBIALUS POSTICUS NERVE AND PLANTAR ULCERS

J. Van Droogenbroeck, A.Carayon

The present study deals with the observations carried out on 52 cases where the T.P. nerve was recently affected (91 localizations and 7 ulcers). It also deals with studies made on 74 more advanced cases with plantar ulcers (106 localizations). The 126 cases selected were in a group composed of:

- 45% whose T.P nerve was affected series that was retained
- 32% with anaesthesia due to affection of the cutaneous receptors
- 14% of a correlation of 2 types (5 recent cases have been retained for study)
- 9% of ulcers formed on the lateral border of the foot (isolated SPE)
- on the T.P. nerve have *certain particularities* which set them apart from the lesions of the other nerves
- the appearance of plantar ulcers after a certain time
- pyegenic peri-vascular-nervous lymphangitis and other organisms that cause thickening of the sheath
- more serious hemodynamic disturbances in the legs delays the blood flow,autosympathectomy of the foot whether open or closed (shunts), thickening of the media, thromboses, ischaemia of the foot
- as well as the decompression with the purpose of improving the condition of the nerves decompression aimed at the hemodynamcis and blood vesselos can lead to the cure of ulcers, leaving the deficit unchanged.

The medical treatment given remains the same for the 21 recent cases of lepromatous leprosy and the 31 B and T, with prophylactic decompression in the former, the same treatment is indicated after a month if failure is observed in the latter.

In general, there is no improvement and decompression is indicated.Surgical decompression includes the clearing of the tarsal ligament and the deep aponeurosis, opening of the sheath, the cleaning if necessary of the calcaneal canals and also the dissection of the trunk (of Sunderland type) and finally neurolysis.

Angiolysis may be simple, or more complicated (peri-arterial sympathectomy; resection of a segment of the media, etc.).

Results. In recent cases of neuritis, plantar sensitivity was entirely restored in 1/3 of the cases, partially restored in another 1/3 of the cases and not at all in 1/3. The 7 acute ulcers were cured with 5 cases recovering sensation. 33 of the observed cases of plantar ulcers with moderate bone lesions benefitted from 40 recoveries in 45 localizations. On 17 plantar ulcers with serious foot deformation, there were 22 failures in 22 localizations (contra indication).

V/271(P) RESULTS OF THE TREATMENT GIVEN TO 206 RECENT NEURITIS PATIENTS (C.M.S.P.E.R.)

P. Boucher, A. Carayon and J. Van Droogenbroeck

The term "recent" is somewhat ambiguous and relative. In practice it is variable and depends on:

- early detection and the treatment accorded to the reactions
- the clinical form of leprosy in which neuritis occurs, visible or inapparent forms of reactions (subdermatological, purely neural, or without any obvious signs of reaction in the skin).
- the category of neuritis (ENL reversal). The average LL – ENL neuritis of which the acute reactional stage has been correctly treated, may recover after 10 to 12 months. A neglected reversal neuritis may be reversible after 3 months, and some time even after 2 months.

1. *Reversal Neuritis* – 126 cases

- early medical treatment was given to 44 cases, of which 9 recovered completely, 35 almost completely, dissociated or partial recoveries according to the severity of the attack. 19 out of 44 recovered within 8 days.
- delay in medical treatment – 45 unsatisfactory results after 1 to 2 months. Cases selected at random in 1978-1979 (29 cases observed)

1978	1979
13 cases under exclusively medical treatment failure experiment abandoned	16 associated decompressin + 16 new cases (1980–1982) after the randomisation was given up.
Out of 32 cases	2 out of 10 recovered 5 out of 10 showed slight improvement 3 failures

Emergency cases - 17
– 11 cases of necrosis – 3 recoveries amongst the recent cases of necrosis, no caseation of 2 fibres (excision)
3 acute compression – 2 recoveries
2 narrowing of the carpal canal (children) 2 rapid recoveries
1 painful dislocation- slow recovery
– decompression treatment given to 20 cases (usually failure)

2) *LL - ENL Neuritis – 74*

- 30 cases received only medical treatment; sensory recovery was observed on 2 cases out of 30 neuritis cases in the early stages.
- prophylactic treatment and decompression: 23 cases. Result: 19 sensory recoveries out of 23
- emergency cases : 3 acute compression (acute abces [inflamed]–0) 2 recoveries
- decompression delayed necessarily – 3 persistent sensory deficit 3 recoveries usually failure with the others

3) *LL Resistant Neuritis – 6*
2 non-reactional, medical treatment: I success
2 ENL – partial recovery due to combined treatment
I.R.R. – a failure
I mixed – partial recovery.

V/272(P) MANAGEMENT OF EARLY FOOT-DROP

D. Lobo and Mrs. Margaret Mahato
Nirmala Leprosy Hospital, Dhanbad, India

38 cases of early foot-drop (paralysis under 6 months) in 26 patients are included in the study. All were admitted, given a below-knee plaster cast for a minimum period of six weeks plus a course of predinsolone (oral) starting at 30 mg daily, gradually reducing by 5 mg per week. At the conclusion of this course, the patients were given foot-drop springs for day-time wear and a posterior plaster slab for the night for a further period of eight weeks.

The muscle strengths (VMT Oxford Scale) before and after treatment are compared along with other parameters.

Conclusions: 1. Early foot-drop or any early paralysis is an indication for hospital admission.

2. Management with below-knee cast and a course of cortisone, assures recovery of paralysed muscles in a large proporation of cases. In this study, 81.5% of the dropped feet had complete or partial recovery.

3. We used a below-knee cast instead of the accepted above-knee cast followed by footdrop springs and posterior slabs. This suggests that resting of paralysed muscles in a shortened position is more important than resting of nerves.

References/cost/modifications for out-patients etc., are discussed.

V/273(P) RIGID ROLLER SOLE FOOTWEAR – A FIELD STUDY

Heather Payne, Sten J. Strenstrom and Jayaprakash Muliyil,
CMCH, Vellore, India

Ulceration in anaesthetic feet is still found to be problem despite the use of micro-cellular rubber footwear. There may be several reasons for this, including shear stress in the tissues of the sole of foot and un even weight-bearing while walking.

A rigid sole with a rocker was suggested many years ago by Brand and others, and is known to be effective. The rigid roller sole is an extension of this idea and its design has been gradually developed.Over a period of two years, this type of footwear was tried out on 100 patients, and this paper attempts to evaluate its effectiveness. Some of the aspects assessed were

a) the extent to which the development of ulcers were prevented;
b) patient compliance;
c) social acceptance;
d) cost and durability.

The problems encountered are discussed and the positive aspects described.

V/274(P) AN ANALYSIS OF HAND FUNCTIONS AS AN AID TO RECONSTRUCTIVE SURGERY

Monica Hopkins and Ramachandran Rao
Community Health Department, Christian Medical College and Hospital, Vellore, India.

Before a surgeon undertakes reconstructive surgery on a deformed hand he considers carefully just what function the person needs his hand to perform.

In this presentation, an attempt is made to analyse the enormous variety of these functions, with the aim of clarifying the possible needs. Without this

awareness, it is possible to produce a hand that looks normal, has certain actions which were not possible before surgery, but is a disappointment to the patient because he cannot make it perform an essential function required in his job or his daily life. Finger abduction is not usually replaced in a claw hand,but for playing a musical instrument, it is the chief function required.

Many of these functions are demonstrated in slide form. They are also divided into categories according to the type of grasp needed, the amount of precision and strength required.

Finally, in order to evaluate these functions both pre-and-post operatively, objective tests are described, and the relevant values of these are shown through EMG studies.

V/275(P) LOW COST SPLINTING IN LEPROSY WITH THE LOCALLY AVAILABLE MATERIALS IN DEVELOPING COUNTRIES

N. Palani
Physiotherapy Educational Programmes, Christian Medical College and Hospital, Vellore, India.

This paper is an attempt to promote the splinting techniques with the locally available materials such as bamboo, rubber tubes, used umbrella metal spokes & cycle tubes etc. Since the cost of plaster of Paris bandages has increased, it has became necessary to find substitutes which would not only bring down the cost price of splinting but also make it easily available in rural areas. Some of the lively splints with rubber tubes are also discribed; splinting with bamboo is of particular importance, since it is easily available and very useful as a supportive splint for the limbs; it is not used for weight bearing.

Bamboo splints should be well padded and no part of the bamboo or threades metal wire should come in contact with the skin directly. Generally 1 .2 to 1 .5 cms. diameter good quality bamboo, is selected for this purpose. We have used the above-mentioned splints for leprosy patients and also for patients with spinal cord injuries at the rehabilitation institute at the Christian Medical college and Hospital, Vellore, quite successfully.

V/276(P) TEMPORARY MISSIONS IN SURGERY FOR LEPROSY. RESULTS OF 122 OPERATIONS

C. Oberlin
Hospital Bichat, Service de chirurgie orthopedique et reparatrice, Paris France

The author, who practises in France, completed 6 surgical missions in the Republique of Central Africa (financed by the Foundation Follereau–France).

Each 15-days mission, consisted of: patient selection and surgical intervention, follow-up on formerly operated patients.
The operations performed were:

a. In the upper arm: 51 corrective operations for claw hand (10 metacarpo-phalangeal plasties, 15 Stiles Bunnel operations, 26 Zancolli lasso operation which seemed to give better results). – 40 opponens plasties.

b. In the lower limb: Surgical decompression of the tibialis posterior nerve for plantar ulcerations (39 cases), corrective stripping operation (12 cases).

The results of the first 89 operations with an averagre follow-up of one year are carefully analysed. These missions must not be considered as representative of surgical problems of leprosy as a whole:- most patients are at a sequellar stages of illness, which explains the high proportion of palliative treatment in this series; cases of painful neuritis for which surgical nerve decompresion is the best indication were practically excluded (these having to be performed at the right time by local surgeons).

–The short duration of the mission obliged us to undertake simple and safe operations, needing little reeducation; –operated patients cannot be reviewed as often as desirable. But the quality of results and low cost of intervention encourage us to pursue this practice of short-term units.

V/277(P) A NEW PRINCIPLE FOR THE TREATMENT OF TROPHIC ULCERS

Kalyan Banerjee
Asansol, India

Trophic ulcers are very resistant to treatment. An attempt has been made since 1979 to treat trophic ulcers associated with leprosy with dextran polymers. Tridimensional dry porous hydrophilic beads of, dextran polymers are placed on discharging ulcers; they absorb the exudate and swell to form a gelatinous layer. Inside the gelatinous layer substances separate according to their molecular weights; the smaller freely penetrate the pores of the beads and the larger remain in the interspaces. Since proteins and fluid are removed from the wound surface crust formation is prevented. Wound exudate contains a large quantity of fibrin-fibrinogen split product and no coagulable fibrinogen; as a result, clotting inside the gel layer does not occur. So long beads are dry, the product can easily absorb exudate, bacteria, degradation products and toxins from the ulcer surface. The treatment with dextran polymers in profusely discharging infected trophic ulcers ensures excellent improvement. Within seven days inflammation subsided, foul-smelling discharge disappeared and granulation tissue appeared. Most of the trophic ulcers healed up within 8-12 weeks.

Pharmacia AB, Sweden should make it available to all the leprosy treatment centres of the world at a cheap price.

V/278(P) TEACHING AND TRAINING IN RECONSTRUCTIVE SURGERY AND REHABILITATION FOR LEPROSY IN A SOUTH AMERICAN SETTING

Frank Duerksen, Diltor V.A. Opromolla and Marcos Virmond
American Leprosy Mission, Paraguay

It is the purpose of this paper to share our experience and philosophy in motivating and training health personnel at all levels, in order to improve or start Rehabilitation Programmes for Hansen Disease patients.

The concept of rehabilitation in leprosy is fairly new in South America and very much needs to be done in order to make an impact on the large number of disabled patients. The first step is to train qualified workers in this field. Our training programme is based at the Lauro Souza Hospital in Bauru Sao Paulo State in Brazil where regular courses are offered on general leprosy and leprosy control, prevention and rehabilitation. In all these courses, prevention is stressed but the possibilities that a rehabilitation programme can offer are also shown.

The aim is to motivate people, and then provide for further training in the different sub-areas of surgery-physiotherapy, occupational therapy, orthopaedic shoeworkshop, prostheses, etc. Our aim is that whenever possible, the Rehabilitation services get integrated into the general health servics. Surgeons should not become "Leprosy Surgeons" since this is economically not possible, but rather stay in their field of practice which *includes* H.D. patients.

Our five years' experience in Brazil and Paraguary has been gratifying and we thought that it could be of benefit or serve as a model for other areas in the world with medium prevalence rates, where the general medical and health situations are similar to ours.

V/279(P) EFFECT OF WALKING CASTS ON PLANTAR FOOT PRESSURES

James A. Birke and David S. Sims, Jr.
National Hansen's Disease Centre, Carville, Louisana, USA

Padded walking casts have been used in the management of plantar foot ulcers in Hansen's Disease since the 1930's. Brand in the 1960's recommended the use of a total contact walking cast, utilizing minimal padding and a carefully moulded inner shell.

Angel demonstrated the benefit of walking casts in reducing oedema,but evidence for the effectiveness of walking cast in reducing plantar foot pressure has yet to be established.

The purpose of this study was to measure the effect of a padded cast and a total contact cast on plantar foot pressure during walking. Hercules Orthoflex pressure transducers were attached to 4 sites of the right foot of 6 normal subjects. Plantar foot pressure measurements were made while subjects walked in a shoe, padded cast, total contact cast and again in a shoe.

Plantar foot pressure significantly decreased while walking in both the padded and total contact cast as compared to the shoe. Plantar forefoot pressures were slightly lower in the total contact cast compared to the padded cast.

V/280(P) A PRELIMINARY REPORT ON THE USE OF CANE & BAMBOO AS RAW MATERIAL FOR PROSTHETIC/ORTHOTIC APPLIANCES.

J.B. Banerji.
Viklang Kendra, 13, Allahabad, India.

Cane and bamboo have been found as a viable alternative basic construction material for Orthotic/Prosthetic Appliances. The Night Splint and Upper Extermity Splints proved effective in fields trials. The Lower Extremity Orthotic appliances and Prostheses, however, are at an experimental stage. Amongst the Rehabilitation Aids, Walkers, Crutches & Wheel Chairs have been found remarkably useful, cheap and light.

V/281(P) A METHOD OF CORRECTION OF CLAW HAND REQUIRING NO RE-EDUCATION

R. Kazen.
Masanga Leprosy Hospital, Magburaka, Sierra Leone, West Africa

Ten cases of ulnar paralysis have been operated on with a combination of synergistic methods. Observation time: one and a half years or less. Func-

tional and cosmetic results primarily good. The method seems to be especially suitable for young patients, nursing women (in an African village) and in circumstances where trained physiotherapists are lacking.

V/282(T) REHABILITATION – A DOMICILIARY APPROACH

G.R. Srinivasan, R.S. Mani, William Gershon and T. Jayaraj Devadas
German Leprosy Relief Association Rehabiliation Fund, India

In a developing country like India, leprosy is only one of the problem diseases from which the population is suffering. Being an overpopulated country which is disorganised in social sectors, it is definitely improper to spend large sums exclusively for vertical programmes.

Fear of stigma compounded by ignorance has prejudiced the minds of people. If society could regard leprosy like any other disease, the problem would not have assumed today's enormous proportions.

Rehabilitation of leprosy patients starts when he is diagnosed. In this process, the family bondage has to be kept intact.

Against this background, the German Leprosy Relief Association launched a scheme to rehabilitate them in their natural home environment through different services such as helping to reactivate traditional occupations, starting fresh ones, placing for academic courses, job settlement, training etc. whichever suits to their needs, capacities and aptitides.

By this domiciliary rehabilitation programme, 2828 leprosy patients have been helped through its 11 centres located in urban and rural areas.

The encouraging results of the programme in the economic and social fronts prompt us to say that the problems of leprosy in the developing countries are not merely that of the individual sufferers but the concern of the society as a whole.

V/283(T) RELUCTANCE IN REHABILITATION (MEDICAL AND SURGICAL)- REASONS AND REMEDIES

Mukesh Bhatt, N. Bhagat, A. Shah
Shram Mandir, Sindhrot, Baroda, India

The unusual survey of reluctance in rehabilitation at a rural leprosy village complex (run by voluntary organization) consisting of 450 deformed and handicapped persons, its out-patients and a matching sample urban patients revealed the findings as to why the patients are not punctual, what their outlook is towards the treatment (and supervised therapy will help) and whether they view surgery as a necessary evil. The reasons as understood and stepwise remedy offered, with consistent demonstration to a group in a community of the effectiveness of the total health care approach (including reconstructive surgery in the very heart of the colony) and how it has transformed the psychological attitude is presented in this paper.

V/284(T) PLASTIC SURGICAL REMEDY FOR LIMITED CHRONIC LEPROMATOUS PATCH AND CHRONIC PENETRATING ULCERS.

Jacob Cherian
Christian Fellowship Community Health Centre, Santhipuram, Ambilikkai, India

During the last 25 years of our service, in this area covering about 150,000 of rural population in almost 1½ complete Development Block at Oddanchatram, we have come across a few cases of Chronic hypopigmented thickened limited patches on the face and trunk and extremities which are resistant to treatment and the patients always insist on getting them removed. These are isolated clearcut patches of, on the average, 2 to 3 inches on prominent areas like face and limbs and chest, etc. After a minimum period of treatment, about 3 years, and in some cases less than that when the lesion becomes paucibacillary and the disease is controlled, we have excised them cleanly, using a plastic technique and the surrounding area was well mobilised keeping intact its nerves and blood supply and finally the edges are apposed with fine silk sutures.

They heal very well with full sensation and minimum scar, and the patient is happy because he has had removed suspicious white patches which have bad reputation even mong illiterate public. The patient would not mind a scar but he reacts badly to a hypopigmented thickened patch because of its social stigma.

The same technique was applied for many a chronic limited deeply penetrating so-called trophic ulcers on sole and palm with excellent results. Sometimes the hard bone at the base of the ulcer may have to sacrificed. Of course refreshening of margin of ulcers leaving bleeding edges in an elliptical fashion is essential for proper treatment. The healing was good and the recurrence was avoided by proper education, physiotherapy and appliances like well-planned resilient microcellular rubber foot-wear.

Full thickness free graft, transplant is also well taken by superficial clean small ulcer less than 1 cm in size, but fine sensation may be lost. All the above surgical procedures are done under full multi-drug therapy.

SESSION VI

OPHTHALMOLOGY

Chairman: Brand, M.

Rapporteur: Lim

WEDNESDAY, 22ND FEBRUARY, 1984

Commission Hall 'H' 10.30–12.00

Abstracts

A* : 285-290
P* : 291-296

*A : accepted for reading
*P : for poster presentation.

VI/285(A) SURGICAL MANAGEMENT IN OCULAR LEPROSY

Renuka Srinivasan, P.A. Lamba
Department of Ophthalmology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry (India)

The main cause of visual loss in leprosy is the combined effect of corneal and lens opacities associated with uveitis. Surgical management of ocular leprosy has, in most instances, been restricted to extra ocular surgery, viz. tarsorrhaphy, correction of ectropion etc. The probable deterrents to intraocular surgery have been the presence of uveitis with a bound-down pupil, the risk of its possible exacerbation, and the presence of corneal involvement.

In this study, 626 eyes of leprosy patients were examined with a view to evaluate the possibility of surgery in the management of ocular disability. About 115 patients with ocular leprosy who were likely to benefit from surgery were selected. The surgical procedures performed included lens extraction (44), tarsorrhaphy (54), keratoplasty (2), glaucoma surgery (4), ectropion correction (8) and temporalis sling surgery for lagophthalmos (3). Contrary to previous reports, the cataracts in this study were mostly of senile type and were not complicated by uveitis. The results of lens extraction performed were comparable to those of cataract surgery in non-leprous patients, with good visual recovery (90%). Our observations differ from those of Fftyche (1981) who performed cataract extraction in 81 patients with ocular leprosy and reported a high frequency of complications. We were able to perform intracapsular cryo-extraction of the lens with peripheral iridectomy in most of the cases. Only a very small number with poorly dilating miosed pupils required a large iridectomy.

Other operative procedures, like those for lagophthalmos, are of great benefit in protecting the cornea and in preventing the development of corneal opacities. Penetrating keratoplasty and glaucoma surgery were also carried out in some patients with good results. Successful surgical removal of the lens in patients whose blindness is due to cataract, offers a new hope for the restoration of sight in leprosy patients. Detailed observations will be presented and discussed.

VI/286(A) THE ULTRASTRUCTURE OF THE EYE IN LEPROSY : PATHOGENIC CONCLUSIONS.

Ph. Gendre, Ph. Verin and Nguyen Duy Tan
Department of Electron Microscopy, University of Bordeaux, France.

Twelve years ago, we showed that the ocular complications of leprosy could in the main be attributed to lepromatous leprosy, except certain cases of lagophthalmos. The lesions of the anterior segment of the eye, keratitis and iritis, result from direct invasion of these structures by leprosy bacilli.

The ultrastructural study of the lacrimal ducts and the conjunctiva reveals the presence of the bacilli and their migration from the cold areas of the nasal fossae to the anterior segment of the eye. The data thus obtained lead us to consider more specific treatment of the ocular complications of leprosy, such as subconjunctival injections of anti-leprosy compounds.

The evolution of these local disorders may be sought by taking small biopsy specimens for ultrastructural investigation. The present studies reveal pathognomonic changes or the regression, or even the disappearance of the ocular lesions themselves.

VI/287(A) A FIELD STUDY ON OCULAR INVOLVEMENT IN LEPROSY IN COASTAL ANDHRA PRADESH OF INDIA

S.C. Reddy and B. Dharmaraju
Rangaraya Medical College, Kakinada, India

In a field study of 11,697 leprosy patients screened for eye problems, during the period from 1978 to 1982, 1193 patients (816 males and 287 females; 602 lepromatous and 591 non-lepromatous) showed ocular involvement. Patients with eye lesions not related to leprosy were not included in this study. The patients were in the age group 12-75 years. The mean duration of leprosy was 11.8 years with a range between 2 and 40 years.

Multiple eye lesions were seen in the majority of patients. Various ocular lesions observed, in the order of frequency, were : diminished/absent corneal sensation 843, madarosis 395, lagophthalmos 197, chronic iridocyclitis 179, infiltration of eyebrows 82, exposure keratitis 53, nodules over eyebrows and eyelids 32, pannus 26, corneal ulcer 19, scleritis 19, episcleritis 14, acute iridocyclitis 13, superficial keratitis 13, interstitial keratitis 11, patch on the eyelids 10 and sclerosing keratitis in 4 cases. Twenty patients were found to be blind in both eyes and 38 in one eye because of ocular leprosy.

Periodical eye checkup of all leprosy cases by an Ophthalmologist is essential to detect and treat the eye lesions in their early stages in order to prevent complications and blindness.

VI/288(A) OCULAR MANIFESTATIONS OF HANSEN'S DISEASE

Gloria D. Lim.
College of Medicine, Manila, Philippines

This compassionate project, which started in 1976, reports on the ocular findings of Hansenite patients seen at the Dr. Jose N. Rodriquez Memorial Hospital, (formerly known as the Central Luzon Sanatorium) Tala, Caloocan. Blinding disease is brought about in two conditions:

1. Lesions involving the external adnexae, e.g. facial nerve involvement with resulting lagophthalmos and exposure.
2. Lesions involving the anterior segment as a direct invasion with *M. leprae* or as a drug reaction, and/or as a sequela of the above.

The problems encountered in the study and the control of ocular leprosy are given.

VI/289(A) UVEITIS IN LEPROSY PATIENTS AND THE ROLE OF INTRAOCULAR SURGERY

I.S. Roy, S.K. Samanta

About 2,600 leprosy patients (1,100 from Leprology O.P.D. of School of Tropical Medicine, Calcutta, 1,400 from the Leprology O.P.D. and Indoor of Gouripore Leprosy Sanatorium, Bankura, West Bengal, 100 patients from the Gandhiji Prem Niwas, Titagarh, a leprosy sanatorium founded by Mother Teresa in West Bengal) were studied in search of the pattern of Uveitis in leprosy patients and the role of intraocular surgery.

500 patients were treated at the initial phase (first five years of their treatment) with hydnocarpus oil, chaulmoogra oil, etc., in the pre-sulphone era – complications of uveitis were marked in them (about 8%). 1,800 patients were treated with dapsone at the initial phase – indications of uveitis were found in 3% of them. The rest of the patients were treated with multidrug regimens in the initial phase (only for the last 2 years) – uveitis was found in only 1% of them. The different clinical findings are described in these three groups of patients.

Uveitis was manifested in the form of cold iritis, posterior synechiae, complicated cataract, occlusio pupillae with subsequent blindness.

100 cases of cataract (60% of them had complicated cataract with posterior synechiae and the remaining had senile cataract) had also been operated in the Gandhi Prem Niwas and the iris was examined histologically. The iris tissue was obtained during iridectomy in the course of the cataract operation. Dormant lepra bacilli in globi form were seen in lepromatous cases, with a minimal amount of cellular infiltration.

The overall success in cataract extraction was excellent, and under the umbrella of dapsone, rifampicin, ethionaimide and clofazimine, intraocular surgery has been possible with a much better progrosis.

VI/290(A) CATARACT SURGERY, IMMUNOLOGY OF AQUEOUS, AND IMMUNOHISTOPATHOLOGY OF IRIS IN PATIENTS WITH LEPROMATOUS LEPROSY IN SOUTH KOREA

M.G. Kerr Muir
Institute of Ophthalmology, London, England

Cataract contributes greatly to the morbidity of lepromatous leprosy and its effect is compounded by an extreme miosis. Surgery is complicated by low pre-operative intraocular pressure, decreased scleral rigidity, atrophic miosed iris and on occasion, subluxation of the lens. A low-grade chronic iritis is believed to produce these clinical features.

A suitable method for cataract extraction in these circumstances is described, with a one to three-year follow-up.

Evidence for a low-grade iritis is submitted in the examination of aqueous immunoglobulin, which shows a chronic breakdown of the blood-aqueous-barrier.

In an attempt to elucidate the cause of the extreme miosis and pattern of iris involvement, with predominant dilator atrophy, the results of examination of broad iridectomy specimens of iris using light microscopy, electron microscopy and immuno-histochemical techniques will be presented and the pathogenesis of iris changes discussed.

VI/291(P) CLASSIFICATION OF OCULAR DISABILITY IN LEPROSY

P.A. Lamba and D.Santoshkumar
Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, INDIA

The incidence of ocular leprosy varies widely in various reports. On the basis of a survey of 650 eyes of leprosy patients, a new approach to the analysis of the ocular manifestations of leprosy has been suggested. For purposes of uniformity of observations by future workers, a term 'Sight-threatening Lesions (STL)' has been suggested to differentiate between lesions of academic interet *versus* lesions produced which may be detrimental to the functioning of the eye. The prevalence of potential 'Sight-threatening Lesions' was seen to be 33.6%. The lesions have been identified and classified according to their severity as well as the chronological order of their appearance.

On the basis of the survey, a new classification of the grades of ocular disabilities produced in leprosy is proposed. The proposed classification gives a better undestanding of the progress and the prognosis, and also signifies the grade, up to which the preventive measures are likely to be successful. According to this classification, the progress of the condition can be arrested or prevented only upto stage III of the grading. The details of proposed classification will be presented and discussed.

Other operative procedures like those for lagophthalmos are of great benefit in protecting the cornea and in preventing the development of corneal opacities. Penetrating keratoplasty and glaucoma surgery were also carried out in some patients with good results. Successful surgical removal of the lens in patients whose blindness is due to cataract offers a new hope for the restoration of sight in leprosy patients. Detailed observations will be presented and discussed.

VI/292(P) FACTORS INFLUENCING CORNEAL INVOLVEMENT IN LEPROSY STUDY OF PRECORNEAL FILM

Santosh Kumar, P.A. Lamba
Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, (India)

The incidence of corneal involvement in leprosy varies between 25 and 90%. The corneal involvement includes punctate keratitis (superficial and deep), interstitial keratitis, corneal infiltrates, leprotic pannus and exposure keratitis. Although some factor, such as corneal anaesthesia secondary to trigeminal nerve involvement and lagophthalmos secondary to facial nerve involvement, undoubtedly play a role in the causation of the corneal lesions, the exact etiopathogenesis of corneal lesions is not well understood.

Precorneal film composed of secretions of the Meibomian glands, lacrimal glands and conjunctival globlet cells plays an important role in the maintenance of the functional integrity of the cornea. The role played by the disturbance of the precorneal tear film will be critically analysed with respect of corneal involvement.

Lacrimal secretion and its disturbance have been assessed with Schirmer's test, and precorneal tear film evaluated by the break-up time of the tear film. In addition, the involvement of conjunctival globlet cells has been estimated by subjecting the conjunctiva to biopsy and histopathological examination.

In 200 leprosy patients with or without corneal involvement, Schirmer's test and break-up time were estimated and about 50 patients subjected to conjunctival biopsy and histopathological examination. Vital staining with Rose Bengal was also carried out to study the corneal epithelium. The results have been critically evaluated with relation to the corneal involvement, in order to assess the role played by the precorneal film in the causation of corneal damage.

VI/293(P) INVESTIGATION OF REGIONAL VARIATIONS IN THE OCULAR COMPLICATIONS OF LEPROSY

T.J. Ffytch
St. Thomas's Hospital, London, England

The manifestations of ocular involvement in leprosy and their resulting impact on vision vary throughout the world and are influenced by many factors. Knowledge of these factors should help to identify those patients who are at risk and provide guidelines on preventive measures.

A programme designed to investigate these influences has been started,

involving the collection of data on ocular complications from cross sections of the world leprosy population. These surveys can be undertaken by medical and paramedical workers and the initial results will be discussed together with an evaluation of the methods used.

VI/294(P) OCULAR MANIFESTATIONS OF LEPROSY IN BUNDELKHAND REGION

G.D. Gupta, M.C. Agarwal, D.C. Govil.
M.L.B. Medical College, Jhansi, U.P., INDIA

A study of a complete ophthalmic examination of 180 leprosy patients attending the leprosy clinic in M.L.B. Medical College, Jhansi from July, 1982 to April, 1983, shows that the prevalence of ocular lesions was 56.7%.Eye lesions were more common in lepromatous leprosy (72.6%), followed by borderline (47.0%) and tuberculoid (40.3%). The prevalence of ocular lesions was greater in patients of advanced age (about 80% in patients > 50 years) residing in a rural community (72.1%), belonging to a low socioeconomic group (79.6%) suffering from disease of long duration (100% in patients with > 14 years duration), and irregular in treatment.

The part observed to be most commonly affected was the ocular adnexa, followed by lesions of the conjunctiva, the cornea and the iris.

No specific fundus lesion was found. Vision was seriously affected mostly in patients with lepromatous leprosy. Special emphasis on colour vision was given.

VI/295(P) A STUDY OF EYE LESIONS IN LEPROSY

P.K. Kar,R.C. Rawal, F.E. Bilimoria, B.H. Shah
Department of Dermatology, Military Hospital, Ahmedabad, India

A study was conducted to discover the incidence of ocular complications in leprosy. 1800 cases were examined at random and 150 (8.2%) patients had eye lesions. The lesions were found in 6.6.% of lepromatous leprosy patients (LL) and 1.6% of non-lepromatous leprosy patients. Out of the 150 patients, 111 (74%) were male and 80% of them had leprosy (LL). Ages varied from 3rd to 6th decade and 60% were over forty.The mean duration of leprosy in the LL cases was 6.2 years and in non-lepromatous leprosy patients 5.8 years. Loss of eyebrows was found to be most common (76%), followed by lesions of the conjunctiva (64%), cornea (62%) and eyelids (30%). Important eye complications were iridocyclitis (24%), corneal ulceration (10%) and lagophthalmos (8.1%). 20% of patients were not having treatment at the time of diagnosis of the eye lesions. 40% patients had received irregular treatment for one to four years. It is concluded that examination of the eyes is essential in all types of leprosy.

VI/296(P) CLINICAL MANIFESTATIONS OF IRIDOCYCLITIS IN LEPROSY, ITS EARLY RECOGNITION AND MANAGEMENT

N.B. Suryawanshi
Department of Ophthalmology, Schiefflin Leprosy Research and Training Centre, Karigiri, India

Iridocyclitis is most common in lepromatous leprosy. It is the chronic type of iridocyclitis that produces devastating damage to the eyes, leading to a partial or complete blindness.

In this paper, the clinical manifestations of iridocyclitis are given. Its early recognition and management are discussed.

Chronic iridocyclitis manifests clinicIly as recurring acute attacks.These acute attacks of inflammation may be suppressed by corticosteroids and a mydriatic. The affection is bilateral and may be independent of generalized reactions. Patients who have a positive skin smear over a long period are more prone to get this type of iridocyclitis.

It is important to recognize the early signs. Medical Officers and Paramedical Workers taking care of the leprosy patients should be taught how to recognize the early signs, so as to prevent serious complications.

SESSION VII

NERVE DAMAGE

Chairman: Balina, L.M.

Rapporteur: de las AGUAS, J.T.

WEDNESDAY, 22ND FEBRUARY, 1984

Auditorium 13.00–16.00

Abstracts

A* : 297-312
P* : 313-317

*A : accepted for reading
*P : for poster presentation.

VII/297(A) SOME NEWER APPROACHES TO THE STUDY OF NERVE DAMAGE IN LEPROSY

N.H. Antia
The Foundation for Medical Research, Bombay, India

Besides the conventional techniques used for the study of nerve damage in leprosy, the following newer methods have been evolved and used at The Foundation for Medical Research, for an overall understanding of the various mechanisms underlying nerve damage in this disease. They consist of:

1. Ultrastructural morphology;
2. Electrophysiology – *in vitro* recording;
3. Sciatic nerve damage in the mouse model;
4. Nerve tissue culture;
5. Immunological methods – *in vitro* and *in vivo;*
6. Biochemical – protein and lipid profiles *in vivo* and *in vitro.*

Results of these studies will be presented to give insight into pathological changes at cellular level,host-parasite interaction, biochemical changes accompanying such a relation and immune mechanisms involved in the process of nerve damage.

VII/298(A) HISTOPATHOLOGICAL ANALYSIS OF PURE NEURITIC LEPROSY

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Central JALMA Institute for Leprosy, Agra, India

The neuritic type of leprosy does not find a place in the Ridley and Jopling Classification. In the Indian Classification, polyneuritic type of leprosy has been included under non-lepromatous group since there is a lack of histopathological support. This study reports on a series of 20 cases of pure neuritic type of leprosy from the clinical and histological aspects. It is possible to identify the immunological spectrum in the nerve lesions similar to what is found in the skin. The histopathological findings are also correlated with the lepromin response. The importance of including the neuritic type in the classificiation of leprosy is stressed.

VII/299(A) STUDY OF THE PATHOLOGIC CHANGES IN THE POSTERIOR TIBIAL NERVE IN ARRESTED BORDERLINE LEPROSY PATIENTS

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Department of Dermatology, First Affiliated Hospital of Nanjing Medical College, China

This paper reports the pathologic changes in the posterior tibial nerve in 8 arrested BT leprosy patients. Observations on light microscopy showed marked thickening of the epineurium and perineurium. The endoneurium was fibrotic. The perineurium was infiltrated by inflammatory cells. The vessel walls were thickened and had a narrow lumen, or were obliterated with hyaline degeneration. Within the nerve bundle, there were focal infiltrations of lymphocytes and epithelioid cells. Schwann cells showed proliferation. Nerve axon degeneration and demyelination were demonstrated: in some cases they had completely disappeared. Acid-fast bacilli were identified in infiltrated foci in all cases. Transmission electron microscopy showed marked proliferation of collagen fibrils. The Schwann cells were long and thin. Mitochondria in cytoplasm were swollen and their crista disintegrated. There were vacuoles of varying sizes within cytoplasma. Some myelin sheaths were in cracks, separated or twisted. The lamina structure was not clear. The degenerated axon showed decrease of microfilaments, with vacuoles of varying sizes. A few bacilli were found in nonmyelinated nerves. The factors that prevent *M. leprae* being eliminated from Schwann cells and axons are discussed. It is noted that the Schwann cells and the axons can be considered as a "shelter" for *M. leprae.*

VII/300(A) THE INFLAMMATORY EXUDATE AND NERVE DEGENERATION — SOME EXPERIMENTS

S.S. Pandya, S.S. Naik, S. Gurnani
Acworth Leprosy Hospital Society for Research, Rehabilitation and Education in Leprosy, Bombay, India

Peripheral nerve degeneration in leprosy may be non-specifically induced or aggravated by lytic factors released into the endoneurium from the inflammatory exudate, or by the immunologic effects of nerve constituents. Experiments were designed to examine these hypotheses.

Mouse sciatic nerves were crushed in the thigh to cause Wallerian degen-

eration distally and also to destroy the perineurial barrier. A homogenate of mouse peritoneal macrophages "induced" by casein injection was injected weekly for 16 weeks around the crush site. Comparison of the progress of nerve regeneration in experimental and saline-injected controls clinically, electrically and histopathologically showed no significant differences. One reason could be the inability of test macromolecules to penetrate even compromised perineurium in sufficient concentration.

Guinea-pigs were sensitised intra-dermally with tubulin, neurofibroma membrane protein, *M. leprae*, leprous immune complexes and some lysozomal enzymes in Complete Freund's Adjuvant. They were challenged six weeks later by intraneural injection of the same antigen. Histologic examination of experimental and control nerves 5 to 10 days later showed no significant inflammation and degeneration, except in tubulin injected specimens.

VII/301(A) A STUDY OF INTRACARPAL AND INTRANEURAL PRESSURES IN THE ACUTE MEDIAN LEPROUS NEURITIS

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We measured 15 intracarpal and intraneural pressures in acute median leprous neuritis, during neurolysis. The patients were operated on after ten days' medical treatment (oral steroids and antibacterial agents). At present, we use a standard protocol for surgery: a wide extraneural neurolysis, respecting the mesoneurium and an epineurotomy.

Operative pressures were measured with a catheter in each patient, with the wrist in neutral position.

The overall results are as follows:

The mean intracarpal canal pressure was 40 millimeters of mercury and the mean intraneural pressure was 25 millimetres. The pressure in the control subject with the wrist in neutral position was 4 to 6 millimeters of mercury, and 1 to 2 millimeters of mercury for intraneural pressure.

It appears that there are differences between the tuberculoid form in which the intraneural pressure can be localized, and the lepromatous form in which the intraneural high pressure is extensive.

A better understanding of the physiopathology of the neuritis of Hansen disease should encourage surgeons to operate early before definite nerve damage has occurred.

VII/302(A) DIGITAL DERMATOGLYPHICS AS A CRITERION OF RISK FOR THE DEVELOPMENT OF SEVERE NERVE DAMAGE IN LEPROSY

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It is generally known that the peripheral nervous system is always involved in the leprosy process; however, severe nerve damage resulting in disabilities does not develop in all patients with leprosy. Retrospective analysis showed that out of 131 patients with lepromatous leprosy who died before 1950, and who had never been treated with sulphones, 57 (43.5%) had no nerve damage in spite of the long duration of the disease, indicating that the development of nerve damage seems to depend on some inherent constitutional liability. The dermatoglyphic study revealed a significant increase ($P < 0.001$) in the frequency of whorls and total ridge count in the fingers of leprosy cases with severe nerve involvement, compared to those patients without such damage and with healthy persons. Furthermore, male patients had a significant increase in whorls in the area innervated by the ulnar nerve (IV and V fingers), and females – in the area innervated both with the ulnar and median nerves (mainly the III and IV fingers). The results obtained may provide additional criteria for assessment of the risk of severe nerve damage in leprosy patients.

VII/303(A) SERUM FACTOR AND MYCOBACTERIAL ADJUVANT ACTIVITY AS CAUSES OF NERVE DAMAGE IN LEPROSY

V.P. Shetty, N.F. Mistry, N.H. Antia
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Predominant segmental demyelination in clinically normal nerves of tuberculoid and lepromatous patients was reported earlier by us in the absence of cellular infiltration and AFB. This indicated a role for circulating factors as a possible secondary cause of demyelination at a site distant from the primary focus of infection. The role of antibody was investigated by intraneural/subcutaneous injection of ammonium sulphate precipitated serum from randomly chosen leprosy patients, into sciatic nerves of random bred Swiss white mice.Three out of eighteen samples showed positive demyelination.

Since mycobacteria are known to exert adjuvant effects, this property was studied for its role in the causation of primary nerve damage of Swiss white mice.Animals were injected subcutaneously with 20×10^6 live and heat-killed *M. leprae*, with and without normal sciatic nerve extract. Biopsies of the sciatic nerves were performed one and four months after injection. Degenerative changes in the nonmyelinated fibres were obtained at the first month in the sciatic nerves of mice injected with live and heat-killed *M. leprae* along with nerve extract. These changes were identical to early changes seen under the electron microscope in footpad-inoculated mice at the fourth post-inoculation month and in early human nerve lesions.

VII/304(A) NEUROPATHY OF LEPROSY, CLINICAL AND ELECTROPHYSIOLOGICAL STUDIES AND ITS CO-RELATION TO VASCULAR STATUS AND HISTOPATHOLOGY

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43 leprosy patients were classified clinically as lepromatous, dimorphous and tuberculoid, and were subjected to motor nerve conduction tests in the median, ulnar, lateral popliteal and posterior tibial nerves. Brachial percutaneous arteriography was performed in 20 patients under the age of 40 years. Histopathology of biopsied sural nerves was made in 40 patients. Significant slowing of motor conduction velocity as compared to controls was found. Vascular involvement was severe in 6 patients, moderate in 5 and mild in 7 patients. No relation between the vascular insufficiency and nerve thickness was clinically detected. Motor nerve conduction abnormalities were not affected by the severity of vascular insufficiency. Structural changes in the sural nerve were axonal loss, myelin fibre loss, peri and endo-neurial fibrosis in all biopsies. Segmental demyelination, remyelination and axonal degeneration were demonstrated by single nerve fibre teasing. The pathogenesis of these histological observations are perhaps unrelated to vascular involvement. However a direct relation exists between the degree of thickened nerves clinically and abnormal histopathological changes in the sural nerve morphology.

VII/305(A) THE PRESENTING PERIPHERAL NEUROPATHY IN LEPROMATOUS LEPROSY: A COMPARATIVE STUDY OF TESTING MODALITIES:

Kaplan, M., Gelber, R.
Seton Medical Center, California, USA

To define the extent of peripheral neuropathy at initial presentation and compare the utility of frequently utilized methods for assessing that neuropathy, 28 previously untreated lepromatous leprosy (LL_p, LL_s, BL) patients underwent manual motor and sensory testing of the upper extremities and electrophysiologic nerve conduction studies of ulnar, median and radial nerves. All but 3 patients demonstrated some abnormality by at least one of the testing procedures. Only 12 had abnormalities found in manual motor testing. Manual sensory testing was found to be the most sensitive testing procedure with abnormalities found in 25 patients. Eleven had loss of sensation, 6 had loss of protective sensation, 5 had diminished protective sensation, 3 had diminished light touch and 3 had normal sensation. Electrophysiologic testing demonstrated neuropathy in 21 patients, 20 having sensory abnormalities (15 ulnar, 17 median, 17 radial) and 20 motor irregularities (17 ulnar, 4 median, 1 radial). Nerve conduction velocity was more commonly abnormal than latency, which was more frequently abnormal than amplitude. Manual sensory testing revealed peripheral neuropathy in 5 patients with normal electrical studies, and electrophysiological testing detected 2 patients found normal by manual sensory examinations.

VII/306(A) A COMPARATIVE STUDY OF MEDICAL AND SURGICAL TREATMENT IN THE MANAGEMENT OF EARLY ULNAR NEURITIS

Pannikar,V.K., Joseph, M., Taylor, P.M., Prasad, R., Kolumban, S., Andrews, P., Rosi Reddy, N., Fritschi, E.P.
Schieffelin Leprosy Research and Training Centre, Karigiri, Tamil Nadu, India

62 patients with functional evidence of early ulnar neuritis were randomly allocated into two groups. One group received a full course of steroids only, the other group, in addition to the full course of steriods, had medial epicondylectomy and epineurectomy done within seven days of admission to the study. These patients were followed up periodically for a minimum period of one year.
Analysis of the data indicates that there were no added benefits with the surgical intervention as compared with steroid therapy alone, in the treatment of early ulnar neuritis. This study analyses the data taking into consideration occupation, age, sex, classification, smear positivity, duration of neuritis, duration of treatment and reactive episodes.

VII/307(A) EFFECT OF A STANDARD CORTICOSTEROID TREATMENT ON NERVE DAMAGE IN ETHIOPIAN LEPROSY PATIENTS

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ALERT, Addis Ababa, Ethiopia

A group of 133 leprosy patients with loss of nerve function of less than 6

months duration was given a standard 6 month treatment of prednislone in decreasing dosages.

Nerve function of the ulnar and median nerves was regularly assessed by means of voluntary muscle tests and sensory tests. The use of a nerve index, composed of the added scores in these tests, proved to be a simple, adequate and reliable method of monitoring functional recovery.

An adequate follow-up was obtained for 6 months in 95 patients (71%), for 1 year in 80 patients (60%) and for periods ranging from1.5 to 3 years in 71 patients (53%)

The nerve function recovery observed in this group of patients is presented and discussed. The parameters, influencing the speed and extent of recovery, are analysed.In addition, the patients who have undergone neurolysis and those whose nerve function deteriorated after initial improvement will be discussed separately.

VII/308(A) AFFINITY OF *M. LEPRAE* TO MOUSE GANGLION CELLS OF THE PERIPHERAL NERVOUS SYSTEM

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Affinity of *M. leprae* (ML) to cultured mouse ganglion cells of the peripheral nervous system was compared to that of *M. lepraemurium* (MLM) and several other mycobacteria. When the 72-h cultured ganglion cells (10^5) were infected with 10^7 ML or MLM at 33°C for upto 24 h, affinity of ML to the cells was higher than that of MLM: percent phagocytosis of ML by cells ranged from 70 to 80% as compared to about 20% of MLM, and the number of ML phagocytosed in a cell ranged from 6 to 8, as compared to about 2 of MLM. ML also showed higher affinity to mouse neuroblastoma cells than MLM did. However, ML did not have high affinities to other cultured cells, such as mouse kidney cells or BHK 21 cells. The high invasive activity of ML to ganglion cells was also proved by both the scanning and the transmission electron microscopes. Affinity of *M. tuberculosis* and several mycobacteria other than tubercle bacilli to ganglion cells was weaker than that of ML. Treatment of ML or ganglion cells with receptor-destroying enzyme caused reduction of affinity of the organism to cells.

VII/309(A) SENSORY NERVE CONDUCTION STUDY OF DORSAL CUTANEOUS BRANCH OF ULNAR NERVE IN LEPROSY

M. Gourie-Devi
National Institute of Mental Health and Neuro Sciences, Bangalore, India

The ulnar nerve is one of the commonest nerves to be affected in leprosy and it has been observed that the dorsal cutaneous branch is often thickened. For the early diagnosis of nerve involvement in leprosy, sensory conduction studies have been found to be useful. A technique of determining sensory conduction of DCB is described and its usefulness in leprosy is evaluated.

Sensory conduction of DCB and motor and sensory conduction studies of ulnar nerve by conventional techniques were performed in 30 control and 28 leprosy patients. It was observed that DCB sensory conduction abnormalities were found in 82.1% (23 patients), conventional ulnar sensory conduction in 46.4% (13 patients) and motor conduction in 25% (7 patients).

In all the 17 patients with skin lesions in the area innervated by DCB, the sensory conduction was abnormal. Of interest are 6 out of 11 patients, who had no skin lesions, but still showed abnormal DCB sensory conduction. All the 9 patients with sensory deficit in the ulnar nerve territory, and 14 out of 19 patients with no clinical evidence of sensory deficit, had abnormal DCB conduction.

VII/310(A) ELECTROPHYSIOLOGICAL STUDIES OF THE SCIATIC NERVES OF RATS INOCULATED WITH M. leprae

Alain Sebille, C.C.Guelpa, N.Tabti, A.M.Giroir
Physiol. Lab., Paris, France

Although nerve trunk involvement is one of the most striking features in leprosy, there is no experimental model today for therapeutic research. We tested the female Wistar rat for such a purpose, owing to the length of the sciatic nerve which permits precise electrophysiological measurements.

Nerve conduction velocities are known to be slowed in leprosy patients. We therefore investigated the plantar muscles monosynaptic reflex resulting from sciatic nerve stimulation, in order to calculate its segmental motor (MCV) and sensory (SCV) conduction velocities in 60 rats, inoculated in the left hind footpad (70 or 7000 AFB). *M. leprae* multiplied half as rapidly as in mice simultaneously inoculated . No AFB were found in nerves.

MCV and SCV were not changed at the level of the thigh, in comparison with a similar group of normal animals. 21 months after inoculation, the MCV was bilaterally significantly decreased ($p < .01$) in all animals, as well as the left SCV in the 7000 AFB-inoculated animals. Distal bilaterial slowing of the sciatic MCV might suggest that the presence of AFB is not necessarily required in a nerve to cause neuropathy. Asymmetric SCV slowing of the proprioceptive fibres could indicate the late involvement of the largest fibres of the nerve. These features are identical to the experimental model of slow compression of the nerve.

The electrophysiological abnormalities observed in the rats inoculated in the sciatic nerve are so slow to develop. Since it is not possible to use this model for extensive therapeutic experiments, we are looking for a better model.

VII/311(A) HISTOCHEMISTRY OF LEPROSY NERVES IN HUMAN AND MOUSE

Moameen Doryadi, L. Mehta, N. Antia
Anatomy Department, Grant Medical College, Bombay, India

Five enzymes, acid and alkaline-phosphatases, thymine pyrophosphatase, SDH & Cytochrome oxidase were studied in peripheral nerves of mice infected with *M. leprae* and human leprosy. The crushed mouse sciatic nerve served as control, as these enzymes are not demonstratable in normal nerves. Cryostat sections were taken and semiquantitated under L.M. The electron histochemistry of acid-and alkaline-phosphatase was done. Acid- and Thymine-pyrophosphatase were markers for Golgi and lysosomes. oxidative enzymes for mitochondria and alkaline phosphatase for vascular endothelium.

Except alkaline phosphatase all the enzymes were comparable in mouse, crushed and leprosy nerves. The human leprosy had a different pattern. Low acid phosphatase activity was seen in LL while it was elevated in TT. SDH and cytochrome oxidase were also significantly different in the two groups. Ultrastructural studies helped in identifying functions of some cellular and subcellular constituents of the nerves. The role of these enzymes in the neuropathy of leprosy is discussed and the role of blood vessels as barriers is hypothesized.

VII/312(A) NEUROPATHY ASSOCIATED WITH EXPERIMENTAL MYCOBACTERIAL INFECTION

Maurice J. Lefford, Anne M. Skoff, R.P. Skoff, K. Liu
Wayne State University School of Medicine, Detroit, USA

Mice of the CBA strain developed hind-quarter paralysis after infection with *M. lepraemurium* (Mlm). The frequency of paralysis was highest in mice of the CBA/J strain, and was less prevalent in mice of the CBA/N, CBA/H-T6J and CBA/CaJ strains. No paralysis was observed in numerous other mouse strains. The prevalence of paralysis was higher after intravenous (iv) than after subcutaneous infection. Paralysis occurred late in infection and the interval between infection and paralysis was inversely related to size of the infectious inoculum. A similar frequency of paralysis was observed in CBA/J mice that had been depleted of T lymphocytes. Histological studies revealed no invasion of the central or peripheral nervous system with Mlm bacilli; nor was any inflammatory reaction observed in the nervous system. The only abnormal histological feature consisted of demyelination and abnormal myelination of peripheral nerves of the lumbo-sacral plexus.

VII/313(P) CLINICO-PATHOLOGICAL REVALUATION OF NEURITIS IN HANSEN'S DISEASE – 1. CATEGORISATION

P. Descamps, A. Carayon, J.J. Salaun, P. Ravisse, J. Van Droogenbroek

Besides the ENL reaction neuritis which has been known for some time and reversal reaction knowledge of which is comparatively recent, there exists also a 'pars incognita' which we propose to evaluate —

- with reference to the cardinal elements of reaction;
- and specially with reference to physical examination, essential in subdermatological neuritis without evident reactions.

Histopathology, essential in these cases (skin biopsies of the smaller nerves, the epineurium and the endoneural fibres) is discussed in detail in the paper.

Of 258 cases of recent neuritis studied, 81 were of an evident ENL etiology and 91 were caused by a reversal reaction. This makes a total of 172 or 2/3 of the cases under observation.

86 or 1/3 of the cases were thoroughly investigated both clinically and pathologically. (pars incognita).

a) 14 were cases of ENL without manifest dermatological reactions.

b) 66 showed some form of reversal reaction
   - 15 without skin lesions
   - 28 subdermatological forms termed purely neural
   - 19 subpolar BT-TT
   - 3 delayed (migration from LLs - BL - BT)
   - 6 secondary microangitis (microangiopathic)

- 18 were forms arising from BL (elimination of ENL)
- 3 were cases of necrosis of the nerve in the early stages
- 2 were mixed kinds with 2 successive reactions

c) 6 were resistant to dapsone
- 2 paradoxical reversals reactions (BT endoneurium and LL perineurium)
- 2 ENL
- 2 non-reactional

On a total of 258 cases investigated, 95 were found to be suffering from ENL neuritis, 157 from reversal reaction neuritis and 4 from reactional neuritis (2 ENL, 2 R) during resistance. Only 2 cases showed no reactions.

VII/314(P) APPRAISAL OF THE PHYSIOPATHOLOGICAL RESEARCH UNDERTAKEN OF HANSEN NEURITIS

L.J. Courbil, A. Carayon
Dakar, Senegal

Disorders caused by the Gell and Coomb III immunopathological phenomena with a predominance of oedema and vascularization and IV - infiltrations of inflammatory cells.

1. *EFFECTS OF HYPERTENSION IN THE LARGE MIXED NERVE TRUNKS THUS TRIGGERED OFF*

— *mechanical phenomena* are determined by the role played by the perineurium and the haemo-vascular barrier and on the resistance of the epineurium. Distension associated with cellular infiltration makes the epineurium porous and opens the barrier. The epineurium infiltrated by *M. leprae* results in hypertrophy of the trunk. These phenomena are more distinct in LL - ENL neuritis. The action on the axis cylinder produces an invagination with demyelination at the level of Ranvier's nodes.

— *Vascular disorders:*
- opening of the vaso-dilation circulation reserve.
- venous compression
- progressive segmented arterial compression of the endovenous vessels of the satellite artery.
- hyper-infiltration by capillaries on the venous side.

— *Consequences:* hypoxia then anoxia and then truncal ischaemia by segments, increased demyelination and Wallerian degeneration.

2. *AGGRAVATION OF EXTRINSIC ORIGIN*

Conflict in the canal caused by hypertrophy of the major ulnar nerve (canal measuring 6 cm in extension and 3 to 4 cm when flexed). Nerve: 1st stage: 5 to 7mm; II: 7 to 10, III: over 10).
- elongation and compression (lengthened by 2 cm when flexed) - canal venous to 3 to 4 cm, which localises the elongation to a short segment.

3. *CONJUGATION OF CHANGING PHENOMENA AND PHYSICO-PATHOLOGICAL DISORDERS.*

VII/315(P) PRIMARY NEURITIC LEPROSY, AN EARLY, EVOLUTIONARY FORM OF LEPROSY: A CLINICO-PATHOLOGIC STUDY

S.M. Chandi, C.J.G. Chacko, M. Jacob, S. Arunthathi, P.M. Taylor
Department of Pathology, Christian Medical College Hospital, Vellore, India.

Sixty-five patients with primary neuritic leprosy were studied in an effort to identify clinico-pathological features that might help towards a better understanding on the nature of this entity and its place in the classification of leprosy. The pathological reaction in peripheral nerve biopsies of these patients was studied relative to histological changes observed in the skin and nasal mucosa and the host response to lepromin. The observations suggest that primary neuritic leprosy is an early and evolutionary form of leprosy temporarily restricted to peripheral nerves and capable of developing into one or other of the borderline or polar forms of leprosy.

VII/316(P) ORGANIZED NERVE CULTURE – A MODEL FOR THE STUDY OF NERVE DAMAGE AND CULTIVATION OF *M. LEPRAE.*

R. Mukherjee, N.H. Antia
The Foundation for Medical Research, Bombay, India

Neonatal dorsal root ganglia of mice cultured *in vitro* to obtain organized bundles of nerve fibres containing Schwann cells and fibroblasts, were infected with *M. leprae* and maintained for extended periods after infection. In these cultures, *M. leprae* interfered with the DNA synthesis and association with axons of the host Schwann cells. Within four weeks, there was 9–14 – fold multiplication of bacilli as evidenced by close correlation of numerical increases with the ^{3}H-thymidine incorporation and viability of the organism. The magnitude of this bacillary growth was well tolerated by the host cells and the culture as a whole, as these actively incorporated precursors of basic metabolism. There was no evidence of release of toxic factors due to host-bacillary interaction. Neurons and axons looked healthy.

Cytotoxicity of the cells in the form of vacuolation, chromatolysis and slowed metabolism became evident only when *M. leprae* was added with immunocompetent cells.

This study reveals that in the organised nerve culture, *M. leprae*
(i) alone produces subtle alterations of the Schwann cells only;
(ii) with immunocompetent cells, produces cytotoxicity; and
(iii) itself shows substantial intracellular growth.

VII/317(P) CHANGES IN CUTANEOUS NERVES IN SKIN LESIONS PRODUCED BY SENSORY PERIPHERAL NERVE AS ANTIGEN

C.L. Crawford, P.M.D. Hardwicke
Charing Cross Hospital, London, England

We have previously demonstrated mononuclear cell infiltration and unmyelinated fibre degeneration in cutaneous nerves in rabbits with granulomatous hypersensitivity to sensory peripheral nerve.

Skin lesions have also been produced in Dutch Bantam rabbits after injection of human sural nerve plus Freund's complete adjuvant. Cutaneous nerves in 8 skin lesions from 5 rabbits were studied ultrastructurally. There were changes in the perineurium with loss of tight junctions and caveolae. Also projections of perineurial cells into the endoneurium had occurred leading to compartment formation. Mononuclear cells were present in the endoneurium, together with degeneration of unmyelinated fibres. Endoneurial capillaries were also present and some of these contained homogeneous dense bodies.

The perineurial changes are similar to those reported in leprosy. The significance of these findings in contributing to nerve damage and the involvement of degenerating unmyelinated fibres in producing these perineurial changes is discussed.

These studies provide further evidence for the hypothesis that nerve damage in cutaneous nerves in skin lesions in nonlepromatous leprosy may involve an autoimmune response to an antigen in sensory peripheral nerve rather than being a direct effect of *M. leprae*.

SESSION VIII

EXPERIMENTAL LEPROSY

Chairman: Job, C.K.

Rapporteur: Waters, M.F.R.

WEDNESDAY, 22ND FEBRUARY, 1984

Commission Hall 'H' 13.00–16.00

Abstracts

A* : 318-334
P* : 335-337
T* : 338-340

*A : accepted for reading
*P : for poster presentation.
*T : for title reading

VIII/318(A) EPIDEMIOLOGY OF LEPROSY IN WILD ARMADILLOS

Eleanor E. Storrs, H.P. Burchfield
Medical Research Institute, Florida Institute of Technology, USA

It is not yet known if leprosy in wild armadillos in the U.S. is a threat to public health. Leprosy must be transmitted from armadillo to armadillo in the wild to account for the widespread infection found in Louisiana and Texas. Of 1,286 animals captured between the Mexican border and the Mississippi River, 6.2% harbored leprosy infections. By contrast, of 1181 armadillos captured east of the Mississippi, only one was positive. No injected animals, out of 964 examined, have been found in Florida, presumably because these are descendants of a few disease-free animals that were imported into the State and then escaped 50 to 60 years ago. About 90% of Florida animals develop disease after inoculation. So, resistance is not a factor. However, armadillos from Louisiana are moving across the Gulf States into northwest Florida and could carry *M. leprae* with them. Thus animals from central and south peninsular Florida are the only proven source of leprosy-free animals that are also known to be highly susceptible to the disease.

VIII/319(A) THE EFFECT AND SIGNIFICANCE OF LEPROMIN REACTION IN ARMADILLOS INFECTED WITH *M. LEPRAE*

Rita M. Sanchez, Charles K.Job, Robert C. Hastings
National Hansen's Disease Center, Carville, LA, USA

A group of 28 armadillos were first lepromin-tested by injecting 0.1 ml of integral lepromin containing 1.8×10^7 armadillo-derived heat-killed *M. leprae* and the reaction at the end of 21 days was biopsied and evaluated histopathologically. Of the 28 animals, 18 were infected intravenously with 10^8 and 10 were infected intradermally with 10^7 armadillo-derived *M. leprae*, 4 to 8 weeks after the first lepromin test.

The Mitsuda reaction of these 28 animals was studied histopathologically at the end of 3 months and every six months thereafter, for a period of 18 months.

At the beginning of the study, 4 of the 28 animals showed collections of epithelioid cells, signifying a positive response. At the end of 3 months, a 5th animal developed a positive lepromin response. At 6 months, 7 animals were positive. None of the 28 animals has yet developed a detectable infection.

The data at the end of 18 months when a disseminated infection is expected in almost all susceptible intravenously infected and in some of the intradermally infected armadillos will be analysed and presented. The relation of lepromin reaction to disseminated infection and the effect of repeated lepromin testing on the development of lepromatous disease in armadillos will be prsented and discussed.

VIII/320(A) NATURAL HISTORY OF EXPERIMENTAL LEPROSY INFECTION IN ARMADILLOS

C.K.Job, Rita M.Sanchez, W.F. Kirchheimer
National Hansen's Disease Center, Caraville, LA, USA

A retrospective study of 3 groups of feral armadillos screened carefully and experimentally infected with armadillo-derived *M. leprae* was conducted. One group of 20 received 10^3 *M. leprae* intradermally, another of 14, 10^7 intradermally in 7 sites and the third group of 15, 10^8 intravenously. In the second group, there were 11 animals born in captivity and were less than 4 months old.The first two groups were monitored by examining blood smears and ear-clip biopsies every 3 months and the third group every 6 months to find out the development of generalized disease. All animals except one were autopsied and bacterial counts per gram of tissue were done on liver, spleen and lymph nodes and histopathological studies were carried out on all the above organs, sciatic nerve and ears.

It has been found that neither age nor sex had any relation to susceptibility of the armadillos to the infection. It is possible that the only difference that dose and route of infection may have on the experimental disease is on the period of development of generalized lesions. There is good correlation between bacterial counts and histopathology which showed much variation. Most of the animals in all 3 groups had developed lepromatous leprosy with high bacterial counts, several had borderline disease associated with low counts and a few are totally resistant. In one infected litter, of the 2 which survived, one developed disseminated disease in less than 2 years and the other was resistant and lived up to 6 years.

The details of all these findings will be presented and their significance in experimental leprosy in armadillos will be discussed.

VIII/321(A) EXPERIMENTAL REPRODUCTION OF LEPROSY IN *DASYPUS HYBRIDUS*

L.M. Balina, R.P.Valdez, M. de Herrera, H. Costa Cordova, J.Bellocq, N. Garcia
Buenos Aires, Argentina

Generalized infection in *Dasypus hybridus* (South American Armadillos) inoculated with *M. leprae* from a human patient.

Dasypus hybridus is an armadillo, common in the humid region of Argentina, that has been bred in captivity in our outdoor colony where 36 animals were born.

About 12 to 16 months after inoculation by the intravenous route, 4 of these animals presented symptoms of generalized infection with generalized lymphadenitis and nodules on the ear.

The bacteriological study revealed A.F.B. which do not multiply in culture for common bacteria and tuberculosis. The pyridine test confirmed the presence of *M. leprae* and the footpad inoculation test is in progress in a laboratory in the U.S. The necropsies of 3 of the animals revealed microscopical features of disseminated lepromatous leprosy in the spleen, the lymphademic nodules, the liver, the meninges, the lungs and skin which is not only full of bacilli in the dermis but also in the epidermis where the phenomenon of trans-epidermal elimination is the subject of an ultramicroscopic study.

The medium period of incubation has been 14.5 months.

VIII/322(A) OBSERVATION ON THE LEPRA REACTION IN ARMADILLO WITH EXPERIMENTAL LEPROSY

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Under the IMMLEP-programme (project ID 780259) of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, 3 batches of armadillos *Dasypus novemcinctus* were obtained in our Institute in March 1979 (26 animals), in July 1981 (20 animals), and in March1983 (22 animals). The first lepromas appeared in the skin of the animals 18-20 months after the intravenous inoculatin of *M. leprae* from untreated LL patients. In the next 4-6 months, groups of nodules 0.5-1 cm in diameter began to appear at other sites: on the outer surface of the legs, on the abdomen and in the places of junction of the abdominal skin with shields. In some animals the first manifestations were macular eruptions which were later followed by lepromas. After prolonged observation a year after the appearance of lepromas in one animal, a hypopigmented desquamative eruption began to develop in the skinover the lepromas and in the apparently normal skin. During the next 3 months the desquamation and hypopigmentation spread all over the abdominal skin. In a further two months, the animal twice underwent a state resembling lepra reaction in human patients with leprosy. Total skin hyperemia was noted, against a background of which foci of more marked erythema and even erosion stood out. In that period, the animal showed increased body temperature and hurried breathing. After the reaction had subsided, the lepromas became flat and decreased in size. Thus, experimental leprosy in armadillos may be used for studying the mechanisms of the development of leprosy reactions.

VIII/323(A) LEPROSY IN MANGABEY MONKEYS—NATURALLY ACQUIRED INFECTION AND TRANSMISSION STUDIES

Wayne M. Meyers, Gerald P. Walsh, Chapman H. Binford, George D. Imes, Peter J. Gerone, Robert H. Wolf, Bobby J. Gormus, Louis N. Martin
Armed Forces Institute of Pathology, Washington, D.C. USA

Lesions were first noted in a female mangabey monkey (*Cercocebus atys*) in September 1979. This monkey was imported from West Africa in 1975, and had never been experimentally inoculated with *M. leprae*, or any other etiologic agent. Biopsy specimens showed typical changes of multibacillary leprosy (? BL-LLs) and the mycobacterium was indistinguishable from *M. leprae* by all standard criteria, including DNA sequence homology studies on armadillo-passaged organisms. The Mitsuda was non-reactive. The disease responded favorably to Rifampin and sulfone therapy, but the monkey developed paralytic deformities of the hands and feet. There was anti-Antigen 5 and 7 activity (Harboe) in the serum. Peripheral blood leucocyte markers, using anti-human monoclonal antibodies revealed low helper/suppressor cell ratios.

Two monkeys of the same species were inoculated with organisms from the index animal and both have developed advanced lesions of leprosy. Two other mangabey monkeys were injected with armadillo-passaged *M. leprae* of human origin, and these animals have progressive disease.

These observations are of interest for two reasons: 1) they offer promise for a non-human primate model of leprosy, and 2) they add a third species to the list of reported animals that have acquired leprosy in nature.

VIII/324(A) EXPERIMENTAL LEPROSY IN THE RHESUS MONKEY AND THE AFRICAN GREEN MONKEY

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Armed Forces Institute of Pathology, Washington D.C., U.S.A.

The transmission of leprosy to the mangabey monkey (*Cercocebus atys*) in our laboratories prompted us to study the susceptibility of other non-human primate species to the disease. Two rhesus monkeys (*Macaca mulatta*), 3 African green Monkeys (cercopithicus aethiops) and 3 squirrel monkeys (*Saimiri sciureus*) were inoculated with mangabey-derived *M. leprae*. Fourteen months after inoculation, one of the 2 rhesus developed lesions at several dermal inoculation sites. A prominent feature of the infection in this animal was the extensive involvement of the scrotum, an uninoculated site. Histopathologic examination confirmed disseminated lepromatous leprosy. The second rhesus monkey has not developed any evidence of infection. The nasal smears of the 3 African green monkeys were positive for acid-fast bacilli, 20 months after inoculation and subsequently lesions became apparent on the ears of all 3 animals. Histopathologic evaluation revealed changes consistent with lepromatous leprosy. The 3 squirrel monkeys show no evidence of infection 31 months after inoculation. Our results suggest that the rhesus monkey and the African green monkey have significant potential as non-human primate models and may prove to be suitable alternatives to the mangabey monkey, a species not readily available in most laboratories.

VIII/325(A) ELECTRON MICROSOPIC STUDY OF LEPROSY IN A MANGABEY MONKEY NATURALLY ACQUIRED INFECTION.

Frank B. Johnson, Yukiko Fukunishi, Gerald P. Walsh, Wayne M. Meyers, Chapman H. Binford, Peter J. Gerone, Robert H. Wolf, Bobby J. Gormus, Louis N. Martin
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A female mangabey monkey (*Cercocebus atys*) was first observed to have lesions of leprosy in 1979. This monkey was imported from West Africa in 1975, and had never been experimentally inoculated with *M. leprae*. Histopathologic changes were typical of multibacillary leprosy, and all microbiological and immunological studies revealed that the etiologic agent was indistinguishable from *M. leprae* .

Freeze-etched preparations of infected tissues were studied by modifications of the method of Nishiura *et al* (IJL 45:248, 1977). Classic procedures were employed for the electron microscopic study of ultrathin sections.

Lepromas of the index monkey, and tissues of the following animals inoculated with*M. leprae* isolated from this animal were studied: lepromas and livers of nine-baded armadillos, lepromas of mangabey monkeys, a rhesus monkey and an African green monkey.

In all tissues there were bacilli typical of *M. leprae* in phagolysosomes of macrophages. Small spherical droplets surrounded the bacilli. These findings are beleived to be unique for leprosy and are seen in leprosy in humans, and animals susceptible to multibacillary leprosy.

These data provide further evidence that the naturally acquired disease in the mangabey monkey is similar to multibacillary leprosy in humans, and that the etiologic agent is M. leprae.

VIII/326(A) REVERSAL REACTIONS IN *M. LEPRAE*-INFECTED NUDE MICE

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Reversal reactions are manifestations of delayed hypersensitivity to *M. leprae* and are thought to be usually accompanied by manifestations of effective cell-mediated immunity (CMI) as measured by bacterial clearing. These experiments were designed to study the induction of reversal reactions in *M. leprae* -infected, congenitally athymic nude mice using adoptive transfer of CMI. Allogeneic splenic cell suspensions derived from unimmunized heterozygous nu/+ mice, and those vaccinated with heat-killed *M. leprae*, viable BCG and a mixture of the two antigens were diluted to contain 10^4, 10^5, 10^6, 10^7 cells/0.1 ml. and infused intravenously into multibacillary nude mice. The production of reversal reactions in leprous nude mice in response to adoptively transferred CMI was studied in a quantitative fashion.

Dose responsive induction of reversal reactions, apparent by footpad inflammation and swelling, decreased Morphologic Indexes of the bacteria and mononuclear cell infiltrations, histopathologically, were observed. The effective dose 50% (ED50) in response to immunized cell infusions was in general lower than that observed in unimmunized cells. The effect of immunotherapy and comparative efficacy of heat-killed *M. leprae*, viable BCG and the mixture of the two antigens as immunogens for anti-leprosy CMI in heterozygous donors, indicated by induction of reversal reactions in nude mice recipients of immunized splenic cell suspension, will be presented and discussed.

VIII/327(A) THE NFS/N NUDE MOUSE, LASAT MOUSE, AND CARRAGEENAN-TREATED NUDE RAT AS A NEW MODEL FOR EXPERIMENTAL LEPROMATOUS LEPROSY

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Since 1976, we have successfully established the nude mouse as an experimental lepromatous model, and have in addition, established the congenitally asplenic athymic (lasat) mouse, and the Rowett nude rat, since 1980.

We compared the susceptibilities among various strains of nude mice, and then, lasat mice (nu/nu Dh/+) and their athymic mice (nu/nu +/+) compared to BALB/cA nude mice, furthermore, by using nude rat and carrageenan-pretreated nude rat. The development of a heavy lepromatoid infection in the congenitally athymic mice was influenced by both the genetic background and/or asplenia of the animals. With nude rat infection, a heavy lepromatoid infection in nude rats was influenced by both the genetic background, and/or macrophage blocking agent-administration.

In summary, we have established the NFS/N-nu as a new model using an intra-upper lip inoculation method, comparing with BALB/cA-nu, C57BL/6-nu, CBA/N-nu, C3H/HeN+MTV-nu, and then, established the lasat, their athymic littermate, and carrageenan-treated nude rat as a new model for experimental lepromatous leprosy.

VIII/328(A) INFECTIVITY OF *M. LEPRAE* IN THE NUDE MOUSE

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The nude mouse is highly susceptible to *M. leprae* and develops an infection strongly resembling human leprosy. Modes of transmission were investigated in the hope of providing information useful in controlling leprosy. Further studies were designed to determine whether all strains of *M. leprae* were equally infectious.

Nude mice were inoculated by various routes including intradermal, intravenous, intracardiac, intraperitoneal, by aerosol and gavage; results will be presented. Of particular interest was disseminated infection in nude mice fed 10^7 *M. leprae*.

Nude and control mice were inoculated in the footpads with small numbers (10^2, 10^1, or 10^0) fully-sensitive or rifampicin-resistant *M. leprae*. In one experiment all nude, thymectomized/irradiated and normal mice inoculated with 10^2 sensitive bacilli showed growth at one year. In a later experiment, using a less viable inoculum, there was no growth in nudes or controls receiving 10^1 or 10^0 bacilli/footpad, indicating similar susceptibilities to small numbers of "fully-sensitive" *M. leprae*. With a rifampicin-resistant strain, there was growth in 4–5 nudes receiving 10^2; 1/1 receiving 10^1 (sole survivor) and 1/4 nudes receiving 10^0 bacilli compared with a complete absence of growth in normal CDI mice, suggesting that rifampicin-resistant *M. leprae* may be less virulent.

VIII/329(A) TRANSMISSION OF LEPROSY IN NUDE (NU/NU) MICE USING VARIOUS PORTALS OF ENTRY.

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National Hansen's Disease Centre, Carville, USA

In spite of a long familiarity with the causative agent of leprosy, very little is known about the transmission of the disease. Arthropod vectors, fomites, airborne droplets and mother's milk have been implicated in the transmission of leprosy, suggesting the skin, respiratory tract and gastrointestinal tract as possible portals of entry for *M. leprae* into the susceptible hosts.

Experiments were designed to simulate exposure of humans to *M. leprae* through lengthy physical contact, upper and lower respiratory tracts, upper and lower gastrointestinal tracts, and intact and abraded skin, using athymic nude mice (nu/nu), an established model for disseminated leprosy infection. The animals were divided into groups of ten, and each animal was exposed to 1×10^7 freshly isolated, armadillo-derived *M. leprae* (Morphological Index = 12) in desired volumes according to the site of delivery. Animals were tracheostomized for nasal and pulmonary deliveries and gavaged for gastric introduction. They were anaesthetized and maintained under anesthesia as indicated by the procedure. Harvests are scheduled for 8, 12, 15, and 18 months post-exposure to evaluate the bacterial dissemination and histopathological changes. The significance of the portal of entry in the establishment of infection and pathogenicity of *M. leprae* in nude mice will be presented and discussed.

VIII/330(A) MOUSE SCIATIC NERVE MODEL FOR THE STUDY OF (A) CHARACTERIZATION OF *M. LEPRAE* (B) ROLE OF DAPSONE IN NERVE DAMAGE

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The Foundation for Medical Research, Bombay, India

It has been demonstrated previously by us that the inoculation of *M. leprae* in the footpad of the mouse produces sciatic nerve damage, which is almost identical to the early lesions of the peripheral nerve in human leprosy. Since this may prove to be a very improtant character for the identification of *M. leprae* from other bacterial infections, a comparative study was undertaken using various mycobacteria inoculated into the hind footpads of normal Swiss white mice. The footpad growth and sciatic nerve lesions, if any, were studied.

Since there have been several reports indicating occurrence of dapsone neuropathy in patients taking regular treatment with dapsone, a study was undertaken to see the effect of dapsone on the sciatic nerves of normal mice and on established sciatic nerve lesions produced in mice following footpad inoculation with *M. leprae*.

The study indicated that a daily dose of 50μg dapsone administered for six to eighteen months, as well as a high dose of 150μg dapsone given daily for a period of three months had no deleterious effect on the nerve. On the contrary, when dapsone was administered at an early stage in the *M. leprae* infected mice, further neural damage was arrested as compared to that in the untreated controls.

VIII/331(A) RESISTANCE OF BALB/C AND C57BL/6 MICE TO SUBCUTANEOUS INFECTION WITH *M. LEPRAEMURIUM* IS DEPENDENT ON BOTH T-CELLS AND NON-T-CELLS OF BONE-MARROW ORIGIN

Hannah O. Adu, Jill Curtis, John L. Turk
Department of Pathology, Royal College of Surgeons of England, London, England

Thymectomized or sham thymectomized mice were lethally irradiated and reconstituted with their own type of bone marrow cells or bone-marrow cells from H-2 matched congenic mouse strains. Resistance was found to be due in part to effector T-cells and effector cells of bone-marrow origin which did not require thymic processing, in both resistant and susceptible strains. The effector mechanisms were regulated by suppressor T-cells and non-T suppressor cells. Low resistance in BALB/c mice appears to be due to both inefficient effector mechanisms as well as an over-stimulation of suppressor mechanisms.

VIII/332(A) EFFECTS OF *M. LEPRAE* MACROPHAGES ON LOCAL AND GENERALIZED IMMUNE RESPONSE IN MICE

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National Hansen's Disease Centre, Carville, USA

Vaccination of the mouse footpad with 1×10^7 killed *M. leprae* leads to a local cellular immune response in the draining popliteal lymph node (LN) which is assessed by an increase in lymphoblastic transformation (LBT) to *M. leprae* antigen, and in the natural killer (NK) cell activity, the local activation of macrophages, and subsequent protection against *M. leprae* challenge infection. Contralateral popliteal LN or spleen cells usually exhibit none of those modifications, suggesting the lack of circulation of sensitized cells. Because of the intracellular (IC) nature of *M. leprae* and because macrophages seem to play an important role in *M. leprae* infection, mice were injected in the footpad with macrophages containing IC radiation-killed *M. leprae*. Measurement of NK activity and LBT response to Cancanavalin.-A, *M. leprae* antigen, and *M. leprae* antigen plus Con-A showed an increase in the draining LN and spleen.These results emphasize the important role of macrophages in the induction of a circulating memory-cell population and/or for the facilitation of presentation or dissemination of *M. leprae* antigen to the immune system. Additional studies of the cellular modifications following treatment with macrophage-laden *M. leprae* are under way. Parallel studies are concerned with determination of the relevance of these observations in terms of protection against viable *M. leprae* challenge.

VIII/333(A) MOLECULAR BIOLOGY OF HOST-PARASITE RELATIONSHIP IN MURINE LEPROSY

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We have made reassociation kinetic analysis using DNAs from bacilli of various species of salmonella and mycobacteria and from cells of various species of animals to clarify the presence or absence of correlation between the manner in which an infected host responds to microbial invasion and the basic sequence homology of DNAs of hosts and parasites, with following results:

In salmonellosis, homology between host's DNA and DNA from bacteria which behave as facultative intracellular parasites in the host was significantly greater than that between the DNA of bacertia which grow only extracellularly and its host's DNA.

In tuberculosis, higher relatedness was detected between bacterial DNAs and DNAs from cells of animals which are susceptible to natural infection with the bacilli concerned.

In the present studies, labelled DNA from *M. lepraemurium* was tested for its homology to unlabelled DNAs from 8 strains of uninfected mice with distinct susceptibility to murine leprosy, and the degree of DNA homology between hosts and parasites was calculated to be proportional to the level of susceptibility to the infection of the given strains of mice.

VIII/334(A) GENETIC CONTROL OF RESISTANCE OF SUBCUTANEOUS INFECTION WITH *M. LEPRAEMURIUM*

Jill Curtis, Hannah Adu, John L.Turk
Department of Pathology, Royal College of Surgeons of England, London, England

Studies of mice with high and low resistance to subcutaneous infection with *M. lepraemurium* indicate that resistance is controlled by several genes. It appears that control is mainly by more than one gene unlinked to the major histocompatibility (H-2) complex and resistance is modified by an H-2 linked gene or genes. Control of the granulomatous reaction at the site of infection is by a gene in the I-A region of the H-2 complex.A rapid granulomatous response occurs in mice with b in the I-A region, and this response is associated with increased resistance in mice of the high resistance strain but not in mice of the low resistance strain.

VIII/335(P) ATROPHIC CHANGES IN NORMAL MICE INFECTED WITH HUMAN *M. LEPRAE*

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Department of Dermatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Swiss Albina inbred normal mice were inoculated into the right hind footpad with 10^4 *M. leprae* obtained from human lepromas. The experiment was conducted under room (34°C) temperature. Animals were harvested at 3, 6 and 9 months post–inoculation and bacillary counts were made. Atrophic changes were observed in the tail, tips of ears, hind and forepaws 10-12 months after inoculation. The changes noted were necrosis, swelling and nibbling of the tail and ears; the paws in addition revealed erythema, clawing, loss of a digit and were huddled together. The histopathology of the tail showed lympho-mononuclear infiltrate in the dermis with possible giant cells. The tissues are being processed for the presence of acid-fast bacilli. Further observations and studies are being conducted on the paws, ears and internal organs for evidence of dissemination of the infection.

Details will be presented.

VIII/336(P) A LOCAL REGULATION MECHANISM OF FIBRINOLYSIS INVOLVED IN THE HOST REACTION FOR MYCOBACTERIAL INFECTION: A STUDY WITH MURINE LEPROSY

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Fibrinolytic enzyme and inhibitor were investigated in tissue extracts during the development of two polar types of murine lepromas. (1) A DFP-sensitive, trypsin-type, relatively heat stable,weakly alkaline, plasminogen-dependent fibrinolytic enzyme (g-PA, granuloma-associated plasminogen activator) was demonstrated in high-responder mice (C57BL/6) during the middle stage of granuloma development. Sephacryl S-200 gel chromatography revealed a single peak with g-PA activity at 23,000 in M.W. However, g-PA was not detected in low responder mice (CBA/N). (2) Two species of the regulatory inhibitors for g-PA, with 82,000 and 45,000 M.W., respectively, were revealed in the high responder mice, during the early weeks of granuloma development. However, the inhibitor activity in the low-responder mice was found only in a low level. (3) The tissue induction of g-PA and the regulatory inhibitor was correlated with fibrin deposition, infiltration of lymphocytes, activation and differentiation of macrophages, and proliferation of fibroblasts, all of which were dominantly demonstrated in the high responder mice but not in the low-responder mice. (4) A role of a local regulation of fibrinolysis by g-PA and g-PA inhibitors was suggested in the host defence, as an effector mechanism of delayed hypersensitivity.

VIII/337(P) EXPERIMENTAL LEPROSY IN *LORIS TARDIGRADUS*

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The slender loris, *Loris tardigradus* (Linn) has been shown to be susceptible to experimental infection with *M. leprae* following intradermal inoculation with 3.0×10^7 bacilli. Out of a total of 66 animals studied, five lorises (7.5 percent) showed dissemination and preferential localization of the bacilli to the uninoculated sites such as nose, ear-lobes and peripheral nerves. The experimental disease in these lorises showed features resembling lepromatous leprosy.The usefulness of the slender loris as an experimental model for the study of leprosy is discussed.

VIII/338(T) A TRIAL TO TRANSMIT LEPROSY BACILLI TO NORTHERN OPOSSUMS *(DIDELPHIS MARSUPIALIS LINNAEUS)*

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Opossums are animals of low body temperature (31.9±0.99°C (N=28), four young animals, two females). The binding of their hemoglobin to oxygen is unstable. Expenditure on purchasing and feeding was less than that for armadillos. They were separately fed in remodelled rabit cages. After training for 46 days, a suspension of leprosy bacilli (2.1×10^9/ml) grown in the footpad of Balb/c female nude mouse, was inoculated subcutaneously (0.2 ml) in their right hind footpads and left earlobes and in their left femoral veins (0.5 ml). Erythromycin (15mg/kg× 3) was given before the inoculation. Azathioprine (3-5mg/kg× 11) was also given from the 8th day before the inoculation till the 19th day. It was further given (10mg/kg× 5) to male animals between the 112th and the 132nd days. One suppurative swelling and other indurative ones on the left ear-lobes were observed between the 43rd and the 55th days. Three temporary swellings (during 2-3 mnths) and a single persisting swelling were seen in their footpads. An increase of monocytes was detected, though very gradually.The smears from the suppurative swelling revealed clusters of pyridine-sensitive acid-fast bacilli after six months. Details will be given later.

VIII/339(T) STUDY OF THE USE OF NUDE MICE IN THE CULTIVATION OF *M. LEPRAE* IN A NORMAL, NON-SPECIFIC PATHOGENI-FREE ROOM AT A TEMPERATURE OF 30-35°C, WITHOUT AIR-CONDITIONING

Seri Rungruang, Teera Ramasoota, Surasak Sampattavanich
Raj-Pracha-Samasai Institute, Phrapradaeng, Thailand

From a study of cultivation of *M. leprae* in nude mouse footpads in a normal, non-specific pathogen-free room at a temperature of 30-35°, without air-conditioning, it was found that the nude mice in the trial could survive longer than 16 months, which is a sufficient period for laboratory and research activities with this model.Leprosy bacilli cultivated in nude mouse footpads could then multiply as well as those cultured in air-conditioned and specific pathogen-free conditions. The authors have some recommendations for the cultivation for *M. leprae* in nude mouse footpads and the care of the mice as follows: (1) The room for nude mice in the trial must be kept closed on all sides but an electric fan may occasionally be used to extract foul-smelling air. (2) Prevent ultraviolet rays from sunlight entering the room in order to protect mice from phototoxic dermatitis. (3) The room must be located on the upper floor so that contamination and changes in land temperature are avoided. (4) During breeding and feeding, nude mice must receive special care from birth, in order to maximize survival.

The cultivation of leprosy bacilli in nude mouse footpads using the method described will -"until *in vitro* growth is achieved"- benefit research in chemotherapy, biochemistry, immunology, immunopathology, epidemiology and other related fields, at relatively low cost.

VIII/340(P) ENDOTHELIAL CELLS CULTURES IN LEPROSY

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The role of blood vessels is evaluated in leprous neuropathy (Budingus 1977). Endothelial cells cultures are standardised and their growth and organization time sequential studies were recorded. Their phagocytic function is being studied after inoculating different types of bacteria and *M. leprae*.

SESSION IX

EPIDEMIOLOGY AND CONTROL (A)

Chairman: Das, K.C.

Rapporteur: Louhenapessy, A.A.

THURSDAY, 23RD FEBRUARY, 1984

Auditorium 08.30–12.00

Abstracts

A* : 341-359

EPIDEMIOLOGY AND CONTROL (B)

Chairman: Nkinda, S.J.

Rapporteur: Neelan, P.N.

THURSDAY, 23RD FEBRUARY, 1984

Auditorium 13.00-16.30

Abstracts

A* : 360-378
P* : 379-409
T* : 410-415

*A : accepted for reading
*P : for poster presentation.
*T : for title reading.

IX/341(A) A REALISTIC LONG-TERM GLOBAL STRATEGY FOR LEPROSY CONTROL

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World Health Organization, Geneva, Switzerland

As a result of the problems encountered with the dapsone-based strategy for leprosy control, the difficulties expected in the implementation of multi-drug therapy, and of the great hopes raised by the recent progress towards the developent of immunoprophylactic methods, there seems to be some uncertainty about what can be realistically expected from the use of the presently available control measures.

It is true that important questions can only be answered by experience in the field. However, on the basis of past experience, including that with dapsone monotherapy, current epidemiological views and identified operational constraints, it seems possible to define what achievements can realistically be expected from the secondary prevention approach, based on multidrug therapy until an antileprosy vaccine becomes available.

As for the future, the likelihood of developing an effective vaccine against leprosy should not lead to over-optimism. It has to be realized that if and when we have an effective vaccine, chemotherapeutic tools will continue to remain necessary.

It is also clear, and this cannot be overemphasized, that despite the socio-economic development process, operation constraints will continue to play a crucial role. Among these, the serious difficulties faced in the use of active case-detection methods, and the irreversible trend towards integration of leprosy activities within general health activities, will greatly influence the field procedures. In particular, because any significant impact on the leprosy endemicity must be the result of sustained efforts over a lengthy period of time, the building up of an adequate infrastructure should receive more attention than obtaining a wide coverage which can be destroyed when supplementary inputs, particularly if they come from foreign assistance, are withdrawn. The gradual development of an adequate infrastructure is rooted essentially in the political will of governments,from which derive such essential components as allocation of human and financial resources and community participation.

Finally, a long-term effective strategy for leprosy control should include a continuing long-term effort in research because: (a) tools which are satisfactory at a given time may later become ineffective (e.g. drugs), and (b) most methods require constant improvement and simplification (e.g. vaccines).

In this respect, experience has already shown that significant progress in research can best be achieved through the multidisciplinary approach of "Scientific Working Groups". Also, at any time it is essential to take advantage of new advances in basic research, or in areas not directly related to leprosy. In addition, the long-neglected field of operational research has to be given proper attention. Lastly, central to all efforts in leprosy research must be the view that the strengthening of the research capability in endemic countries is essential to prepare future improvements in leprosy control.

IX/342(A) SAMPLE SURVEYS IN LEPROSY COVER THE WHOLE OF INDONESIA

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Reliable information about the leprosy situation enables a government to build up an effective control system. To get this information and to collect base-line data for evaluation purposes later on the Department of Health of Indonesia embarked in 1975 upon a nation-wide sample survey programme.

A system of cluster sampling was regarded as the most appropriate design for obtaining an overall picture of the nature and extent of the leprosy problem in the various provinces of Indonesia at comparatively low cost.

Different categories of leprosy workers were trained and an effective system of supervision introduced to confirm all findings.

A total of 22 surveys was planned, of which 18 will be completed by the end of 1983, leaving 4 surveys for 1984.

Striking findings underline the usefulness of sample surveys. In S. Sulawesi Province, the sample survey shows an estimated prevalence of up to 15 per thousand against a registered of only 3. The survey in E. Nusa Tenggara Province indicates overdiagnosing some 10 years ago, while in Bali Province the prevalence was found to have declined significantly.

Financial and technical assistance was given by the Danish, Dutch, German and Belgium Leprosy Relief Associations as well as the World Health Organization, a demonstration of fruitful co-operation between a government and foreign agencies.

IX/343(A) NATIONAL LEPROSY CONTROL IN TANZANIA: 5 YEARS' ACHIEVEMENTS AND FAILURES

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Leprosy control on a country-wide scale was started in 1978 as part of a combined National Tuberculosis and Leprosy Programme (NTLP) which is a government project with external support. NTLP is coordinated at three levels by managerial/supervisory staff, but the implementation of the control measures is fully integrated into the general health structure in accordance with the recommendations of the 5th report of the W.H.O. Expert Committee on Leprosy. Betwen 1978 and 1982, a total of 21,000 new cases was registered. The estimated prevalence is about 6 cases per 1000 popula-

tion and 50% of the estimated prevalence are registered. Achievements and failures are outlined, and operational and epidemiological statistical data are presented. Advantages and disadvantages of a joint leprosy and tuberculosis programme and the problems encountered during the process of integration into the general health services are briefly discussed. In a programme whose mainstay of control has been dapsone monotherapy until 1982, the final part of the paper mentions briefly the operational problems of introducing multiple drug treatment.

IX/344(A) THE ROLE AND RESULTS ACHIEVED BY THE PRIMARY NETWORK IN LEPROSY PREVENTION IN JING ZHOU PREFECTURE IN HUBEI PROVINCE

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The author describes the organization of the leprosy prevention programme in the county of Jing Zhou, and compared the results of prevention before and after the establishment of this programme.

In Qian Jiang, for example, before 1970 prevention work mainly depended on a few professional doctors. Apart from some achievements in the investigation of epidemiology and the treatment of infectious patients, they did not do quite as well in other respects, because of lack of time. In 1969, the treatment rate of index cases was only 27.8%, the regular treatment rate 42.8% and contact tracing 80.9%. After 1970, a mass system of leprosy prevention was established and gradually amplified.

The establishment of the mass leprosy prevention programme ensures the implementation and improvement of all preventive measures. Since 1978, the above mentioned rates have been raised to 96%, 90% and 93% respectively. The grassroots programme of leprosy prevention has played an important role.

By the end of 1982, the prevalence rate had fallen from 0.38 per thousand in 1966 to 0.06 per thousand and the incidence from 6.78 per 100,000 in 1965 to 0.13 per 100,000. The prevalence of leprosy was noticeably reduced.

The author points out that the grassroots net work of leprosy prevention has both the character of cooperation between professional institutes and ordinary health institutions and the character of cooperation between professional doctors and grassroots medical personnel. Moreover it is emphasized that medical personnel of all ranks should not just wait for the leprosy patient in their out patient departments or clinics but go to the endemic areas to treat them, distribute medicine and carry out reexamination and follow-up.

IX/345(A) SYSTEMATIC RESEARCH OF LEPROSY IN MOROCCO

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The authors relate the results of their experiences on systematic investigations of four rural centres where the endemicity of leprosy is near 10%, carried out from 1980 to 1983, viz: Oulad Ali (Middle Atlas), Zoumi (Rif) where the endemicity has been steady since the last investigation in 1972, Tanakoub (Rif) and Khemis Mtouh (Atlantic coast-line). The census taken in these 4 rural centers shows a population amounting to 29246. The number of people examined amounts to 25214, i.e. 87.67%. 308 patients were registered before the investigation i.e. 12.2%. 106 new patients were found out which shows a new rate of 16.3% A widespread investigation is being prepared . It will take place in September and will cover an area of 3500 kms, situated in the North West of Moroco in the Rif. Because of the mountains its geographical position is too difficult to be reached by the usual means of transport and therefore its population is still living on self-sufficiency. For these reasons, the investigating team will use the force of gendarmes' helicopters.

IX/346(A) CURRENT LEPROSY ERADICATION PROGRAMME IN VIETNAM.

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Based on a health infrastructure widespread throughout the country and also on the characteristics of the disease prevalence and dissemination (limited contagiosity, long incubation, rapid cessation of infectivity by adequate chemotherapy, etc...), the current leprosy eradication programme in V.N. has been successfully implemented over the last 10 years.

The main principles of the programme are as follows:

"Leopard skin" eradication commencing in chosen zones (one district for each province and one village for each district) and step-by-step extending them.

Intensification of health education mainly among patients, general health personnel and administrative authorities, so as to bring about a correct perception of the disease and consequently a wide and active detection in time.

Institution strengthening of the existing basic antileprosy network with a view to assuring a regular intake of drugs and prevention of deformities.

Even with dapsone monochemotherapy, the 3 criteria for leprosy eradication put forward in the programme have been reached in several areas of the country. Recently introduced multidrug regimens promise still better results.

IX/347(A) AN EPIDEMIOLOGICAL STUDY IN GHARBIA, EGYPT.

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The Gharbia governorate was selected for a mass survey for leprosy and skin diseases for the following reasons:

1. Data available for prevalence of leprosy in Egypt are far from satisfactory.
2. The selected area has a population of 2.4 million. Registered leprosy cases are 1,224. The incidence is much higher than in other areas. The study of comparable areas of both high and low incidence may give an indication of the prevalence of the disease in Egypt.
3. Detection, recording and treatment of all leprosy cases and skin diseases in the area are studied.
4. A socio-economic study is planned to evaluate the role played by environmental and cultural factors on the prevalence and type of leprosy as well as on other skin diseases.

Staff: 14 Dermatologists, 2 Pharmacists, 10 Laboratory workers, 10 Nurses, 10 Social workers, 10 Secretaries.

Mobile teams were organized for home visits and fixed teams for detailed medical, bacteriological examination and treatment. Training, case recording, case follow-up and treatment are all discussed in detail. Contributions received from W.H.O., Damian Foundation, German Leprosy Relief Association (DAHW), Ciba Geigy, Le Petit, Caritas, Egypt. The results of the survey are discussed.

IX/348(A) EPIDEMIOLOGY AND CONTROL OF LEPROSY IN SPAIN

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After a brief historic summary of the origins of leprosy in Spain, the present situation, prevalence index, incidence and lepromatous leprosy are studied.

The geographic distribution in four centers: Levante, Andalucia, Canary Island and Galicia is explained.

Spain is hardly an endemic country; its prevalence index is 0.140; although there are provinces with indices as high as 0.490. The total number of patients is five thousand and two hundred. We estimate there might be about two thousand more, the majority of them are nature born.

The organization of the fight, control and therapies employed will be discussed, as well as aspects of rehabilitation and social problems.

IX/349(A) EPIDEMIOLOGICAL AND CLINICAL ASPECTS OF LEPROSY IN INDIAN ARMED FORCES.

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Epidemiological and clinical aspects of leprosy in 1911 cases of the disease in armed forces personnel were studied. Typewise distribution of cases was – Tuberculoid 53.53%, Lepromatous 20.57%, Indeterminate 8.74%, Borderline 11.67% and Polyneuritic 5.49%. Maximum leprosy cases occurred in those belonging to Uttar Pradesh 17.11%. Maximum number of cases were detected (88.55%) in the age group 20-39 years. Incidence of leprosy increased with increased years of service. 11.82% patients were illiterate. 89.85% patients earned Rs 200 to 499 per month. 56.08% patients had no landed property. Houses of 47.29% cases were located in congested areas. 68.23% patients had to support large families. In 95.94% cases, no family members were examined for leprosy. Diet, smoking and alcohol appear to have had no relation to the disease in cases studied. Clinical presentation of cases was classical and type- specific. Skin eruption and loss of sensation were the commonest symptoms. Leprosy lesions were detected on almost all parts of body. Thermal sensation was the commonest modality lost. Ulnar, lateral popliteal and greater auricular were the frequently affected nerves. Amongst complications, paralytic deformities were common (16.09%). 545 complications were detected in 1911 cases. While 84.29% patients had put in more than 4 years of service, the source of infection was known only in 0.57% positively (intrafamilial). Various modes of transmission of disease are discussed.

IX/350(A) A "VIRGIN-SOIL" LEPROSY EPIDEMIC IN A POLYNESIAN POPULATION.

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A new epidemic of leprosy among the Kapingamarangi (about 1100 people in two villages) of Ponape, Micronesia, is reminiscent of the explosive Nauru epidemic 50 years earlier. From 1964 to 1967, four *index cases* (2 lepromatous, 2 tuberculoid) appeared after exposure at school and elsewhere to Pingelap people, among whom leprosy has been hyperendemic, since introduced in 1918 from Nauru.

Single *secondary cases* (contacts of the 2 index lepromatous cases) appeared among Kapinga people in 1966, 1969, 1970, 1974 and 1975, when sporadic treatment started.Two more cases appeared in 1977, three in 1978 and again in 1979. Active case-finding started in 1980, identifying 5 cases with onset that year, 26 in 1981 and 90 in 1982. By December 1982, these 138 cases,most histologically confirmed at Carville, reached a cumulative incidence rate of 12.5%. Among these cases, 18% are multibacillary, 65% are children, and the male/female ratio is 1.5. Contact histories have related virtually all secondary cases to 9 lepromatous cases with onset from 1964 to 1979. Minimum incubation is 2 years, and the youngest age at onset is 2 years.

Of 755 Kapinga non-cases tested in 1982, 43% were seropositive by ELISA. Data from 1983 will also be presented.

IX/351(A) VARIATION IN THE OCCURRENCE OF LEPROSY WITHIN SMALL GEOGRAPHIC AREAS; SOME POSSIBLE EPIDEMIOLOGICAL CLUES

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It is a well-known fact that leprosy incidence and prevalence rates, even within relatively small areas, show considerable geographical variation. The epidemiological background of this phenomenon, however, is not well understood.Variation in host and environmental factors should therefore be considered. Possible factors are poor hygiene, poverty, overcrowding and malnutrition. The epidemiological importance of *M. leprae*–like microorganisms found in the environment should also be taken into account. To illuminate these aspects, socio-economic and nutritional status were studied in 35 villages in Tamil Nadu, South India, covering a considerable range of prevalence rates. Data on socio-economic status have been obtained from a survey undertaken by a rural health and development programme, RUHSA. The nutritional status of the inhabitants has been assessed by anthropometric measurements in 798 persons, a 13.6% sample of all inhabitants in 31 of the villages. Furthermore, water samples were taken for the detection of *M. leprae*–like microorganisms. Prevalence and incidence rates are known through detailed house-to-house surveys undertaken by Schieffelin Leprosy Research & Training Centre.Associations between host and environmental factors on the one hand, and leprosy prevalence and incidence rates on the other, will be presented.

IX/352(A) URBAN LEPROSY

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It is interesting to form an impression about urban leprosy, for such an impression is likely to influence future planning for its eradication.Accordingly, we examined the details of 1661 new leprosy patients in order to delineate clearly the pattern. Our study suggested that males in the age group of 20-29 years had high rates of disease, though no age group was exempt from leprosy. The commonest age at onset was between 20-29 years. The latter had a significant association with the leprosy groups, while it was unrelated to sex.Additionally, the patients were largely derived from unskilled workers and belonged to the low-income strata. Urban leprosy as such appears to be a small problem. However, it is now becoming serious because of the influx of large numbers of migrants from endemic areas, a pattern seen in most similar studies. The importance of the study of urban leprosy becomes more important, since the majority of such cases are infectious, from borderline to lepromatous leprosy.

IX/353(A) AGE-SEX-TYPE-SPECIFIC INCIDENCE RATES IN LEPROSY. OBSERVATIONS ON 45,000 LEPROSY PATIENTS DETECTED IN POLAMBAKKAM, SOUTH INDIA, OVER A 27 YEAR PERIOD.

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The Polambakkam Leprosy Centre, South India, covers a rural population living in some 880 villages.

The age-sex-type characteristics of the 45,000 patients detected over 27 years were studied.

Age-sex-type-specific incidence rates for this period were analysed.The following patterns were observed: the ratio of males to females was stable (3:2), but it was higher in lepromatous than in tuberculoid cases. In both sexes, age-specific incidence rates show a bimodal distribution for tuberculoid leprosy, with the first peak occurring in the age group of 10-14 years and the second in adult life.This bimodality is not observed in lepromatous leprosy, although the peak observed in adult age does not occur at the same age for males and for females. Explanations for these phenomena are discussed, in relation to the mechanisms of infection and duration of latency.

In both sexes, the overall incidence decreased similarly over the period, the decline being greater in lepromatous than in tuberculoid leprosy.

A global review of similar rates and trends is made with the aim of developing predictive indices for the epidemiology of leprosy.

IX/354(A) EPIDEMIOMETRIC STUDIES IN LEPROSY. AN AGE DEPENDENT MODEL FOR THE SIMULATION OF VACCINATION AND RESISTANCE

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The original epidemiometric model of leprosy has been refined taking into account the age structure of the population and making allowance for age-specific incidence rates. Prediction of incidence with present control measures yielded results similar to the simplified model.

Various assumptions regarding the effects of vaccination, both immunoprophylaxis and immunotherapy, were tested. With both methods the effect on incidence is delayed. Immunotherapy required periodical revaccination. The periodicity can be calculated for different coverages of vaccination, and use for cost-benefit estimates comparing the two types of vaccines.

A major innovation was simulation of drug-resistance. The model suggests that even a small increase in the proportion of patients with primary resistance may rapidly upset the trends of incidence. Considerable methodologicl difficulties were met to design appropriate ways of introducing resistance parameters in the model. Data on secondary resistance as presently collected by cross-sectional surveys are not appropriate to mesure the dynamics of resistance.

IX/355(A) EPIDEMIOLOGY OF HANSEN'S DISEASE: A THEORETICAL ANALYSIS

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Based on descriptions of Hanseniasis epidemiology, a theoretical model of the modal standard occurrence of the disease in regions of high and low prevalence is presented.

This model, allied with accepted knowledge of immunology and transmission of Hanseniasis, is utilized to explain the different behaviour the disease presents in regions with different levels of prevalence: a higher prevalence in young patients in regions of high prevalence, in comparison with regions of low prevalence and the predominance of paucibacillary forms in high prevalence areas, in contrast with higher proportion of multibacillary forms in regions of low prevalence. The same model could explain the predominance of paucibacillary forms among the young patients and the higher frequency of the multibacillary forms among persons who acquire the disease at a more advanced age.

IX/356(A) SAMPLE SURVEY FOR ESTIMATING LEPROSY PREVALENCE IN WARDHA DISTRICT, INDIA

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A sample survey was carried out in rural population in Wardha district (Maharashtra State, India) during February and March, 1982, to understand the baseline situation of the endemicity of leprosy. This exercise was undertaken for the multidrug regimen project against leprosy in the district. (The programme in the district has help from SIDA and WHO and is executed by the Government of India and the Government of Maharashtra). It was cluster-sampling based on stratification. Stratification was done according to existing information about leprosy prevalence and also according to the population size of villages.

Information obtained from the survey is given below:

(1) 44,331 individuals were enumerated and 40,370 were examined (91.00%) from 84 selected sampling units.

(2) 20 leprosy technicians from outside the district participated in the survey, each technician examined on average 45.05 persons per day.

(3) 519 patients of leprosy were detected in the survey: About 30% of these patients were lepromatous or borderline type. There were 86 bacteriologically positive patients.

The results are discussed with respect to estimation and variability of prevalence of the disease and sampling and non-sampling errors.

IX/357(A) A STUDY OF THE RESULTS OF THREE COMPARABLE STRATIFIED SAMPLING SURVEYS CONDUCTED EVERY 10 YEARS TO EVALUATE THE IMPACT OF LEPROSY CONTROL WORK IN THE KHONKAEN PROVINCE OF THAILAND FROM 1962 – 1982

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A study has been made of the changes in the epidemiological situation in the province of Khonkaen, N.E. Thailand, the pilot area of the national leprosy control programme, after 28 years of operation. The data are derived mainly from the results of three comparable stratified sampling surveys conducted in this province in 1962, 1972 and 1982.

The results of epidemiological and operational evaluation of leprosy control in Khonkaen Province from 1962 – 1982, particularly on the decline of the main indicators of the trend of the disease, are reported and discussed.

IX/358(A) A STUDY OF THE RESULTS OF TEN YEARS OF EARLY TOTAL INTEGRATION OF LEPROSY CONTROL INTO LOCAL HEALTH SERVICES IN THE PHUKET ISLAND, THAILAND

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Phuket Island in Southern Thailand is the pilot area where total integration of leprosy control into local health services has been undertaken since 1972. A study is reported of the changes in the epidemiological and operational situation in the province after 10 years of operation.The data are derived mainly from the results of two comparable stratified sampling surveys and operational assessments conducted in this provincce in 1972 and 1982. With a present population of 135,194 there has been an increase in the prevalence rate from 1.45 to 5.84 per thousand.

The possible reasons for poor achievement of early total integration of leprosy control into local health services as well as strategies for improvement will be presented and discussed.

IX/359(A) DIAGNOSTIC EFFICIENCY OF PARAMEDICAL WORKERS INVOLVED IN LEPROSY CASE DETECTION PROGRAMME

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The diagnostic efficiency of four paramedical workers (PMWs) involved in leprosy case detection during a recent survey, was assessed on 1394 cases detected by them and subsequently confirmed by an experienced medical officer. The inter-observer variation in diagnosis and classification of leprosy, between two equally experienced PMWs, was also studied on 216 patients.

Of the 1394 cases detected by PMWs, 257 (18.4%) were wrongly diagnosed as leprosy, mostly as non-lepromatous (N) type. Amongst the corrctly diagnosed cases, all the lepromatous (L) and 98% of N-type cases were correctly classified by them; however, 26% of the borderline (N.L) cases were either under-diagnosed as N-type (18%) or over-diagnosed as L-type (8%). The clinical activity status of 11%-L, 19%-N, and 33%-NL types of cases was wrongly assessed by PMWs. The discrepancy between two PMWs in diagnosis, classification and assessment of activity status of leprosy, was found in 1.4%, 7.4% and 25.7% cases, respectively.

The implications, and suggestions to improve the technical skills of workers to achieve optimal efficiency in their work, will be discussed.

IX/360(A) OPERATIONAL CLASSIFICATION IN HANSENIASIS CONTROL

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Some classifications of Hanseniasis currently used are reviewed and the difficulties of their application in field work are analysed.

While recognizing the scientific value of these classifications when used to indentify precisely the clinical, bacteriological, histological and immunological aspects of the disease, we suggest an alternative simplified system of classification to be used in control programme. In this classification, clinical forms that require the same kind of public health action are grouped. Thus clinical forms are reduced to three basic groups. The I form, or Initial, potentially pauci-or multibacillary, the T form, Tuberculoid or Paucibacillary and V, Virchowian (Lepromatous) or multibacillary. The clinical and laboratory criteria that define each group are presented as well as the correlation between this simplified system and the classic one.

IX/361(A) THE USE OF LIFE TABLE TO ELIMINATE FROM THE ACTIVE RECORD THE HANSEN'S DISEASE PATIENTS OUT OF CONTROL AND OF UNKNOWN WHEREABOUTS.

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Three criteria for the withdrawal of Hansen's disease patients of unknown whereabouts from the active register are presented. In the first criterion, patients who have been lost and who have mathematical probability of being alive lower than 50% (calculated according to patient's age, time they have been out of control and the regional mortality table) had " statistical discharge ". In the second and third criteria negative Mitsuda patients who have been lost for more than 20 years and positive Mitsuda patients who have been lost for more then 10 years and who had not been included in the first criterion had " statistical discharge ".

During the six years the method was used in the state of Rio Grande do Sul, Brazil, 506 patients of unknown whereabouts were taken from the active register, 4 of whom were found to be alive with the disease progressing. The results suggest an accuracy rate of about 100% for the first criterion of "statistical discharge" and about 98% for the two other criteria.

IX/362(A) A STUDY ON OPTIMUM METHODS OF ACTIVE CASE-DETECTION AND UTILIZATION OF PRIMARY HEALTH CARE VOLUNTEERS TO STRENGTHENING INTEGRATED LEPROSY CONTROL SERVICES IN 66 PROVINCES OF THAILAND (1977-1982)

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Leprosy control in Thailand was started as a vertical programme to cover all 43 highly endemic provinces from 1955-1970. From 1971-1976 early total integration of integrated expansion of leprosy control was made into the remaining 29 new provinces where the endemicity of leprosy appeared to be rather low, meanwhile partial integration of vertical programme into provincial health services covering 37 provinces was also conducted.

From 1977- 1982, epidemiological and operational assessment was undertaken. It was found that the decline in prevalence and incidence appeared to be somewhat slower than the level expected to be achieved by the work of vertical programme. One of the main factors involved was poor case detection by integrated Health Workers.

An attempt to conduct optimum method of active case-detection and utilization of Primary Health Care Volunteers as key strategies to strengthening the intergrated control services in 66 provinces of Thailand from 1977-1982 will be discussed.

IX/363(A) IMMUNO- EPIDEMIOLOGICAL STUDIES ON SUBCLINICAL INFECTIONS AMONG LEPROSY HOUSEHOLD CONTACTS IN THAILAND.

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The fluorescent leprosy antibody absorption (FLA-ABS) test and the lepromin test with Dharmendra's antigen were used for detecting subclinical leprosy infection among 2,317 contacts with household leprosy patients. The percentage of positive FLA-ABS test was higher in the contacts with suspicious neural symptoms such as enlargement of peripheral nerves without sensory loss than in those without this symptom. The lepromin test was more frequently positive in the contacts with suspicious dermal symptoms than in those without these symptoms. However, this test showed a significant correlation with the PPD skin test, irrespective of a history of BCG vaccination. Both the FLA-ABS and lepromin tests were positive in 329 contacts (14.2%). The other 766 contacts (33.1%) were positive in the FLA-ABS test but negative or doubtful in the lepromin test. Neural symptoms were more frequently found in the latter group than in the former.

There were three among 549 contacts who developed neural signs of leprosy in the second year follow-up in one leprosy colony; these cases were poisitive in the FLA-ABS test, detail study will be presented. The significance of these findings will be discussed from the immunological and epidemiological points of view.

IX/364(A) AN INVESTIGATION OF FAMILY SIZE AND BIRTH ORDER AS RISK FACTORS IN LEPROSY

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The factor affecting effective exposure to *M. leprae* and the establishment of the disease are not well understood. Several factors have been investigated including age at exposure. If earlier exposure to *M. leprae* is important for the development of the disease, it would be expected that patients with leprosy in general or with a particular form of the disease would have a different frequency distribution with respect to sibship size and/or birth order from unaffected persons. We have investigated the sibship size and birth order distribution of 187 patients with leprosy (114 LL and 73 TT) and the corresponding distribution of 528 hospitalized patients as controls. We have undertaken the classical Greenwood -Yule analysis as well as a multivariate analysis controlling for age, sex, social class, and leprosy among parents.

No significant association was observed with respect either to sibship size or to birth order of leprosy in general or of any form of the disease in particular. Our findings indicate that variation of age of first exposure to *M. leprae* between 2 and 6 years among children born to families without a leprous parent does not substantially affect the probability of development of the disease of a particular form of the disease at a later age.

IX/365(A) TIME TRENDS IN THE DEFORMITY RATE AMONG NEWLY REGISTERED PATIENTS IN GUDIYATHAM THALUK-1962-82

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Previous studies on deformities and disabilities among leprosy patients by the first author indicated that 42.5% of the patients had deformities and disabilities of various kinds. These studies were done in the same area as the present study and utilized data gathered up to 1966.

The present study analyses the time trends in the deformity rates among newly registered patients from 1962-1982. Preliminary analysis indicates that intensive leprosy control activities carried out in the area for the last two decades, have resulted in a significant fall in the deformity rate among newly registered patients. Specific declines in the deformity rate in relation to various socio-demographic variables and programmatic factors are presented and discussed.

IX/366(A) DIFFICULTIES FACED IN THE CAMPAIGN AGAINST LEPROSY AND PROPOSALS FOR ACTION TO BE TAKEN IN THE FRENCH SPEAKING COUNTRIES IN AFRICA.

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In the French speaking countries in Africa, the campaign against leprosy was until recently the domain of the Health Services dealing with Epidemics. Active detection of leprosy cases was undertaken during the annual visits made by specialised mobile units. Treatment-mainly dapsone-was assured by health services personnel who distributed the medicines monthly.

Due to economic reasons, the mobility and thus the efficiency of the mobile units has sadly diminished. Moreover, the mobile units are no longer suited to control the daily intake of two antibiotics dapsone and clofazimine nor to the monthly supervision administration of rifampicin and clofazimine as required by WHO.

The organisation of the campaign against leprosy must be adapted to new scientific requirements and of course to available resources. The scientific requirements are (i) treatment with 3 medicines for cases of multibacillary leprosy and with 2 for those suffering from paucibacillary leprosy, (ii) treatment for a defined duration for all patients, and (iii) organisation of the campaign by a specialised unit at national level capable of orienting, motivating and supervising the non-specialised peripheral medical teams. Amongst the resources that are available, mobile units and fixed treatment centres must be effectively used according to actual availability keeping in mind that (i) an active participation from the patient is indispensable, (ii) supply of medicines must be organised in time and (iii) every case diagnosed must be given a follow through treatment.

IX/367(A) THE RELATIVE IMPORTANCE OF IMPROVED TOOLS *VERSUS* IMPROVED WORKING IN LEPROSY CONTROL

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It is often assumed that the development of more effective tools against leprosy will automatically lead to disease control. On the other hand, it is also assumed that even with the existing tools, one can achieve rapid leprosy control, if one can improve the operational performance to the maximum level required. While development of new tools, or improvement of existing tools is gernerally the responsibility of the scientific community, who are often from the developed countries, the improvement of operational performance is the responsibility of programme managers and field workers in the developing endemic countries. A third dimension is the perception of the affected community towards the disease and the methods used for control.

The paper discusses the problems inherent in both developing better tools and improving operational performance. While the former is linked essentially to progress in biomedical sciences and organization of effective and coordinated research programmes,the latter is largely tied to improved performance of the health services as a whole and in the definition of priorities for leprosy. Lastly, it should be recognized that it is difficult to envisage effective leprosy control without significant improvement in the socio-economic conditions of the affected countries.

IX/368(A) IMMUNOEPIDEMIOLOGICAL STUDIES ON SUBCLINICAL INFECTION IN LEPROSY.

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Various methods have ben tried in the past to detect subclinical infection in leprosy, but due to the great problem of cross reactivity with other mycobacteria, the tests were found to be nonspecific.

In our laboratory, the indirect immunofluorescence test (commonly known as FLA-ABS test) elaborated by Dr. M.Abe has been standard and found to be highly specific and sensitive. At present, the FLA-ABS test and the lepromin test are being used simultaneously in healthy contacts of all types of leprosy with the aim of showing that the FLA-ABS test would detect *M.leprae* specfic antibodies and the lepromin test would be an indicator of cell-mediated immunity.

The FLA-ABS test has been found to indicate a higher percentage of subclinical infection amongst the contacts of multibacillary patients, when compared to the contacts of paucibacillary non-lepromatous patients.

The present study has revealed that contacts showing a positive FLA-ABS test and a persistent negative lepromin response are at risk of developing serious forms of leprosy.

The detailed results of this ongoing study will be presented and discussed.

IX/369(A) STUDIES ON HEALTHY CONTACTS OF LEPROSY PATIENTS

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In a longitudinal study of healthy contacts of leprosy patients, investigations consisting of nasal biopsies, a serological test (FLA-ABS) for subclinical infection, lepromin test for bacillaemia have been performed. The children are being followed up. Based on the results of the study, two types of subclinical infection have been discerned. (1) A transient subclinical infection which terminates with either the appearance of lesions of the tuberculiod or indeterminate types or the appearance of well-marked CMI or (2) A prolonged subclinical infection characterized initially by bacillaemia and the occurrence of a serious form of the disease.

The significance of the findings with regard to prophylaxis is discussed.

IX/370(A) COMPARISON OF ELISA ANTIGENS FOR THE EARLY DETECTION OF PRECLINICAL LEPROSY.

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Three antigens are compared by ELISA for the early detection of elevated antibody levels in individuals prior to their development of leprosy. These new patients live in a hyperendemic areas for leprosy in Ponape, Federated States of Micronoesia (FSM). With the cooperation of the health department of Ponape and FSM, we have been collecting blood specimens in this region since the summer of 1980, in part to develop an effective test for the preclinical surveillance of leprosy. By the summer of 1982, 32 people from whom we had collected sera in 1980 had developed leprosy. Of these 32 individuals, 30 had elevated antibody levels of *M.leprae* up to two years prior to the onset of clinical leprosy. These sera and serial sera from any new patients who have developed leprosy by the summer of 1983 are compared with the ELISA reactivity of representative sera from the general population. Two whole cell antigens: *M. leprae* (armadillo derived) and autoclaved *M. smegmatis* (TMC No. 1515) are compared with one specific antigen: purified phenolic glyolipid I of *M. leprae* (PG-I) for their effectiveness in the detection of preclinical leprosy. *M. leprae* and PG-I were received from P.J. Brennan.

IX/371(A) VACCINATION IN LEPROSY: PRELIMINARY RESULTS IN A TRIAL IN VENEZUELA

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We are presenting the preliminary results of an immunoprophylaxis of leprosy trial in contacts living in highly endemic areas in Venezuela, to determine the protective effect of a vaccine made up of purified autoclaved, *M. leprae* and live BCG.

In this first stage we have studied: (a) The response to skin test with a soluble antigen from *M. leprae*(SA) of 2,659 contacts 6-70 years old and the variations of this response according to sex, age and relation to the index case. The reactivty to SA increases with age to a maxmium in the 20-29 age group and decreases gradually after 40 years. In intra-domiciliary contacts reactivity increases earlier and remains higher throughout. The percentage of "negatives" is less than in extradomiciliary contacts in all age groups.(b) The capacity of the vaccine to induce immunological changes in those contacts considered to have low resistance, due to their initia reaction to SA.

The immunological changes were evaluated at 2,8,14 and 18months after the giving of the vaccine. As control, we have a group vaccinated only with BCG. The initial evaluation indicated that the *M. leprae*-BCG mixture induces an immunological conversion clearly superior to that induced by BCG alone and that this modification is more persistent as shown in the later tests, where the difference in reactivity towards SA in both groups becomes much more noticeable.

Some of the negative reactors remain negative after vaccination (2 months) or lose their acquired positivity rather soon (8 months). It is possible that this group of non-reactors is responsible for the maintenance of the endemic.

IX/372(A) SHORT-TERM CHEMOPROPHYLAXIS AGAINST LEPROSY WITH ACEDAPSONE

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The subjects in the study were 560 disease-free children aged 1-14 years who were household contacts of 264 active multibacillary leprosy cases, taking treatment in 8 leprosy clinics in Madras city, Tamilnadu. They were allocated in equal numbers, through randomisation after stratification by age and sex, to a Prophylaxis group receiving injections of Acedapsone 150 mg. (1.0 ml) and 225 mg. (1.5 ml) once in 10 weeks in the age groups 1-5 years and 6-14 years respectively, and a Control group receiving similar quantities of placebo injections. The contacts received a total of 3 injections covering a period of 30 weeks (210 days) at the beginning of the study. The study used double blind procedures.

Contacts found to have suspicious lesions during periodic screening, were examined independently by two other physicians for confirmation of diagnosis. 23 cases of leprosy were diagnosed among the contacts during the first 2½ years of the study; 4 in the Prophylaxis group (incidence 14.29 per 1000) and 19 in the Control group (incidence 67.86 per 1000). The difference in the incidence is statistically significant (P 0.01). Short-term Acedapsone prophylaxis, in the dose and duration as administered in this study, is found to give a protection of 78.94 percent. The results are discussed.

IX/373(A) PREVALENCE OF HEPATITIS-B VIRUS (HBV) INFECTIONS IN LEPROSY PATIENTS IN NORTHERN THAILAND

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Hepatitis B virus (HBV) infections have been reported to be more prevalent in patients with lepromatous leprosy (L) than in those with tuberculoid leprosy (T) or in healthy adults in areas where HBV carrier rates are high. This association could be related to more frequent hospitalization and medical procedures, e.g. skin smears, in L cases, to shared genetic predisposition to L and HBV, or to immunologic changes in L patients increasing the risk of HBV infection. To define the rate and risk factors of HBV infections in L patients, we studied HBV markers by RIA in 438 individuals living in 2 leprosy resettlement villages, 1 normal village or in patients not from resettlement villages with newly diagnosed leprosy. Markers of HBV infection were presented in 82.9% of 323 persons living in leprosy resettlement villages: 45 (13.9%) were HBsAg positive, 232 (71.8%) were anti-HBs positive. In the normal control village,markers were present in 29.5% of 71 persons: 3(4.2%) were HBsAg positive, 18 (25.3%) were anti-HBs positive. The prevalence of HBV markers was equally increased in both T and L patients, in healthy village contacts, and in newly diagnosed leprosy patients not living in resettlement villages and significantly greater than in residents of a normal control village. Since HBV infections are increased in both L and T patients, health care and socio-economic factors are probably more important risk factors for HBV than genetic or immunologic factors.

IX/374(A) MULTI-CENTRE EVALUATION OF A SPOT TEST FOR DETECTION OF DAPSONE IN URINE.

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In 1966, in its third report, the WHO Expert Committee on Leprosy mentioned a simple spot test to monitor dapsone intake. Successful field applications were reported by Noordeen and Balakrishnan in 1972, and by Kumar and Balakrishnan in 1983, but others found the test insensitive. In 1981, some of us compared a number of dapsone tests in a patient compliance study at Addis Ababa. The spot test was found to be reliable, and, in a way, superior to all other methods because of its simplicity. The multicentre evaluation presented here confirms this finding.

The test was tried in 16 leprosy control projects spread over 12 countries in Asia, Africa and South-America. In all centres, the spot test was experienced as easy to do. The general feeling was that it could be performed by any leprosy field worker under any field conditions. The reliability of the test in the various centres was evaluated by re-examination of more than two thousand urine specimens in Amsterdam, using the same test and two sulphone-specific immuno-chemical methods. It is the intention of most of the centres to use this spot test henceforth to routinely monitor compliance in individual patients, and occasionally in overall surveys.

IX/375(A) THE GENETIC-EPIDEMIOLOGY OF LEPROSY

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Completion of a leprosy investigation (Karimui, Papua New Guinea) revealed: although most of the first ten years of life are spent with mother, affected mothers had no greater risk to have affected offspring. It appears that within the study environment, genetic susceptibility most likely caused individual variation. Kindred data analysis ascertained from 552 probands demonstrated: leprosy was frequently observed vertically through multiple generations and typically only in one side of the kindred (99/261 unilateral, 15/261 bilateral); 48/688 affected half siblings; of 24 cases with both parents affected, 28% of their offspring (10 years) were affected; leprosy prevalence first through third degree relatives of index did not decrease logarithmically as expected for multifactorial traits; 13 cases: affected fathers and sons; individuals with multibacillary forms (LL, LI, BL) had a significantly greater chance of being in multiplex kindreds, but had no greater risk than all other forms of leprosy to have multibacillary offspring. Discussion of preliminary genetical tests of the hypothesis that multiplex kindreds segregate a leprosy susceptible genotype including kindred analysis by computer program GENPED and LIPED genetic linkage analysis of 40 marker loci (including HLA).

IX/376(A) GENETIC FACTORS IN LEPROSY : EVIDENCES FROM POLYMORPHISMS AND TWINS

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In leprosy, individual liability is an important factor in the interplay between the germ and the human host. The apparent differences in susceptibility may have many cases but available data make a genetic influence possible.

Besides familial clustering and ethnic difference, twin study has shown genetic importance. One-hundred-and-two twin pairs with at least one twin affected by leprosy were examined in the endemic leprosy areas of West Bengal and Andhra Pradesh in India.

The concordance rate in MZ (59.7%) is significantly higher than in DZ (20.0%). In addition, in many of the affected pairs, the course of the disease, as well as the extent of the lesions, showed striking similarity. The intra-pair differences at the age of onset of all concordant (MZ and DZ) twin pairs tended to be smaller in MZ than in DZ twins.

Examination of several genetic polymorphisms, some having significant associations, have not contributed additional knowledge about the interplay between the human organism and the germs in the pathogenesis and course of leprosy.

The transplantation antigens of the HLA system have been examined and the data indicate a contribution of some HLA types to genetic susceptibility.

IX/377(A) ASSESSMENT OF LEPROSY CONTROL PROGRAMME AT POLAMBAKKAM, SOUTH INDIA (1955-1975)

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An operational and epidemiological assessment of the Leprosy Control Programme was undertaken at Polambakkam in South India. From about

40,000 cases detected during 1955-75, a stratified random sample of 10,272 was selected for study. Voluntary referrals accounted for 78% of the cases, contact examination for 9% and population survey for 13%.

The profile of newly-detected patients was analysed with respect to various characteristics in the 5 periods, 1955-57, 1958-60, 1961-64, 1965-69 and 1970-75. The ratio of males to females was 3:2 and the child rate 30%, and both were fairly stable. The lepromatous rate declined from 15% in 1955-57 to 6% in 1970-75. Deformities were present in 11-15% of new cases.

About 90% of the diagnosed cases commenced treatment within a year, and 37-47% of these collected at least half their drug supplies in the first year of treatment; subsequently, the regularity was lower. Information regarding clinical status at 5 years was available for half the patients, and of these, 60% had inactive or arrested disease. Bacteriological positivity in lepromatous cases was 86% initially and decreased to 39% by 5 years. The implications of the findings are discussed and recommendations made.

IX/378(A) THE INFLUENCE OF DIFFERENT DIAGNOSTIC CRITERIA ON THE OBSERVED PATTERN OF LEPROSY IN AN ENDEMIC AREA IN NORTHERN MALAWI

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The diagnosis of leprosy prevalence is difficult in a community where both inpatient treatment in leprosaria and outpatient treatment have ben available on a large scale. Likewise the diagnosis of untreated leprosy can pose considerable diagnostic difficulties in people with skin lesions suggestive of early leprosy. The difficulties cannot always be resolved with the help of histopathology. Three different case definitions have therefore been adopted for use in an ongoing survey in Northern Malawi.

i) a "narrow" definition which should include few, if any, false positives;

ii) a "middle" definition which includes some apparent leprosy patients omitted from the "narrow" group. Inevitably there will be a large number of false positives in this group than in the "narrow" group;

iii) a "wide" definition which should now include all or virtually all remaining leprosy cases but will also include a high number of false positives.

The detalis of these definitions and methods of allocating cases using either a flow-chart or a scoring system will be presented.

A total of 744 people suspected to have clinical leprosy have been allocated into the three groups. The implications of these definitions for the observed age and sex distribution of leprosy and the distribution of risk factors will be shown.

IX/379(P) EPIDEMIOLOGY OF LEPROSY IN TRIBALS

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A point prevalence survey of leprosy was undertaken in the Adhaura plateau of Rohtas district Bihar. This palteau consists of an area of 1549 square miles and is situated at a height of 1594 feet above sea level and is part of the Vindhyachal hills. The population is sparsely distributed, living at scattered places and there is no real road in the whole plateau. A house to house survey was done in the scheduled tribes of the plateau. The survey teams consisted of a doctor, a paramedical worker and voluntary health workers from the village. Each member of the family was examined in daylight.

The prevalence rate was found to be 20.72/1000 population. The prevalence in males (27.89/1000 population) was higher than that in females (13.37/1000 population). The mean age at onset was 44.83 years for males and 33.97 years for females. The majority of the patients were suffering from non-lepromatous leprosy. There was a focal distribution of leprosy.

A nutritional assessment of the tribal villages was also made and the possible relation between the nutritional status and leprosy was studied.

IX/380(P) DERMIJET IN SKIN TESTING WITH MITSUDA LEPROMIN

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The dermijet has been used all over the world in recent years for various skin tests that indicate the susceptibility of the individual to the test substances. It has been regularly used in the Mantoux test for tuberculosis, the Frei test for lymphogranuloma inguinale, in sensitivity tests on patients suffering from allergic states such as bronchial asthma and hay fever and in mass vaccination at times of epidemics. In the present era of progress towards a vaccine for leprosy where mass scale skin testing is involved, the advantages of the use of dermijet in field conditions were examined.

It is concluded that the dermijet can be used effectively for lepromin testing on a mass scale since there is minimal wastage of material and less time consumption in comparison to the tuberculin syringe. It is ideal in field conditions, as it does not call for sterile techniques. The dermijet can be loaded in sterile conditions at the hospital and then used in the field for about 40 shots.

IX/381(P) THE CURRENT STATUS OF HANSEN'S DISEASE IN QUEENSLAND, AUSTRALIA

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Leprosy is known as Hansen's Disease in Queensland and has been identified since 1855.Its origins are vague but writers like Thompson,Cantlie, Cook and Hargrave suggest that leprosy did not occur among the Australian Aborigine before the arrival of Europeans or migrants from endemic countries.Two phases of migration appear to have had an important impact on the infection of Queensland, namely, the influx of Chinese to the gold fields (1850, 1860) and the importation of South Sea Islanders as indentured agricultural labourers (1868). Leprosy occurs throughout the population and still persists around Cairns, Townsville, Rockhampton, Palm Island and Brisbane. The epidemiological relevance of the incidence of leprosy in recent intakes of South-East Asian migrants stresses the need for greater awareness on the part of health authorities and educators. The earliest attempt at control was the establishment of a quarantine hospital at Dayman Island in 1889, followed by the Leprosy Act of 1892 and the establishment of lazarettes at Peel Island (1907) and Fantome Island (1940). This paper discusses the status and progress of 214 patients on domiciliary care at present, following the phasing out of lazarettes, amendments to legislation and the integration of Hansen's Disease treatment into the State Health Services.

IX/382(P) LEPROSY IN INDIA BY 2000 A.D.

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Bihar is a moderate endemic area for leprosy. The Government of India started its National Leprosy Control Programme (N.L.C.P.) in 1955. Muzaffarpur Leprosy Hospital started its work as a referral hospital in 1968, and in 1976 the Government alloted an area for its N.L.C.P. Patients attend this hospital from all over Bihar.

The endemicity, severity of a disease and effectiveness of a control programme are measured by (a) Prevalence rate (b) Infection load (c) Prevention of a disease and deformities by detecting early cases. Inspite of treatment and control programmes, the prevalence rate and severity are increasing; this implies that the eradication of the disease will be difficult.

We observed that the prevalence rate, multibacillary cases, deformity rate and patients with multiple patches are all increasing year by year in all age groups.

The prevalence rate in 1976 was 9/1000 and in 1982 it was 12.8/1000. The multibacillary percentage in 1973 was 15.4% whereas in 1982 it was 20%. The deformity rate has increased from 15.7% to 21.9% during last ten years. The detection rate of early cases, such as patients with single patches, has been reduced from 16.5% to 15.9% during the last decade.

After observing the above facts, it seems with this approach it would be very difficult to eradicate leprosy by 2000 A.D. in India.

IX/383(P) LEPROSY CONTROL IN LESOTHO

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Lesotho is a small,independent, mountainous country in Southern Africa, with a population of under 1½ million. The prevalence of leprosy is possibly only 2 per 1,000. About 450 cases are on treatment. Leprosy is integrated into the general health service, with a Leprosy Hospital and 4 specialised field workers.

A low prevalence of leprosy generates much ignorance and fear, even among senior health staff. Health education by means of radio, literature, meetings and school talks, and training for health staff are priorities if cases are to be found early. Careful contact checking is important though difficult, as roads are few in the mountains and villages must be reached on horse or by foot. Most young men work in the South African mines and are out of the country for long spells. Of the newly registered cases, 60% are multibacillary.

Since March 1982 all new cases have been treated with multidrug therapy. 25 old lepromatous cases have been very successfully treated with 3 drugs at the Hospital's outpatient clinic. We aim to extend multidrug therapy to all health units as staff develop their primary health care programmes and improve their case holding methods.

IX/384(P) LEPROSY IN NORTH-EAST LIBYA

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Health services are provided for all residents through the National Health Services, including dermatology services to every hospital and polyclinic. The leprosy clinic in Benghazi is the main centre for leprosy care in North-East Libya. Cases are suspected by dermatologists working in their clinics and are referred to the leprosy clinic, Benghazi for confirmatioon of diagnosis, treatment and follow-up.

There were 71 Libyan patients and 3 foreign patients registered before 1977. The number of new cases added in 1978, 1979, 1980, 1981 and 1982 were 14, 14, 19, 13, and 11 respectively. The total number of cases registered to date is 153.

The pattern of disease before 1977 was lepromatous leprosy: borderline leprosy: tubercoloid leprosy: polyneuritic leprosy: 8, 1, 0.5, 0.5. The pattern of disease since then shows lepromatous leprosy: borderline leprosy: tuberculoid leprosy: polyneuritic leprosy as 4.5: 2: 2: 1.5.

The median age of onset of the disease of the newly registered cases was 30 years.

IX/385(P) PREVALENCE OF DAPSONE-RESISTANT LEPROSY IN UPPER VOLTA. COMPARISON WITH OTHER AFRICAN COUNTRIES.

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During 1981-82 a dapsone-resistance survey was done in 3 Sectors of Upper Volta: Ouagadougou, Koudougou and Bobo-Dioulasso. All registered lepromatous patients were visited, skin smears taken and from all patients treated with dapsone during more than 5 years, who had a BI of 2 or more, a biopsy was taken and sent on wet ice to Antwerp.

Data from 2 sectors are available for analysis. In a population of 1,677,000 there are 14,700 patients of whom 551 were multibacillary; (4%) 60 biopsies were inoculated into mice, 15 did not multiply in mice; eight strains were sensitive to dapsone, 35 were resistant, for two the interpretation of the results was impossible. Prevalence of secondary dapsone resistance among the multibacillary leprosy patients in Haute Volta is therefore 6%, a figure that is comparable with that observed in Mali and Burundi.

IX/386(P) EVALUATION OF LEPROSY CONTROL PROGRAMME

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Leprosy Control Programme was organized in response to the problem which existed as a result of measurement. Hence, it should be possible to measure whether the programme in operation is reducing the problem. The classical way to show this is to have controls to elicit the difference, but such a method has no logistic support in a health programme which is meant for the whole area. It cannot leave out pockets to be used as controls. Showing a gradual downward trend in the indices (like prevalence or incidence etc.) is only an assessment rather than an evaluation.

A real evaluation must indicate the amount of change produced by the programme in relation to the amount of change which is originally aimed at (objective). To calculate the change, we must estimate the status as it would have been in the absence of the programme.Thus in the proposed evaluation plan, three measurements are required:

(1) No. of estimated leprosy cases that would appear without the programme.

(2) No. of active cases, the programme would like to have after the work (objective).

(3) No. of active cases the programme actually had after the work.

The effectiveness of the programme may be calculated in percentage as $\frac{(1)-(3)}{(1)-(2)} \times 100$ and adequacy as $\frac{(1)-(3)}{(1)} \times 100$.

While expanding the above ideas, other aspects like cost- effectiveness, appropriateness and side-effects are also discussed

IX/387(P) PROJECTION OF A DECADE OF URBAN LEPROSY CONTROL

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The rapid urbanisation taking place all over the country has resulted in an influx of people from rural to urban areas, and the mushrooming of slums. Overcrowding and environmental distress has resulted in the spread of communicable diseases like tuberculosis and leprosy.

Against this background, the Greater Madras Leprosy Treatment and Health Education Scheme (Gremaltes) was conceived and launched in 1971 to control leprosy and to demonstrate an operationally feasible methodology in an urbn set-up.

The urban community profile presents a variegated pattern. To reach the different cross sections of people, different methods of approach are being employed:

Health education to change the attitude of the community towards leprosy;
Individual screening of slum dwellers;
Physical examination of school children;
Periodic surveillance of contacts of patients.

Considering the density of population, North Madras with a population of 1.6 million was selected as the project area.The area is divided into 3 compact zones and served by 18 peripheral clinics.

Observations after a decade:

38.9% of cases are self-reported;
The majority of new cases detected have single lesions;
A significant decrease in the detection of lepromatous cases;
A gradual decrease in the disability rate;
48% of the multibacillary cases have become negative.

IX/388(P) EVALUATION OF THE CAMPAIGN AGAINST HANSEN'S DISEASE IN URUGUAY

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The geographical location and the characteristics of the country are given in the paper. There follows an analysis of the first three years of the Five Year Plan, prepared under the guidance of WHO and the help of the International Association for Leprosy. The programme came into operation in 1981 using an already existing infrastructure of health services.The restricted size of Uruguay and the even smaller area where high endemicity exists, together with a good road and communication network, has made an efficient control of the disease possible. A study has been made of the special conditions that prevail taking into account the nearly 3 million inhabitants, 85% of whom live in the affected districts. The ratio of the sexes (52% women and 48% men), the quantitative and qualitative aspects of housing, population density, the immunological respnse to "Lepromin" in rural and urban areas are mentioned in the paper. The estimated prevalance is 1200 cases of which 670 are registered.

IX/389(P) EPIDEMIOLOGY OF THE HANSEN'S DISEASE IN THE STATE OF R1O GRANDE DO SUL – BRAZIL

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The authors describe briefly, the geographic, climatic and population aspects of the State of Rio Grande do Sul, Brazil. They give a short historic report about the problem of Hansen's disease in the region and show the present policy adopted in the control of this disease and its relation to the existent health system.

They point out the results of a seven-year programme after the implantation of a nominal index computer based file of sick persons and contacts.

They outline the distribution of new cases by the clinic, sexual and age range, and by the coefficients of incidence during the period of 1975 to 1981. They also describe the patients discharged during this period, the variation of the coefficients of prevalence and the rate of control of sick persons and contacts. Together with this description, the standards of classification, specially of type 1, the criteria for discharge and the policy of segregation of sick persons in the Colony Hospitals are analysed.

IX/390(P) CENSUS AND EVALUATION OF HANSENIASIS PATIENTS' CONTACTS IN THE STATE OF RIO GRANDE DO SUL – BRAZIL

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Brazil

The authors describe the results of the census of the Hanseniasis Patients' Contacts in the State of Rio Grande do Sul, Brazil. The census began in 1/1/1977 and lasted until 31/12/1982; the following data were obtained; 2850 (83.5%) of our total number of patients (3461) had their contacts registered; the total number of registered contacts was 7141 with 2.47 contacts for each patient. This number (2.47) is smaller than the average composition of the families in Rio Grande do sul (4.13 persons per family). Probably the explanation for this fact is that there is often more than one patient for each family. We also present an estimation of the real situation regarding the control of contacts.

IX/391(P) SOME CASES OF HANSEN'S DISEASE IN MILAN

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In 20 years, 14 leprosy patients and other suspicious cases presented at the Dermatological Dept. of the University of Milan. Eight of these patients were males and six females. Thirteen were positive on microscopic examination with many bacilli, whereas the fourteenth (a native of Lombardy) had some well defined achromic and anaesthetic areas. The anamnesis of these thirteen cases may be so summarized: Case 1: son of a leprosy patient LL type (his father was admitted to Gioia delColle Hospital, where he died), diagnosed at the age of eighteen. Cases 2,3,4: repatriated from various countries (Germany, Brazil and Tunisia) where they had lived. Cases 5, 6: natives of Potenza (South Italy) where leprosy is endemic. Case 7: native of L'Aquila (South Italy): a LL type. Case 8: native of Albenga (North Italy) where there may be infectious cases. Case 9: native of Oristano (Sardinia), infected by his sister. Case 10, 11: natives of Chile and the Philippines, probably infected by direct contact. Cases 12,13: suspected cases from Lombardy (LL type) who died after hepatic complications. Except case 1 and 9, none of the families were infected.

IX/392(P) DATA OBTAINED IN THE CLINICAL AND PARA CLINICAL STUDY OF 50 CASES OF LR IN IRAN

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During a study programme undertaken between 1970 and 1983, we detected 1400 leprosy cases of whom 200 were of Afghan origin. Of the cases detected, 200 patients have been under regular controlled treatment for 10 years.

The majority of patients had received intermittent treatment and been given only dapsone.

Amongst some 50 patients suffering from reactional leprosy who were hospitalised and under close study from the clinical and para clinical view point, we discovered that cases went from the simple reactional to the ENL, combined and accompanied by other signs or equivalents such as different localisations of neuritis, irido-cyclitis, orchitis, oedema, articular types mixed with RAA, vascular and trophic problems, etc.

Conclusions: we were forced to admit that even in known endemic regions, the different reactional types of leprosy could be easily confused with other infectious syndromes. We would therefore, call the attention of all medical personnel to this urgent and rather remarkable problem.

IX/393(P) USE OF A MICRO-COMPUTER TO REGISTER AND NOTIFY LEPROSY PATIENTS – THE OMSLEP SYSTEM

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The OMSLEP system for registering and notifying leprosy patients has been adapted taking into account both comments made by actual users and new therapeutic methods.The system is being used by a number of treatment centres because:

1) documentation is simple and easily accessible to primary health personnel.
2) the information received allows a ready evaluation of the methods of control and decisions may be taken quickly in the light of established objectives.
3) the terms are strictly defined, centralization of data may be done at different levels.
4) adaptation of local conditions poses no problems.

A programme has been established and allowed the use of a micro-computer. The microprogramme permits:

1) the validated input of individual data which appears as a case sheet on the screen with comments.
2) correction of errors.
3) updating of statistical data.
4) index calculation necessary to evaluation.

This adaption meets the needs of field work due to the fact that

1) this advanced technology is easy to use.
2) the equipment is reasonably priced.
3) it makes it possible to transmit viable data to the different levels of the health services.
4) computer systems are increasingly available.

IX/394(P) LEPROSY IN LESS DEVELOPED COUNTRIES

A. R. Chaurasia
G.R. Medical College, Gwalior, India

Leprosy is a major public health problem in the less developed countries of the world. Its eradication is made difficult not only by the social stigma attached to the disease but also by the lack of suitable data to measure the dimensions of the problem. In many developing countries like India, the disease is regarded as curse of God, and very few people (especially in the rural areas) know that the disease is curable.

The aim of this paper is to present basic data on the incidence of leprosy in 60 developing countries so as to get an idea of the problem. Based on the information collected and store by the World Health Organistion, the article also discusses the age and sex variations in the incidence of leprosy and its trends.

IX/395(P) RESULTS AFTER 5 YEARS OF INTENSIVE LEPROSY CONTROL WORK IN A HIGHLY ENDEMIC AREA

R.S. Mani, A.J.W. Jacob, Ajit Gershon.
German Leprosy Relief Association, Madras, India.

Palamaner Taluk in Andhra Pradesh is hyperendemic for leprosy. 90% of the population lives in rural areas. The project started in 1977 and covers a population of 168,475 dispersed in 91 villages grouped into 54 Panchayats.

The aim of the project is to reduce the quantum of infection by treating all existing cases, thus reducing the number of circulating bacilli.
Case-finding and case-holding activities are standardised so as to identify all existing cases at the earliest stage and bring them under effective treatment. The field organizational set-up is such that every village in the area is covered by the project activities. Till the end of 1982, 4,244 leprosy cases have been detected and 3935 registered (97%) in 9 peripheral clinics.

The following observations are made:
1) 37.9 was the gross prevalence rate, and the point prevalence now is 23.8.
2) 57.2% of the detected cases came voluntarily.
3) The disability rate declined from 23.4 to 4.1.
4) 70% of newly detected cases show only one lesion.
5) 42% of the multi-bacillary cases have become negative.

IX/396(P) THE VALUE OF HISTOPATHOLOGY IN A LEPROSY CONTROL PROGRAMME

F. Gjalt Boerrigter, A.C.Mcdougall, J.M. Ponnighaus
Lepra Control Project, Lilongwe, Malawi.

It is difficult to know if, and to what extent, leprosy is either under-or over-diagnosed in a control programme. Data from a cross sectional study in Northern Malawi were used to throw light on this problem.

One observer clinically examined 85 consecutive persons who during a house-to-house survey were detected by para medical workers to have skin lesions ranging from "definitely" to merely "suggestive of leprosy".

Punch biopsies were taken from all 85 persons and examined by a single observer in the United Kingdom.

The degree to which some definite clinical findings correlate with a definite histopathological diagnosis of leprosy was analysed.

The proportion of persons with early leprosy-like skin lesions who, after one single clinical examination, would have been clinically possibly over-diagnosed, is compared with those who would have been clinically definitely under-diagnosed, on the basis of a single biopsy report.

It appears that in a routine leprosy control programme where observation of persons with clinically uncertain leprosy is not possible, or in a community where the diagnosis of leprosy carries great stigma, histopathological examination is useful to prevent definitely false-negative and possibly false- positive clinical diagnoses of leprosy.

IX/397(P) LEPROSY IN ZIMBABWE

N.F. Lyons
Department of Medical Microbiology, University of Zimbabwe, Harare, Zimbabwe

The first recorded cases of leprosy in Zimbabwe appear from the early 1900's although it is likely that the disease had been present for some time before. Legislation provided for compulsory hospitalisation of all leprosy patients; this caused a tremendous upheaval in their lives and in the families concerned. This policy was abandoned in 1966 when domiciliary treatment was instituted.

The liberation war resulted in the closure of many treatment centres and migration of large numbers of the population. Many patients went without treatment and intensive efforts are now being made to relocate these and discover all new cases.

In August, 1983 it was decided to adopt the W.H.O. recommendations on multidrug therapy to replace existing mono-or dual regimens. Apart from a nucleus of personnel concerned with the implementation of this policy, the leprosy service will be integrated into the general health services. An existing special care centre for leprosy is to be upgraded to provide for teaching to all levels of medical and health workers.

An influx of leprosy patients from neighbouring countries presents a problem, but it is hoped that with regional cooperation this can be overcome.

IX/398(P) LEPROSY CONTROL AND TRAINING OF PERSONNEL

E.S. Thangaraj
The Leprosy Mission, Southern Asia, New Delhi, India

For an effective programme, competent workers are essential and good training is the key.

There is increasing awareness for making training programmes objective orientated.

Present System and the lacunae:

I. *Curriculum*
 i) Does not specify content.
 ii) Over-teaching, since the content is not clear.

II. *Teaching and Learning:*
 Lack of – Integrated learning
 – Teaching in logical sequence
 – Problem-centred learning.
 – Correlation between learning and job needs
 – Emphasis on what one must learn
 – On-job training.

III. *Trainers:*
 a) Lack of continuity
 b) Too many or too little
 c) Guest lecturers
 d) New staff.

IV. *Evaluation:*
 a) Inadequate evaluation system
 b) Too much emphasis on the single final exam.
 c) Lack of course assessment
 d) Lack of on-job evaluation.

V. *Duration of the course*

VI. *Workshops:*
 a) Highly technical
 b) Lack of resource person with orientation in leprosy
 c) Not enough help to apply new technology
 d) Lack of follow-up.

VII. *Implementation of Objective oriented training in 'The Leprosy Mission' for:*
 Medical Officers
 Paramedical Workers
 Non-Medical Supervisors
 Laboratory Technicians
 Physiotherapy Technicians

VIII. *Additional Training for Teams:*
 Role of each member in the team
 Clear learning objectives
 Practical training.

Conclusions:
 i) Find the gaps
 ii) Choose areas where it is necessary to change.
 iii) Plan evaluation as an inbuilt system.
 iv) Bring in change, in phased manner.

IX/399(P) EFFECT OF CONTROL WORK ON NEW CASE DETECTION RATES IN LONG-TERM FOLLOW-UP OF 25 YEARS OF LEPROSY CONTROL WORK

Ranade, M.G.
Gandhi Memorial Leprosy Foundation, Wardha, India

One of the important parameters in evaluation of SET work or in study of the epidemiological characteristics is the incidence rate. In order to obtain a scientific estimate of the parameter, one has to undertake planned prospective study and undertake systematic regular follow-up of people at a specified interval of time preferably as short as possible.

The present paper based on long-term yearly follow-up of the population in 27 villages of Sewagram (Wardha, Maharashtra) leprosy control unit run by the Gandhi Memorial Leprosy Foundation deals with another suitable parameter "New Case detection Rate".

The unit is manned with trained medical and paramedical persons. Systematic recording of data enabled the author to find out the lag between incidence and new case-detection rate and to study further the new case-detection rate in relation to (i) Age, (ii) Sex, (iii) Type, (iv) Earlier total prevalence and prevelence of L + B patients (v) Initial and subsequently added population (vi) Deformity rate in new cases.

The paper also studied the long-term flow of the ratio of new case detection to the prevalence rate to find out whether the ratio can serve as an operational and epidemiological parameter useful in field conditions.

IX/400(P) LEPROSY AMONG LAMBADI TRIBES IN CENTRAL ANDHRA OF SOUTH INDIA (SLIDE PRESENTATION)

A. Paramanda Prasad Babu, Alxander Thomas
The Leprosy Mission, Nuzvid, Andhra Pradesh, India

An intense total population survey has been undertaken to study the prevalence of leprosy among the Lambadi tribes in Krishna District, Andhra Pradesh of South India. The prevalence of leprosy is estimated to be 10/1000 in the Krishna District as per National Leprosy Control Programme records.

Lambadi tribes are said to be nomadic tribes with peculiar customs and traditions. The women wear attractive coloured clothes with glass mirrors over them as laces. They wear beads and bangles to cover the exposed parts of the body. Due to scarcity of water as well as their cultural habits they take only occasional baths. They wash their clothes very infrequently and do not use soap. They do not intermingle with other people. These nomads have started to build houses and no longer wander about.

This study, undertaken to establish the prevalence of leprosy among Lambadi tribes, has revealed a large number of cases among this tribe. Details of the findings of the survey are discussd in comparison to the other similar villages. We find a prevalence of leprosy 3 fold among this tribe (ie) 30/1000. Probable factors influencing this high prevalence are discussed.

IX/401(P) EPIDEMIOLOGY: ENDEMICITY OF LEPROSY IN RURAL HEALTH CENTRE

Bighnaraj Mahapatro
Damien Foundation : Chatrapur (Ganjam) Orissa, India

A house to house survey was conducted in 26 villages with the help of 12 workers, two supervisors, one medical officer with the guidance of Dr. Kapoor, consultant, Demien Foundation. 24,884 persons were enumerated and 83.3% of them were examined. Findings indicate 374 cases of leprosy were recorded, giving a prevalence rate of 17.5 per 1000; the prevalence of leprosy is increasing with age with a maximum in 45+ age group; the leprosy prevalence among male and female was 2 : 1 in most age groups; the lepromatous prevalence was ten times higher amongst adults than amongst children; the prevalence of non-lepromatous leprosy among adults was twice that of children; the new-case detection rate was 6.59%.

IX/402(P) DIVERSITY OF THE VARIOUS TYPES OF LEPROSY ENCOUNTERED IN TURKEY, BLOOD GROUPS OF THE LEPROSY PATIENTS AND COMPARISON OF THEIR DISTRIBUTION IN THE GENERAL POPULATION

Turkan Saylan, Nahide Onsun, Nafi Erdinc, Baharistan Forta, Mustafa Sutlas Turker Ozkan
Institute of Leprosy, University of Istanbul, Turkey

Leprosy patients in Turkey are evaluated clinically, bacteriologically, immunologically and histopathologically and classified according to the Ridley-Jopling classification.

In this study the classification of the patients detected and put under treatment recently was made. Comparison of the various types of leprosy in African countries and India with those in Turkey have been made and the difference are discussed.

The blood groups of patients seen in the last two years have been ascertained and compared with those in the general population.

The types of leprosy and progress of the disease vary from country to country. Evaluation and discussion of these differences would be helpful for the workers of those areas.

IX/403(P) GENETIC RISK FACTORS IN LEPROSY

Schauf, V., Nelson, K.E., Vithayasai, V., Chanarat, P., Gelber, R., Ryan, S., Smith, T. Jonasson, O., Scollard, D.M., Brown, A., Wagener, D.
Chiang Mai/Illinois Leprosy Research Project, Chicago, USA

Numerous inconsistent associations between leprosy and major histocompatibility complex (MHC) antigens have been reported. Sib pairs with

tuberculoid (T) leprosy or pairs with lepromatous (L) leprosy shared HLA haplotypes more often than expected. To evaluate further the role of the MHC in leprosy resistance, HLA-A,B, and DR typing were performed for 257 members of 39 families with at least 2 leprosy patients. Physical examinations were performed for all subjects. Patients were classified by clinical and/or biopsy findings. In 13 families with at least 2 affected and 1 unaffected sibs, there were 32 affected offspring (12T + 20L). The majority of the sib sets (8/13) were discordant for leprosy type. Affected sibs in the 13 families inherited different parental HLA haplotypes more often than expected ($X^2=4.17$, $0<.05$). Even in the families with only 1 healthy parent (9/13) affected sibs inherited different haplotypes from the healthy parent more often than expected ($X^2=5.39$, $p<.025$). In previous studies of MHC determinants of leprosy type, sib sets discordant for leprosy type were excluded. In our study of resistance to clinical expression of *M. leprae* infection, all families with multiple affected sibships were studied. Resistance to leprosy may be MHC-associated since affected sibs inherit different HLA haplotypes more often than expected. Now the MHC has been implicated both in resistance to leprosy and its expression.

IX/404(P) EFFECT OF DURATION OF DISEASE AND TREATMENT ON LYMPHOCYTE TRANSFORMATION IN LEPROMATOUS LEPROSY

Brown, A., Scollard, D.M., Moses, V., Nelson, K.E., Schauf, V., Vithayasai, V., Makonkawkeyoon, S.
University of Illinois, Chicago, USA

Patients with lepromatous leprosy have been reported to have decreased responses to lepromin and other antigens or mitogens in lymphocyte transformation tests (LTT). Other workers have reported normal LTT responses of lepromatous patients to PHA and BCG. In order to determine the effect of treatment and duration of illness prior to therapy on LTT responses, we studied 61 untreated patients, 29 inactive lepromatous patients and 94 normals.

LTT responses (△CPM) to PHA, BCG and lepromin were studied and compared using nonparatmetric tests (Mann-Whitney/Wilcoxin). Responses to PHA were significantly depressd only in these untreated BL/LL patients with symptoms present for over 1 year; LTT responses to PHA of inactive lepromatous patients exceeded those of controls. Responses to BCG were depressed only in patients with symptoms ≤1 year prior to therapy. Responses to lepromin were depressed in all patient groups compared to controls, but the inactive lepromatous patients had significantly higher LTT responses than active patients with symptoms ≤1 year.

Depressed LTT responses to lepromin are seen in untreated lepromatous patients even with a relatively short illness history, and persist in many (but not in all) patients after effective treatment. Depressed responses to BCG and PHA are more transient and depend on the duration of untreated leprosy.

IX/405(P) DERMATOGLYPHS IN LEPROSY : GENERATION OF A LINEAR DISCRIMINATING FUNCTION VIEWING THE IDENTIFICATION OF GROUPS AT RISK

Aguinaldo Goncalves, Mario Augusto C. Leao Ribeiro, Diltor V.A. Opromolla, Carlos R. Padovani, Jonas R. Consorte, Julia Maria Belini, Neusa N. da S. Goncalves
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Evidence on behalf of the action of consitutionality in leprosy is well known and has been fully reviewed elsewhere. Difficulty, however, has been found as to a precise genetic methodology, sufficient to make its mechanisms universal: many genetic markers have been used, but the results obtained have not proved to be harmonic or additive.

In this project, 17 dermatoglyphic variables of a leprosy patients' group, besides the qualitative characters, have been studied.

The results have been compared with the corresponding values of the control group, obtained from matching of sex, age and heredity.

According to the adopted pattern, this comparison is made by HOTTLERING T^2 Test, which tests medial vectors, through the calculation of their covariances. If a difference between both studied groups is found, analysis goes on with the generation of a Fisher linear discriminating function followed by the respective probability of inadequate classification, which according to our previous studies, has proved to be desirably low.

The data, presented under tabular and graphic pattern indicate the possibility of discriminating, through the dermatoglyphic analysis, whether a certain individual more probably belongs to one of the two studied populations, that is, indeterminate or healthy. This would contribute to the possibility of early identification of groups at risk of contacting leprosy.

IX/406(P) A STUDY OF ARREST AND RELAPSE OVER THREE DECADES IN A CONTROL UNIT

G.Y. Joshi
Gandhi Memorial Leprosy Foundation, Wardha, Bombay, India.

This paper is a retrospective study of 64 (L&B) & 849(N) arrested cases seen in the Sevagram Unit of the Gandhi Memorial Leprosy Foundation. It is based on data from 27 villages of the oldest unit of the Foundation Sevagram, started in 1952. Work is done on the SET pattern. The unit has well-maintained records and data. Thanks to intensive survey, and follow-up of all arrested cases in the last 30 years was possible. This study refers to 36 relapsed cases. Relapses in non-lepromatous type of leprosy leading to change of type enable the estimation of possible dapsone resistance in leprosy.

The following factors are studied in this paper:

1. Age, Sex, Type and Skin lesions;
2. Nerve involvement before and after relapse ;
3. Study of stress and strain factors like pregnancy and parturition.
4. Effect of intercurrent diseases like tuberculosis;
5. Change of type after relapses;
6. Time elapsing from detection to arrest and from arrest to relapse;
7. Problem of persisters and sulphone resistance;
8. Treatment before arrest and after relapse by monotherapy and multidrug therapy.

IX/407(P) AN INVESTIGATION OF DAPSONE COMPLIANCE USING AN ISONIAZID-MARKED FORMULATION

Ellard, G.A., Jenner, P.J., Stanley, J.N.A., Pearson. J.M.H.
National Institute for Medical Research, London, England

The regularity with which out-patients actually ingest their prescribed therapy is a vital factor in attempts to control leprosy by case finding and treatment. In the past studies carried out in Asia and Africa using the dapsone/creatinine ratio method have demonstrated that dapsone compliance is often poor.

In an investigation conducted among out-patients in Hyderabad, it was shown that the precision of the dapsone/creatinine method for monitoring dapsone compliance could be improved, if patients were prescribed specially formulated dapsone capsules containing 6 mg isoniazid as an innocuous marker. Urine samples were obtained by means of surprise home visits; the ingestion of the isoniazid marker was revealed by a sample colorimetric procedure which gives reliably positive results for about 18 hours.

Such capsules were acceptable to the patients and, in the short run, were taken more regularly than the standard tablets. However, a small proportion of patients took both capsules and tablets very irregularly, indicating that poor compliance was not overcome by simply changing the dapsone formulation.

IX/408(P) STRATEGY OF LEPROSY IN ASSAM

K.N. Barua
Dermatology Department, Gauhati Medical College, Assam, India

Assam covering sixteen districts, has a population of 157 lakhs (1971 census) of which 75 lakhs have been covered by N.L.C.P. so far. Leprosy is prevalent in endemic form in two districts, 11789 cases have been detected and 11516 have been registered for treatment. The prevalence rate is 1.57 per thousand, lepromatous leprosy 21 per cent. 455322 people are living in those endemic districts.

There is only one leprosy training centre for para-medical staff, 10 control units, 236 S.E.T. centres, 10 urban leprosy centres, and 120 beds in total for admitted leprosy patients in Assam. Besides these, a few voluntary organizations offer treatment facilities to leprosy patients. Dapsone is being supplied freely to the patients but the drugs like rifampicin, clofazimine have been given only in a few selected centres. Multi-drug therapy advocated by WHO, has not yet been fully implemented due to lack of drugs and lack of knowledge amongst the workers. Other problems facing the leprosy control programme are poor case detection rate, poor case holding, poor referral system, lack of diagnostic facilities and trained personnel, high defaulters' rate due to lack of proper health education, poor economic condition of the people, poor roads, repeated floods, difficult transportation, etc. Dapsone resistance has been reported though it is difficult to know its exact magnitude due to lack of animal experimental facilities.

IX/409(P) PATIENTS COMPLIANCE TO DRUG THERAPY IN URBAN LEPROSY CONTROL PROGRAMME

J.T. Marshall, Sr. G. Lussu, Sr. Cecile Coulombe, Sr. Alicia Rodriquez, M. Vishwanath
Sumana halli Rehabilitation Training Centre, Bangalore, India

Several studies undertaken to assess the regularity of dapsone intake have confirmed that the drug is not consumed regularly by leprosy patients, whose clinic attendence is more than 75%. Field investigations were carried out over 1½ years on patients (treated in project areas alloted by state government and non-project clinics in established slums or city centre) who were on either a single drug or multi-drug therapy to:

a) Assess the regularity of dapsone and clofazimine intake
b) Monitor the feasibility of methods used to detect dapsone in urine
c) Study these factors that influenced regular drug intake

The self-administration of dapsone by 312 leprosy patients attending project and non-project area clinics was assessed by

(1) Physical count of dapsone tablets and clofazimine capsules for cases on monotherapy (dapsone) or multi-drug therapy. (2) Screening of urine specimens was done by a qualitative spot test and estimating (dapsone) ratio (in Biochemistry Laboratory) from 150 patients out of 312 who underwent the spot test.

As assessed by a surprise count of dapsone tablets and clofazimine capsules on an average, one patient missed taking 5±6 tablets and 1±2 capsules in 28 day period and only 64% on monotherapy and 70% patients on multidrug therapy took more than 75% of their treatment. The spot test was found positive for dapsone in 78.77% patients. Both methods of monitoring regularity of dapsone intake were found to be practical and acceptable, the correlation was also good. The spot test was reliable as judged by the dapsone/Cr ratio. These measures are effective and recommended for more extensive use in urban leprosy control programme.

IX/410(T) CONJUGAL LEPROSY

Guadalupe Ayala Uribe
Secretariat of Health and Medical Assistance, Mexico.

Statistical, clinical and epidemiological characteristics in one hunderd leprosy affected couples were compared with results obtained in other countries as well as with other general data on the endemicity of leprosy in Mexico.

IX/411(T) EPIDEMIOLOGY AND CONTROL – AN INTERPOLATED ENCOUNTER

R. Padmasini, D. Prabhavathy, Thomas Jayakar
44, Giri Road, Madras, India

In this paper the points discussed are: distribution of the disease with regards to Sex, Age, Occupation, Family History, Detection of Source, Detection of Spread, acceptance and treatment.

In leprosy which has world wide distribution, control measures in different countries vary depending upon the enthusiasm of the government, acceptance by the public and by patients, cost involved and type of people involved in the work. To initiate leprosy control, attention must be directed towards the treatment of infectious cases, the protection of people at risk, wide propaganda by devoted workers about modern trends in leprosy, encouragement of employment of non-infectious cases and economic support for the disabled by state and public, research work to reduce the duration and cost of treatment and to raise the economic level of the nation.

IX/412(T) LEPROSY AND IODINE – ARCHITECTURE OF AN IDEA

Arturo O'Byrne-Gonzalez

Foundations:
1811 Courtois discovers iodine.
Pillars:
1886: Danielssen discovers relation between leprosy and iodine. *1928:* Muir makes use of these relations to increase immunity. *1928:* first ideas of goitrogenic substances. *1938* Cairo (Egypt) Leprosy Congress invalidates Muir's hypothesis. *1941:* Astwood and coll. introduce the inhibitors of the iodinated hormones' synthesis.

1952: Accidentally, these inhibitors are found favourable to leprosy. *1960:* This is denied by other investigators.*1964:* It is suggested to analyse the iodine content of lepromatous tissue (rich in lipids), utilizing the technique of Aitkens. *1965:* It is suggested to improve the treatment of leprosy with an iodine-free diet (Remington-Levy-diet). *1972:* In the "Low-iodine zones", leprosy is almost non-existent – eg: Minnesota U.S.A., Switzerland, Mendoza, Argentina and it is probable that in the "high-iodine zones" leprosy increases: eg: Acre (Brazil) – The Ethiopian plateau. (different above sea levels and a low-contact rate in both).

IX/413(T) LEPROSY EPIDEMIOLOGY AND CONTROL

I.H. Cochrane
Heed, Kamalganj, Bangladesh

"Heed" (Health Education and Economic Development) is a group of Christian missions which has worked in the Kamalganj area for seven years. The population covered is 160,000 of which about a third live and work in tea gardens.

In the 80 years preceeding 1947, Hindus from the eastern states of India migrated to the tea gardens of Sylhet in search of work. Some had active leprosy and spread the disease to contacts. Medical staff on the gardens were unable to spend much time on its diagnosis and treatment nor was systematic examination of workers and their families undertaken. Advanced and obvious leprosy was either treated in the gardens or referred to the government leprosy clinic.

Of the total 230 patients whose records have been examined, 71% are from the tea gardens compared with 29% from the villages. The male/female ratios within this total are respectively 1.8:1 (tea gardens) and 2.4:1 (villages).

There is a majority of Hindus in the tea gardens; the Hindu/Muslim ratio is therefore approximately 18:1 compared to 1:1 in villages.

Some reasons for the higher prevalence of leprosy in the tea gardens are suggested. Sex, child and religous prevalence are compared.

IX/414(T) UTILITY OF A DAPSONE "SPOT TEST" & DAPSONE "TILE TEST" IN LEPROSY CONTROL PROGRAMME

Sharad Naik
Acworth Leprosy Hospital, Wadala, Bombay, India

The sensitivity of dapsone "spot test" with modified Ehrlich's reagent and dapsone "tile test" using Barton-Marshall reagents – both being qualitative tests for dapsone screening in urine compared with dapsone/creatinine ratio – a quantitative test. 302 urine samples were processed by paramedical workers in the field for dapsone "tile test" and dapsone "spot test". The same samples were brought to the laboratory and processed for these two tests and dapsone/ creatinine estimation. These three tests correlated well at the level of 91%. The results obtained by paramedical workers and experienced person at laboratory also showed a 97% concordance.

An earlier investigation revealed that monitoring through frequent and supervised check-up of the urine for drug content (4-5 samples/year/patient) and subsequent motivation and persuasion of leprosy patients, the irregularity rate of drug consumption by patients could be brought down from 36% to 17% in one year. The kit for performing dapsone "spot test" and dapsone "tile test " being light and easy to carry in the field and the tests being simple to perform and the results being reliable they can be applied in the field on a mass scale. The routine frequent and surprise checking of urine for drug content will give early idea about irregularity/ regularity status of drug consumption by patient (as compared to the jugement relying on clinical improvement and reduction in bacteriological index of infectious patients) which will help greatly in leprosy control programme.

IX/415(T) A NEW APPROACH TO CONTROL THE SPREAD OF LEPROSY

M.C. Prabhakar, A.V.N. Apparao, D.R. Krishna, T.V.Ramanakar
Kakatiya University, Warangal, India

The two recognized portals of exit of *M. leprae* are the skin and nose of lepromatous patients. The nose is considered to be more important than the skin. Lepromatous patients harbour millions of *M.leprae* in their nasal mucosa which are discharged when they sneeze or blow the nose . Leprologists normally claim that an intectious patient can be rendered non-infectious by treatment with dapsone for 6 months or with rifampcin for three weeks. Contrary to this, we observed in our studies that in spite of continuous and regular treatment with several drugs, orally, for considerable periods, LL patients harboured many *M. leprae* in the nose. Thus it was felt that local treatment of the nose with rifampicin (drops/spray) might destroy all the bacilli in the nose and thus prevent the transmission of the disease. This treatment was applied successfully in 52 patients and resulted in the reduction of the becterial load in the nose to zero within eight days. There was no untoward effect with this treatment and acceptability was excellent.

The trials are proceeding with solid rifampicin, the purpose of which is to reduce the duration of local treatment still further.

During local treatment, the patient receives systemic therapy regularly.

By this treatment, an infectious patient can be rendered non-infectious within a very short time. If this method is implemented generally, the transmission of leprosy could be completely controlled. When the local treatment is started soon after a lepromatous patient is identified, nasal deformity can be prevented.

SESSION X

EXPERIMENTAL THERAPY

Chairman: Cottenot, F.

Rapporteur: Pearson, J.M.H.

THURSDAY, 23RD FEBRUARY, 1984

Commission Hall 'H' 08.30–12.00

Abstracts

A* : 416-434
P* : 435-440
T* : 441-442

*A : accepted for reading
*P : for poster presentation.
*T : for title reading

X/416(A) SYSTEMS FOR THE DEVELOPMENT OF DRUG COMBINATIONS AND QUANTIFICATION OF SYNERGISTIC, ADDITIVE OR ANTAGONISTIC EFFECTS.

M. Rosenfeld, E. Wempe, J.K. Seydel
Research Institute Borstel, Fed. Rep. of Germany

Bacterial growth kinetic techniques, checker board titration and serum activity tests using different mycobacterial strains (*M. lufu, M. marinum*, etc.) as models for *M. leprae* have been used to evaluate and quantify the combined effect of various drugs especially of rifampicin, prothionamide, dapsone, INH and a new combination of brodimoprim and dapsone. The latter is also effective against a highly dapsone-resistant mutant of *M."lufu"*. Drug concentrations in the serum activity experiments were determined microbiologically and chemically (HPLC-method).

The implications of these findings for the development of combined chemotherapy with these drugs against *M. leprae* are discussed. The additive or synergistic effects allow, for instance, reduction of the dose of the single components thus reducing the risk of side-effects.

X/417(A) QUANTITATIVE STRUCTURE-ACTIVITY RELATIONS OF DAPSONE-DERIVATIVES USING MYCOBACTERIAL STRAINS AS MODELS FOR *M. LEPRAE*.

E.A. Coats, V.M. Kulkarni, A.K. Saxena, H.-P.- Cordes, J.K. Seydel.
Research Institute Borstel, Borstel, F.R.G.

As part of our continuing investigations aimed at developing bacterial test systems which can serve as models for screening of folate synthesis inhibitors of *M. leprae*, we have evaluated a series of diphenyl-sulfone derivatives against partially purified folate synthesizing extracts from *E. coli*, and dapsone-sensitive and dapsone-resistatnt mycobacteria *(M. lufu, M. smegmatis* ATCC 607). Multiparameter regression analysis of the data has afforded quantitative structure-activity relations (QSAR) which facilitate a comparison of the *in vitro* test systems with each other. In all cases, a strong dependence on electronic influence of the various constituents on the inhibitory effect is observed. The QSAR- results from the *in vitro* systems will be compared with the QSAR derived from the corresponding *in situ* whole-cell cultures. Special interest is focussed on the similarities in the QSAR equation derived for daspsone-sensitive and dapsone-resistant folate synthetase. The QSAR equations have led to the synthesis of dapsone-derivatives with high inhibitory activity but lower toxicity as compared with dapsone.

X/418(A) A NEW APPROACH TO COMBAT DAPSONE-RESISTANCE OF *M. LEPRAE*

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In recent years there has been a resurgence of Hansen's disease in many countries. The widespread emergence of drug-resistant strains of *M. leprae* poses a serious threat to plans for controlling and eradicating the disease. Dapsone has been the main weapon in the fight against leprosy. Fears have now been expressed that the usefulness of this once effective drug might be lost for ever. The exact mechanism by which dapsone acts on *M. leprae* is not clearly established. The same drug can have more than one mechanism of action. We have found that the HD bacilli contain an unusual form of the enzyme diphenoloxidase. Inhibitors of the enzyme suppressed multiplication of the organisms in the mouse footpad. Clofazimine has been reported to inhibit diphenoloxidase. Dapsone inhibited diphenoloxidases from plant and mammalian sources. The drug had little effect on the enzyme in intact *M. leprae in vitro* and showed only partial inhibition in disrupted bacilli. Evidently, dapsone is unable to penetrate the organism or the enzyme molecule. Possibly it acts at the growing stages of the bacillus.

Polylysine, a homopolymer of the essential amino-acid lysine, is known to interact with lipid bilayers of cell membranes. Methotrexate-resistant leukemia cells have been reported to become susceptible when the drug was combined with polylysine. Development of a permeability barrier is an important means by which bacteria become drug-resistant. The cell membrane of streptomycin-resistant bacteria has been shown to be different from that of sensitvive strains. When dapsone was combined with polylysine, it penetrated the bacillus and completely inhibited its diphenoloxidase. It is likely that this new method we devised has the potential for overcoming dapsone-resistance in *M. leprae* by making the drug readily penetrate the organism.

X/419(A) INTERACTION OF THE ANTILEPROSY DRUG DAPSONE WITH MODEL MEMBRANES AND PROTEINS.

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The interaction of dapsone with biomembranes and proteins is hardly known at the molecular level.

We have carried out thermal investigations of the chain-melting and ice-water transitions in the model membrane systems, DPPC-water doped with dapsone in order to understand dapsone-membrane interactions. Our results show that dapsone is mostly found near the phospholipid head groups of the bilayer lamellae and that it perturbs the structure of the vicinal water. This change in water structure is likely to alter the biological function of the membrane to some extent.

Protein binding properties of dapsone show that it readily binds to serum albumin, lysozyme and brain tubulin. The association of dapsone with albumin and lysozyme involves hydrophobic forces leading to stacking over tryptophan residues of these proteins. Studies with acetylated lysozyme show that lysine residues prevent drug association. At physiological concentration the drug does not inhibit lysozyme activity. The drug (a) binds tubulin dimer and (b) enhances colchicine binding. The noncompetitive binding indicated that the dapsone binds to tubulin at a site other than the colchicine-binding sites. Dapsone also impairs the assembly process of tubulin to microtubule form.

X/420(A) THE SEARCH FOR NEW ANTILEPROTIC DRUGS: N-CYANOIMINO AND NITROMETHYLENE ANALOGUES OF THIOUREAS AND THIOAMIDES.

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The second-line drugs used in the treatment of leprosy include thioureas (thiambutosine) thioamides (prothionamide, ethionamide) and thiosemicarbazone (thiacetazone). The toxic effects of these compounds are possible due to the presence of thiocarbonyl groups in the molecule. Recently we have completed a study in which the thiocarbonyl (>C=S) group in these compounds was exchanged for a similar pharmacophoric grouping; the N-cyanoimino and the nitroethylene groups.

Twenty-five compounds were prepared and tested *in vitro* against *M. tuberculosis*. Some compounds were active at 100 and 50 μg/ml. A key moiety in the active thiourea analogues was identified as the 4-n-butoxyanilino group present in thiambutosine. The majority of the compounds were inactive. Analogues of prothionamide and ethionamide were also found to be inactive in the mouse footpad.

The work was supported by WHO grant 790490 (1980-1982).

X/421(A) INVESTIGATION OF THIOSEMICARBAZONES (TSCs) AND TSC ANALOGUES AS POTENTIAL INHIBITORS OF DEOXY-RIBONUCLEOTIDE SYNTHESIS OF MYCOBACTERIA

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Thiacetone is a second choice chemotherapeutic agent in the treatment of leprosy. Starting with the known but unsatisfactory activity of this drug against *M. leprae* or the leprosy model strain "*M. lufu*", a screening of related TSCs showed that 2-formylpyridinethiosemicarbazone (2-FP-TSC) is considerably more active against "M. lufu" than other non-α-(N)-heterocyclic TSCs. In the literature, similar results are described which were obtained from the investigation of the anticancer activity of this class of compounds. In accordance with the literature, it may be assumed that 2-FP-TSC is acting as a chelator of metal ions and therefore as an inhibitor of the iron-containing enzyme ribonucleoside diphosphate reductase. To investigate the structural dependence of the activity of 2-FP-TSC a series of

derivatives was synthesized and tested against "*M. lufu*". Some results will be presented. Furthermore, structurally divergent compounds which should have comparable chelating properties were synthesized, tested and found to show promising activity. Interestingly also, some Fe(II)-complexes of these chelators were found to be active inhibitors of *M. lufu*. The results of some physicochemical analyses will be discussed (i.e. determination of Fe(II)-chelate stability constants; investigation of the inhibition of a potential model reaction for ribonucleotide reductase catalyzed reactions).

X/422(A) THE SUPERIORITY OF THE NEONATALLY THYMECTOMIZED LEWIS RAT (NTLR) TO MONITOR CLINICAL TRIALS IN LEPROMATOUS LEPROSY.

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Previously untreated lepromatous leprosy patients were treated with either a single initial 1500 mg dose of Rifampin plus daily 100 mg dapsone (7 patients), or weekly 900mg Rifampin plus daily 100mg dapsone (7 patients). Skin biopsies were taken from active lesions at 3-4 days, 1, 2 and 4 weeks following the initiation of therapy. From these biopsies the standard 5×10^3 *M. leprae* were inoculated into footpads of mice, and the maximum number of bacilli (approximately 10^6) were inoculated into the feet of NTLR. Only a single 3-day skin biopsy grew in mice. At least once, 8 of the 14 patients' biopsies demonstrated viable bacilli in NTLR. 22 of 56 biopsies grew in NTLR. Of the 68 separate NTLR footpads in this study that demonstrated viable *M. leprae*, 33 were realized by significant growth in NTLR alone (≥4-fold increases), and 35 required mouse subpassage for confirmation. NTLR inocula of more than 10^6 grew more frequently than smaller inocula. Viable bacilli were detected most commonly from the earlier biopsies, but even at 4 weeks, 29% of the biopsies were found to contain live *M. leprae*. The two regimens were not found significantly different.

X/423(A) CHEMOTHERAPY OF EXPERIMENTAL LEPROSY IN THE NUDE MOUSE

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Histology of tissues of nude mice infected with *M. leprae* reveals an overwhelming infection resembling lepromatous leprosy in man and thus makes the nude mouse a suitable model for studying the most effective drug combinations for use in leprosy.

Nude mice, having disseminated infections after intravenous or footpad inoculation, were treated and observed for periods of up to two years. Progress of the infection was monitored by examination and subinoculation of nasal swabs and ear clippings from living mice and by complete autopsies on mice culled at intervals. Treatment consisted of monotherapy with rifampicin, dapsone, clofazimine or prothionamide or combined therapy using dapsone and prothionamide, rifampicin and clofazimine or rifampicin and prothionamide. Short-term and intermittent chemotherapy using the above drugs was also carried out, and results of these studies will be presented. Particular attention was paid to the treatment of dapsone-resistant leprosy. Having determined the minimum effective dosages and frequency of administration necessary to control a disseminated heavy infection in the nude mouse, we hope these results will form a basis for effective chemotherapeutic regimens and decrease the likelihood of the emergence of more drug-resistant strains of *M. leprae*.

X/424(A) NUDE MOUSE FOR THE STUDY OF CHEMOTHERAPY IN LEPROSY

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Rifampicin showed tremendous killing effect on *M. leprae*. Nude mice were inoculated with *M. leprae* into footpads and given 0.5mg (once) and 0.2mg (for 2 weeks) of rifampicin. The results suggested that single administration of 1,500mg or 2 weeks of 600mg daily of rifampicin may be effective as chemoprophylaxis of human leprosy. *M. leprae* obtained from patients who had been treated with rifampicin daily, were inoculated into footpads of nude mice. The results showed that the bacilli lost their infectivity for nude mice after only 2 days' administration with 450 mg of the drug.

INAH, minocycline and clindamycin were not lethal to *M. leprae* in nude mice.

Dapsone showed a bacteriostatic or partially suppressive effect on the growth of *M. leprae* in the nude mouse. Inoculating with a small number (5.0×10^3) of *M. leprae* into nude mice, 0.01% dapsone in the diet was not enough to depress the growth of *M. leprae*, in contrast to normal mice. Inoculating with a large number (8.0×10^6) of *M. leprae*, 0.01% dapsone suppressed the growth of *M. leprae*.

These results suggested that the nude mouse could be of great value as a model for chemotherapy studies of leprosy.

X/425(A) CHOLESTEROL METABOLISM OF MACROPHAGES IN PRESENCE OF *M. LEPRAE*–AN *IN VITRO* DRUG TESTING SYSTEM

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Macrophages from mice in the presence of phagocytosed *M.leprae* show a preferential accumulation of cholesterol ester. The increase appears to be due to the decreased level of esterase enzyme that could hydrolyse cholesterol esters. Such an increase in the ester level is not seen in the presence of dead bacteria. Using this observation, it has been demonstrated that the presence of anti-leprosy drugs like dapsone and rifampicin inactivate *M. leprae* inside the macrophages and do not allow the bacteria to alter the cholesterol metabolism. Drug-resistant *M. leprae* derived from relapsed patients, behaved like live bacteria in the presence of the drug inside the macrophages. A new compound like deoxyfructoserotonin also showed anti-leprosy activity in this system. The studies show that this could be a new method for assaying anti – *M. leprae* activity of various compounds by determining cholesterol metabolism in infected macrophages. The advantage of this drug screening system is that it can use macrophages derived from the mouse and a readily available lebelled compound ^{14}C-acetate or ^{14}C-Cholesterol and can be completed in 9 days. The method has been correlated with DOPA uptake method and by the mouse footpad method.

X/426(A) *IN VITRO* DRUG SCREENING SYSTEM USING MEMBRANE ALTERATION IN MACROPHAGES BY *M. LEPRAE*

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It has been shown earlier that macrophages from lepromatous patients in the presence of live *M. leprae* would induce changes in the membrane of the cell as monitored by the induction of reduced number of cells with surface receptors like Fc receptors for immunoglobulin, Con A receptors, etc. This property was demonstrable only with live *M. leprae* and host-specific macropohages. It was also shown that anti–*M. leprae* compounds could block this change in the macrophages.

Interestingly the same phenomenon could be demonstrated with macrophages from susceptible Swiss White Mice and *M. leprae*. The normal level of macrophages showing Fc receptors is reduced to less than 50% in the presence of live *M. leprae*. On the other hand if macrophages contained drugs like sulphone (dapsone) or rifampicin before *M. leprae* were added, then there is no reduction in the level of Fc receptor exhibiting macrophages. Bacteria derived from relapsed leprosy patients showed that they are not affected by dapsone and/or rifampicin, by reducing the macrophages with receptors, even in the presence of the drug. The test system correlates well with the mouse footpad method.

Some new compounds have also been tested using this method and thus this method appears to be a new drug-screening system. The entire test system can be completed within 9-10 days using macrophages from Swiss white mice and *M. leprae* from armadillo or human as per the requirement.

X/427(A) AN APPROACH TO LEPROSY CHEMOTHERAPY IN NERVE TISSUE

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The unique behaviour of *M. leprae* in associating with peripheral nerves suggests a relation between the special biochemistry of nerve and *M. leprae*. Since all nerve tissue derives from the neural crest, inducible enzyme pathways concerned with neurotransmitter substances may persist in peripheral nerve; also for myelin biosynthesis. Clear evidence from labelling studies showed that *M. leprae* is unique in incorporating DOPA. Recent studies of fresh biopsy suspensions in culture media indicate much enhanced growth of acid-fast becilli (Khera) with added cold DOPA. In nerves DOPA is converted to DOPAMINE by a decarboxylase enzyme similar to that which converts dihydroxy-tryptophane into serotonin; *M. leprae* may carry related enzymes according to a test with deoxy-fructose serotonin, which acted as an antimetabolite for *M. leprae* by our *in vitro* labelling test. Nerve cultures give additional evidence.

X/428(A) ACTIVITY OF RIFAMPICIN AGAINST *M. LEPRAE* IN THE CONVENTIONAL MOUSE

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To assess the experimental activity of rifampicin (RMP), 75 mice were inoculated with 5×10^3 drug-sensitive *M. leprae*. Six months later, at the plateau phase (mean 4×10^5 acid-fast bacilli/footpad) mice were randomly

allocated to the following 2-month regimens : control (15 mice), RMP six days a week (10 mice), RMP once a week (10 mice), RMP once a fortnight (10 mice), RMP once every 28 days (15 mice), RMP + prothioramide(PTH) + clofazimine (CLO) once every 28 days with daily dapsone (5 mice), and RMP once every 28 days with PTH six days a week and daily dapsone (5 mice). Drugs were given orally at the following dosages: RMP 10 mg/kg, PTH 25 mg/kg, CLO 40 mg/kg. Dapsone was given in the diet at a concentration of 0.01%. At different intervals, groups of 5 mice were killed, footpads pooled and serial ten-fold dilutions inoculated into 50 mice to assess the most probable number of surviving *M. leprae*. The lowest number of surviving *M. leprae* was obtained when RMP alone was given six times a week or when monthly RMP was combined with daily dapsone plus daily PTH or plus monthly PTH and CLO.

X/429(A) SULFONE LEVELS IN ARMADILLO PLASMA ON ADMINISTRATION OF DAPSONE IN FEED AND REPOSITORY DOSES OF DIACETYL DAPSONE

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The nine-banded armadillo is a major source of *M. leprae* bacilli and has great potential for studies on candidate antileprotic drugs. It was shown previously that armadillos acetylate dapsone slowly and hydrolyse acetyl dapsone when the drugs are administered orally. However, intubation or i.v. injection daily is too tedious for routine use. Administration of dapsone in armadillo feed at rates of 0.005 to 1.0% results in peak plasma levels of 0.37 to 16 ug of dapsone per ml and 0.08 to 4.5 ug/ml of acetyl dapsone. When diacetyl dapsone is injected i.m. as a repository dose (Hanselar) at a rate of 30 mg/kg body weight, total sulfone levels in plasma reach 65 ng/ml on day one, peak at 164 ng/ml on day 28, and decline to 30 ng/ml by day 168. Thus either oral administration in feed or i.m. injection of Hanselar can be used, depending on the level of plasma sulfones desired.

X/430(A) A SERIES OF NEW ANTILEPROSY COMPOUNDS DERIVED FROM SEROTONIN

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The initial interest in these compounds as potential antileprosy drugs stemmed from the observation that deoxyfructose serotonin, DOFS, (a normally occurring human metabolite of serotonin) inhibited the uptake of DOPA by *M. leprae in vitro*. From this slender *in vitro* lead, we have confirmed that DOFS, administered by mouth, is active as assessed by the standard mouse footpad technique. The result will be presented based on 5 strains of *M. leprae* (2 resistant to dapsone):- (1) All strains were equally sensitive to DOFS with a MED of 2 mg/kg body weight. (2) By the kinetic assay DOFS was bacteriostatic up to 20 mg/kg body weight. DOFS has very low toxicity (LD_{50} = 1200 mg/kg in mice *per os*).

More recently we have modified the structure of DOFS to produce more lipophilic compounds DFS-L_1(M.W. 535) and DFS-L_2 (M.W. 906). In hamsters these radio-labelled compounds achieve more prolonged and higher blood levels than DOFS. These 2 compounds are presently under test in mice and the results will be available for the Congress.

Pilot trials of DOFS in lepromatous patients are promising.

Production costs should be low; coffee-wax is a rich source of serotonin.

X/431(A) EFFECT OF DESOXY-FRUCTO-SEROTONIN AND RELATED SUBSTANCES ON THE GROWTH OF *M. LEPRAE* IN MOUSE FOOTPADS

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Preliminary studies have shown that Desoxy-fructo-serotonin (DFS) incorporated in the mice diet at a concentration of 20 mg/kg body weight inhibits the multiplication of *M. leprae* in the mouse footpad.

The findings of the mouse footpad studies with this compound, employing materials from 25 cases of LL, clinically suspected to be dapsone resistant, are presented. The result in 12 cases available so far, have indicated a suppression of the growth of six strains of *M. leprae* proved dapsone-sensitive. Of the six dapsone-resistant strains of *M. leprae*, DFS was found effective in only two cases.

In four of the above cases the effects of Desoxy-fructo-hydroxy-tryptophane (precursor of DFS) and a (2: 1) mixture of Desoxy-fructo-serotonin and Desoxy-fructo-5 hydroxy-tryptophane on mouse footpad growth have been studied. Both these formulations were found effective in suppressing the growth of dapsone-sensitive strains of *M. leprae*.

More recently the effects of some liposoluble preparations of DFS are being investigated. The available results will be presented.

X/432(A) PHARMACOKINETICS OF CLOFAZIMINE IN HEALTHY VOLUNTEERS AND ITS IMPLICATIONS FOR THE TREATMENT REGIMEN IN PATIENTS

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The pharmacokinetics of clofazimine were evaluated in healthy volunteers following single and multiple oral doses of clofazimine in form of 50 and 100 mg LAMPRENE capsules. The concentrations of clofazimine in plasma fitted to a two-compartment body model with an absorption and a distribution phase before reaching the slow elimination phase. The mean half-life of elimination of clofazimine, was 10 days.

After a single oral dose of 4 × 50 mg of clofazimine the peak concentrations of clofazimine in plasma were reached after 8 – 12 hours and ranged from 400 to 586 pmol/g when given to 3 fasting volunteers and from 434 to 783 pmol/g when given together with breakfast.

A linear relation between the dose and the area under the clofazimine concentration-time curve in plasma has been obtained from one healthy volunteer receiving 2 × 100 and 4 × 100 mg of clofazimine.

Concentrations of clofazimine in plasma were also measured during repeated daily oral administration of 50 mg of clofazimine for 8 days. The measured through concentrations and the concentrations in the elimination phase were in good agreement with predicted values.

The implications of the slow elimination half-life of clofazimine for the treatment regimen of patients will be discussed.

X/433(A) CLOFAZIMINE STORAGE IN MACROPHAGES OF *M. LEPRAE*

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Patients from Ostasia were treated *per os* with high doses of clofazimine, dapsone and rifampicin. When given orally, rifampicin triggers an enzym induction against its metabolites. Unfortunately, the improvement of these leprosy-patients is very low. Therefore we increased the dose of rifampicin to 300 mg/day. In a short time the well-known ichthyosis of the leprosy lesions was noticeable. In histological and especially in electronmicroscopic slides, we found lipoid-like vacuoles in macrophages of lepromas and also in Schwann and endothelial cells and smooth muscle cells. These vacuoles have a pattern resembling "Maltese - cross". In the same macrophages *M. leprae* could be detected. By means of chloroform and methanol, clofazimine was eluated. This drug could be verified with high pressure liquid chromatography. Clofazimine (and none of its metabolites) is present in the cytoplasm of cells containing *M. leprae*. We conclude that clofazimine plays an important role in the bacteriostasis of *M. leprae*.

X/434(A) HAEMATOXIC ACTIVITY OF DAPSONE

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Methaemoglobinemia and haemolysis are the most frequently reported adverse effects of dapsone. Methaemoglobin (MtHb) formation has been studied in four volunteers, who received dapsone in doses of 50, 100, 200, 300 and (in one case) 400 mg. Blood samples were collected at hourly intervals after ingestion during the first day, and MtHb formation was measured directly. Dapsone and MADDS plasma concentrations were determined by HPLC analysis. Depending on the amount of dapsone taken, peak dapsone plasma-concentrations were found 2-4 hr after intake, and maximal MtHb formation was reached 4-7 hr after intake. No correlation could be found between the plasma concentrations of dapsone and MtHb formation at any particular time, but excellent correlations are obtained, when for each volunteer maximal MtHb formation is plotted against peak dapsone plasma concentrations or against the amount of dapsone taken. Dependent on the volunteer involved an increase of 3-5% MtHb formation was found for each 100 mg dapsone ingested. On the basis of *in vitro* experiments with dapsone N-OH, an explanation for the results obtained may be given. The haemolytic activity of dapsone was studied in volunteers, who were given dapsone depot injections, containing 300, 600, 900, 1200 mg. Haptoglobin and haemopexin plasma-concentrations were used as parameters for intravascular haemolysis. Analysis of 31 dapsone depot injections showed a clear correlation between the decrease in haptoglobin and haemopexin plasma concentrations and the maximal dapsone plasma-concentrations obtained from the depot. These data are in agreement with measurement of low haptoglobin and haemopexin plasma-concentrations in leprosy patients, who are receiving multiple drug treatment, including dapsone.

X/435(P) MODE OF ACTION OF DAPSONE (DDS) IN *E. COLI* AND IN DAPSONE-SENSITIVE AND DAPSONE-RESISTANT STRAINS OF *M. LUFU, M. SMEGMATIS* ATCC 607 AND *M. LEPRAE* – A COMPARISON

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Cell-free folate synthesizing extracts have been isolated from *Escherichia coli*, dapsone-sensitive and resistant *M. "lufu", M. smegmatis* (ATCC 607) and *M. leprae*, and the inhibitory power of diaminodiphenylsulfone (dapsone,) in such cell-free systems on the synthesis of dihydropteroic acid has been determined. *M. "lufu", M. smegmatis* and *M. leprae* extracts show very similar high sensitivities against dapsone.Mode of action studies support the assumption that the observed high sensitivity of these mycobacteria as compared to *E. coli* can be solely attributed to a high affinity for the dihydropteroic acid synthetase. A dihydropteroic acid analogue formation where dapsone is incorporated instead of paminobenzoic acid – as has been observed in *E. coli* – could not be detected. Similar affinities are observed for the dihydropteroic acid synthetase derived from highly dapsone resistant *M. lufu* and *M. smegmatis*, indicating that the receptor enzyme has not changed. Possible other reasons for the development of resistance are discussed. Change in permeability of the cell-wall towards dapsone can be excluded.

X/436(P) A NEW APPROACH TO CELL CULTURE OF *M. LEPRAE* AND *M. LEPRAEMURIUM*

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In order to maintain the tissue culture cells infected with *M. leprae* or *M. lepraemurium* in good condition as long as possible, cycloheximide, an antibiotic specifically suppressive to the protein biosynthesis of eukaryotic cells, was incorporated in the culture medium. The antibiotic at a concentration of 0.1μg per ml in the medium delayed the division of tissue culture cells significantly but did not kill them. Serial increase in the number of *M. lepraemurium* with successful sub-cultures have been obtained in the cell culture with cycloheximide treatment.The infected cells seldom floated off the culture vessels and could be maintained in supporting the bacillary multiplication very well for ten or more weeks without changing the medium frequently. The intracellular bacilli often appeared in bundles arranged very close to each other and formed globi. The advantages of the cycloheximide treatment are that the technique is very simple, frequent changes of the medium are not needed,and the results obtained are highly reproducible. The growth of *M. leprae* however, has not been demonstrated yet in this cell culture system.

X/437(P) ON THE IMMUNOPHARMACOLOGICAL ASPECT OF ANTI-LEPROUS CHEMOTHERAPY

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Coincidentally with the fact that dapsone and clofazimine control some non-infectious exudative dermatitis and ENL, respectively, we recognized the following: dapsone inhibited exudative inflammations, but exacerbated adjuvant-induced arthritis. Clofazimine did not inhibit the exudations, but inhibited the arthritis. Dapsone depressed T-cell immunity of guinea pigs, but exhibited practically no influence on murine B-cell immunity. Clofazimine immunomodulatively suppressed their B-cell immunity, but potentiated their T-cell one. The potentiative effect of diethyldithiocarbamate on their T-cell immunity was also detected, though weakly. To moderate the immunodepression by dapsone and/or rifampicin, a polysaccharide (PSK) from *Basidio mycetes* or its further purified form (ATSO) was introduced. ATSO potentiated both of the T–and B–cell immunities. It was also weakly antiexudative. The results of a strong immunomodulator, Sensitizer Platonin and a mild one, disodium 4– chloro– 2, 2'–iminodibenzoate (CCA) will be reported to indicate a possible usage for controlling ENL.Although the findings do not overlook the intracellular antibacterial mechanisms of chemotherapeutics, it is suggested that in order to regulate the undesirable immunological influence of chemotherapy, the use of mild immunopotentiators or immuno-modulators (control of ENL) combined with chemotherapy is better than the present regimens.

X/438(P) EXPERIMENTAL THERAPY OF LEPROSY, WITH THE USE OF NOVEL RADIOMIMETIC OR BIOSTIMULANT LYSOSOMOTROPIC DRUGS

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We succeeded in reaching, killing and degrading Hansen's bacilli in the mouse footpad by means of three spontaneously lysosomotropic drugs also active in other infections and cancer.

One drug is composed of two enzymes inspired from oxidative lysosomes: a glucose oxidase (GLOX) plus a plant (HRP) or human (MPO) peroxidase. Its wide spectrum of *in vitro* parasiticidal activity would result from the formation of powerful radiomimetic entities. Local and simultaneous injectins of GLOX plus a peroxidase (HRP or MPO) was sufficient to significantly decrease the number of live and dead Hansen's bacilli in the footpad. Similar results were obtained after general administration of two biostimulant drugs with indirect action via the host defence system: Macrocyclon (non-ionic detergent) and yeast glucan (immunoamplifier polysaccharide).

Prompted by the recent recommendations of polytherapy in leprosy we studied each of the associations of these drugs, two by two. A significant tendency towards synergism was exhibited by the associations containing Macrocyclon.

Thus, five out of the six tested drugs or associations considerably reduced the ineffective biomass and the antigenic load of Hansen's bacilli in the mouse footpad.

X/439(P) THE *IN VITRO* STUDY OF NEW ANTILEPROSY DRUGS

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The search of new chemical compounds with antileprosy activity is one of the main objectives of the THELEP programme. As it is known, in recent years attempts of using cultures of *M. lufu*, isolated by Dr. F. Portaels in Zaire, have been made for *in vitro* screening of drugs inhibiting the growth of *M. leprae*. The present investigation is aimed at studying sensitivity, to main antileprosy drugs, of *M.lufu* grown on Shkolnikova's liquid semi-synthetic medium which is used for cultivation of *M. tuberculosis*, and also, with using this system,at selecting the drugs with potential antileprosy activity among new chemical compounds. For the study of drug sensitivity and screening new drugs, the method of serial dilutions was used with test cultures of *M.lufu*, kindly supplied to us by Prof. J.K.Seydel.The viability of *M.lufu* after exposure to some agent was also studied using Murohashi's stain and inoculation into Lowenstein-Jensen medium. It is stated that *M. lufu* is highly sensitive to dapsone, rifampicin, lamprene and ethionamide. Among the new chemical compounds screened, two drugs (coded N 202 & N 203) with potential anti-*M. leprae* activity, were selected. The data obtained were proved in the investigation, using Shepard's technique of inoculation into the mouse footpad.

X/440(P) MORPHO-FUNCTIONAL CHARACTERISTICS OF CELLS IN CULTIVATION OF LEPROMA TISSUE

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For the purpose of establishing a model for *in vitro* screening antileprosy activity of chemotherapeutic drugs, tissue blocks from skin lepromas of LL patients and *M. leprae* infected armadillos were cultivated in special chambers. "Creeping out" of cellular elements from the explant was noted after 7 days of cultivation. They represented single round macrophages with bean-like nuclei. By 10-12 days the number of macrophages was increased, most of them took elongated fibroblastoid form with ovoid nuclei; single and aggregated giant cells with a large number of nuclei (upto 20-30) in the centre appeared. All the macrophages including giant cells contained a large number of acid-fast mycobacteria, massive clusters of which were located extracellularly as well. By 12-15 days, a large number of lymphocytes was noted, located diffusely and in the form of rosettes around the macrophages. On the periphery of the macrophage zone the capsule of fibroblasts with no mycobacteria was formed. The correlation between the number of fibroblasts in leproma tissue and in the culture was noted. Cytochemical investigation of leprous macrophages showed a high activity of succinate, glucose-6-phosphate and, in lesser degree, lactate dehydrogenases as well as of l-naphthyl-acetate esterase. In fibroblasts there was marked activity of succinate – and glucose – 6 – phosphate dehydrogenases with no activity of lactate dehydrogenase and l-naphthyl acetate esterase.

X/441(T) LIVER INVOLVEMENT AND HEPATO-PROTECTIVE ROLE OF INDIGENOUS DRUG LIV-52 IN LEPROMATOUS LEPROSY

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The present study incorporates a study of 42 cases of lepromatous leprosy for hepatic involvement and role of an indigenous herbal preparation in protecting the liver. The liver was enlarged in 32 cases and tender in 8 patients. Alteration in liver functions irrespective of extent and duration of the illness (3 months to 10 years with mean duration of illness of 2 years 5 months) was mainly seen as uniform elevation of serum proteins (6.2 – 9.2 gm%, mean = 7.5 gm%) with hypoalbuminaemia (2.0–4.4 gm%, mean = 2.9 gm%). Highest level of serum bilirubin of 1.6 mg% was detected in 6 cases, emphasising the presence of leprous hepatitis. Raised levels of serum

transaminases (SGOT–65.2 IU, SGPT–78.7 IU) were proportionate to the liver and muscle involvement.

Presence of charcteristic granulomata in the liver around the central vein, periportal area and even distribution at various locations in the liver lobules was the most significant change in 12 out of 15 liver biopsies. Acid-fast *M. leprae* were demonstrated in 12 patients.

The present work emphasises the detection of hepatic involvement in the early stage of the disease and hepato-protective role of indigenous drug Liv-52 in lepromatous leprosy.

X/442(T) THE MECHANISM OF ACTION OF ANTILEPROSY DRUGS IN RESPECT OF PHAGOCYTOSIS

A.A. Rezaev, N. Ya. Ryzhova.
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The influence of antileprosy drugs on the levels of oxidative-reduction processes in mycobacteria-containing tissues (lepromas) of rats infected with *M. leprae* previously adapted to animals, was studied. In lepromas both aerobic and anaerobic processes are increased with predominance of the first. A month's administration of sulphetron results in a moderate inhibition of aerobic metabolism, but a longer administration (3 months) causes a levelling off and some activation of anaerobic glycolysis. Sulphetron in combination with rifampicin or prothionamide within a short time significantly activates aerobic processes without obvious anaerobic changes. With high levels of aerobic processes, a more rapid and marked destruction of mycobacterial cells and complete degeneration of lepromas occur. It is suggested that high levels of aerobic processes promoting the capture phase of phagocytosis activate aerobic metabolism and favour a change to anaerobic metabolism leading to complete phagocytosis.

SESSION XI

PATHOLOGY

Chairman: Ridley, D.S.

Rapporteur: Languillon, J.

THURSDAY, 23RD FEBRUARY, 1984

Commission Hall 'H' 13.00–16.30

Abstracts

A* : 443-456
P* : 457-467

*A : accepted for reading
*P : for poster presentation.

XI/443(A) VENOUS INVOLVEMENT IN PATIENTS OF LEPROSY

Ashok Mukherjee, B.K. Girdhar, G.N. Malaviya, R.S. Misra.
Institute of Pathology, I.C.M.R., New Delhi, India

The involvement of medium-sized subcutaneous veins in leprosy patients has been studied. 65 patients (38-LL and 27 BT) had a 1 cm. long vein resection and skin biopsy performed under local anaesthesia. Histopathological examination showed involvement in 34 out of 38 cases in the LL group and in only one out of 27 in the BT group. LL's showed a pan-phlebitis with predominant intimal involvement. Vacuolar transformation of endothelial cells was seen in early cases and complete occlusion by granuloma in advanced cases. The BT case showed epithelioid cell granulomas in the intima and adjacent media. Bacilli were seen in LL's (Ridley 4-5+) in intimal, medial muscle cells and in histiocytes. Electron microscopy confirmed that lumen lining bacillated cells are endothelial cells and not pavemented macrophages. Both solid and granular bacilli and inclusions possibly of bacterial origin were seen in the endothelial cytoplasm. The medial muscle cells showed little cytoplasmic reaction to the pressence of bacilli.

A high (89%) incidence of phlebitis in LL's and high B.I. in the endothelial cells suggest veins as good sites for persistent bacillaemia. Extensive involvement of the venous channels emphasizes the importance of the vasogenic route in granuloma formation in LL.

XI/444(A) HISTOLOGICAL ALTERATIONS IN THE CUTANEOUS VESSELS IN DIFFUSE LEPROMATOUS LEPROSY

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In nodular lepromatosis the vessels of the skin suffer considerable structural and functional damage as has been demonstrated by several authors. Amongst the most frequent microscopic alterations cited is the presence of *M. leprae* in the endothelium of the arterioles, venules and capillaries; in the larger vessels, the bacilli are found not only in the endothelial cells but also in the membranes of the vessel and frequently there is infiltration of the sheath.

Keeping this in mind we have carried out a comparative study of the alterations observed in nodular lepromas and in diffuse lepromatous leprosy with the Lucio phenomenon. The histological modifications are substantially the same in both forms of leprosy, only in diffuse lepromatous leprosy with the Lucio phenomenon there are also polymorphonuclear infiltrations around the capillaries, venules and arterioles of the papillary and subpapillary plexus. In the small and medium sized vessels of the deep dermis and the hypodermis, obliterative changes are frequent.

XI/445(A) SYNOVIAL SWELLINGS OVER WRISTS IN LEPROSY

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Central Jalma Institute for Leprosy, Tajganj, Agra, India

Soft cystic swellings are noticed in leprosy patients during the course of the disease. The commonest site for these is the dorsum of the wrist but at times they are seen over the dorsum and the lateral aspect of the ankle as well. Such swellings were investigated.

Such swellings were seen throughout the spectrum of the disease. On exploration they are found to contain straw coloured clear fluid. They appear to arise from the synovial covering of the extensor tendons of the wrist and fingers; they may be either unilocular or multi-locular, and have communication with the wrist joint. Histology of the membrane reveals epithelioid cell granuloma in some. Tests for immune complexes in the synovial fluid revealed nothing significant.

XI/446(A) VISCERAL LESIONS DURING EPISODES OF REVERSAL REACTION

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One can accept that patients with borderline leprosy, when not treated, may progressively assume similar characteristics to those observed in lepromatous leprosy (downgrading). Once the specific treatment is established, those patients (apparently lepromatous) may develop reactional episodes with borderline characteristics (reversal reaction, upgrading). Those episodes may be accompanied by symptoms such as neuritic pains, paresis, articular pains, oedema of extremities. However in practice there is no reference in the literature concerning visceral involvement along with this outbreak of borderline skin lesions. In 4 autopsies performed in apparently lepromatous patients, we observed extensive neural, cutaneous, articular and visceral involvement by epithelioid cell granulomas with borderline characteristics. The distribution of the visceral granulomatous involvement varied from case to case; however, the viscera usually affected in lepromatous leprosy appeared to be heavily involved. All those patients died with intense aggravation of the general condition not related to any intercurrent disease. It is possible then that the cause of death is related to the generalized granulomatous involvement. In lepromatous leprosy, there are macrophagic granulomas spread in the viscera without compromising the general condition of patients, but it is possible that the epithelioid-cell granulomas present a greater capacity for tissue aggression justifying the bad evolution in the cases studied.

This conclusion indicates the bad prognosis.

XI/447(A) HISTOPATHOLOGICAL STUDY ON PERIPHERAL NERVES, LYMPH NODES AND VISCERAL ORGANS IN VARIOUS TYPES OF LEPROSY

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Department of Pathology, Zhongshan Medical College, Guangzhou

This report includes results from 103 autopsies of different types of leprosy, biopsies of peripheral nerve tissue from 210 tuberculoid leprosy, cases and inguinal lymph nodes from 106 cases of different types of leprosy.

1. The lesions in peripheral nerve of all types were most commonly found in the ulnar (85.7% in T type, 98.3% in L type), peroneal (77.8% in T type, 97.9% in L type), median (80% in T type, 90.2% in L type), radial (66.6% in T type, 82% in L type), great auricular, tibial and supra-orbital nerves.The ratio of bilateral nerve involvement was higher than unilateral involvement (approximately 5:1). Lesions of the peripheral nerve ganglion as seen in L type (22 cases, 61.1%) and T type (8 cases, 53.3%) are infrequently mentioned in the literature.

2. Superficial lymph nodes were most commonly affected in all types of leprosy, and the lymph nodes in the hepatic splenic and portal area might be involved in lepromatous or borderline cases. Lesions in lymph nodes bet-

ween two polar types of leprosy showed a gradual transformation of a spectrum-like pattern which was similar to the lesions in the skin. This reflects the variability of the immunological state in the host in various types of leprosy.

3. In lepromatous leprosy, lesions could be found in 85.3% in the liver, 41.1% in the spleen, 86.7% in the test is, approximately 50% in the upper respiratory tract (including 36.4% in the nasopharynx), 34.4% in the adrenal gland. 3 cases had ophthalmologic lesions. In borderline leprosy, biphasic lesions of leprosy were found in various internal organs. We consider the development of hepatic cirrhosis in some patients might have a definite connection with lepromatous lesions of the liver.

4. We divided the various lesions shown in each type of leprosy into 3 different stages i.e. progressive, regressive and quiescent. We found in some cases the regressive changes of the lesions in viscera or peripheral nerves were remarkably slower than those in the skin lesions.

5. The most common causes of death in our 103 cases were: tuberculosis (23.3%), acute pulmonary infections (14.6%), various hepatic diseases (11.6%), and cancers (9.7%). Only one case died from renal insufficiency due to severe renal amyloidosis.

XI/448(A) LEPROSY AND LIVER

Huberto Bogaert, Denis Martinez, Bertha Saleta, Luis Aquino
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We report the liver alterations found in 30 patients with lepromatous leprosy and 10 with dimorphous Leprosy (LL and BL). We made a complete medical examination including liver function tests and punction biopsy. Of the patients with lepromatous leprosy, 10 had received a treatment for one year; 10 from 1 to 5 years and 10 more than 5 years.

XI/449(A) NASAL BIOPSY FINDINGS IN PRIMARY NEURITIC LEPROSY

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Nasal biopsies were obtained from 25 patients with primary neuritic leprosy who had no evidence of skin involvement by clinical and smear examination. The diagnosis was confirmed by nerve biopsies in all cases. The changes in the nasal mucosa ranged from non-specific chronic inflammation to nerve inflammation with *M. leprae* present. In five nasal biopsies, lepromatous involvement of the nasal mucosa was seen with macrophages containing numerous acid-fast bacilli.

The significance of these findings in the evolution of primary neuritic leprosy will be discussed.

XI/450(A) SIGNIFICANCE AND INTERPRETATION OF NERVE CHANGES IN SKIN BIOPSIES WHEN PRESENT IN ASSOCIATION WITH COMMON DERMATOLOGICAL CONDITIONS

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Scheiffelin Leprosy Research and Training Centre, Karigiri, Tamil Nadu, India.

Nerve changes and inflammation are the signs justifying a histopathological diagnosis of leprosy. These changes have not been described in any of the other common dermatological conditions other than prurigo nodularis.

This paper reports the experience in SLR & TC, Karigiri of the follow-up of patients with nerve changes that are suggestive of leprosy when seen in biopsies of common dermatological conditions but have no clinical evidence of leprosy. Lupus vulgaris, secondary syphilis, lichen planus and morphoea are some of the conditions in which in addition to histological features of the presenting clinical picture nerve changes are sometimes seen.

Karigiri is an endemic area for leprosy and this paper evaluates the significance of these nerve changes in relation to:

1) Concurrent early leprosy.
2) Spill over effect and influence of dense surrounding inflammation and chronic irritation in producing nerve changes.
3) Dermatological conditions in which these nerve changes are seen and which pose problems in histopathological diagnosis.

XI/451(A) FINGERPRINT STUDIES IN LEPROSY PATIENTS AND THEIR CONTACTS

Sonia Maria Rocha De Almeida, Maria Eugenia Noviski Galloe, Noeli Rodrigues de Oliveira
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The fingerprints of 300 patients belonging to the different forms of leprosy were investigated and alterations in the patterns were found in all.

The present fingerprints of some of these patients were compared with the patterns of the fingerprints existing in the files of the "Instituto de Identificacao Felix Pacheco" and taken at the time of civil identification years ago.

Contacts were also included in this study for the detection of alterations, if any, present in the patterns of the fingerprints.

The data obtained are analysed and some conclusions are drawn.

With this technique we think that:

1– The susceptible population could be identified and selected;

2– The minimum probable time of incubation could be determined;

3– The disease could be detected at the subclinical stage;

4– This method could be used for establishing if the disease is really in remission and as one more criterion for clinical discharge.

XI/452(A) A STUDY OF DERMATOGLYPHICS IN LEPROSY

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Central Jalma Institute for Leprosy, Taj Ganj, Agra, India

A group of 100 leprosy patients consisting of 50 TT/BT and 50 LL/BL were investigated for finger and palmar configurations. Hundred normal persons were also investigated to serve as controls. The study was undertaken in families in which at least one person was normal and was taken as a control. Control group was age and sex matched.

No statistically significant difference was observed when the patterns present on the fingers of tuberculoid leprosy patients were compared with those of controls. In lepromatous leprosy patients loop ulnars were less ($P<0.05$) whereas loop radial ($P<0.001$) and loop twin ($P<0.05$) were more as compared to those of controls.

Meteric analysis of intertriradial intervals a–b, b–c, c–d, perpendicular on 'ad' from axial triradius 't' ($\perp$ ad) and angle 'atd' of palms of leprosy patients and controls were done.

It was observed that LL/BL patients differ from controls in the following patterns:

Right Palm : Intertriradial interval b–c ($p<0.05$) and a–d ($P<0.01$) were more in patients as compared to controls.
Left Palm : Intertriradial interval a–d was more in patients than that of controls ($P<0.001$)

On the other hand, no difference was observed between TT/BT patients and the controls.

XI/453(A) SUBCUTANEOUS CALCINOSIS OF LEPROSY PATIENTS DUE TO CHAULMOOGRA OIL INJECTION

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A specific type of subcutaneous calcinosis was observed in leprosy patients who had been treated with chaulmoogra oil injections. This specific calcinosis was present in the proximal part of extremities where chaulmoogra oil was injected, and it was palpable as a subcutaneous globular induration. Serum P and Ca levels of the patients were within normal limits. None of the patients who did not undergo this treatment developed this type of calcinosis. The calcification was considered to be secondary to the tissue damage due to the chaulmoogra oil injection.

X-ray diffraction of this calcification from one of the patients revealed that it consisted of calcium phosphate (or apatite) and a smaller amount of calcium oxalate. This specific type of calcinosis can easily be differentiated from other types of calcinosis seen in leprosy patients, by means of the clinical and radiological findings.

XI/454(A) FURTHER OBSERVATION ON ULTRASTRUCTURE OF HISTOID LEPROSY

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In this article, 4 cases of histoid leproma (HL) occurring in different forms of leprosy were studied by TEM in connection with clinical manifestations and the histopathological pictrure. Two of them were examined by SEM. The results were as follows:

The cellular components of HL were similar to those described formerly. They were more typical in lesions of less than 6 months, predominantly consisting of fusiform macrophages. Leprosy bacilli were largely of solid form. Some of them were dividing. The proliferation of macrophages was remarkable. Therefore it was supposed that the pathogenesis of HL was closely related to the rapid multiplication of *M. leprae*. However, the typical feature remained for a certain period only, while in lesions lasting for

more than a year, many foamy macrophages and disintegrated bacilli were revealed. Some of the bacilli were found in lysosomes. Cellular proliferation was less remarkable. The reason for this feature is discussed but needs further investigation.

No significant ultrastructural differences were found between HL occurring in BL and LL, in dapsone-resistant and non-resistant cases, or in early and relapsed cases. The ultrastructure of the bacilli in dapsone-resistant cases studied by SEM and TEM was similar to that in non-resistant cases.

The ultrastructural changes of Langerhans' cell (LC) in 4 cases were observed. The main findings noted were : diminution of their processes, widening of the spaces between LC, and keratinocytes surrounding them. It is worthy of further study to determine whether LC participates in the pathogenesis of HL.

XI/455(A) DO THE SUBPOLAR TUBERCULOID CASES EXIST? CLINICAL AND HISTOPATHOLOGICAL STUDY OF 50 CASES

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Subpolar tuberculoid cases (Tsp) have been defined as unstable, low resistant, potentially contagious with no spontaneous healing and with the possibility of running through the immunological spectrum towards the lepromatous pole by means of downgrading reactions.

Trying to identify these cases, 50 leprosy patients classified as tuberculoid were studied clinically and histopathologically. From the clinical point of view, the following data were taken as suggestive of Tsp; numerous lesions, symmetry, persistence without treatment as well as neural damage. Histopathologically the study has emphasized the number of lymphocytes, epithelioid and giant cells, infiltration of small nerves and the epidermotropism of the infiltrate.

The conclusion of our study is that although there are some clinical evidences for the existence of Tsp cases, on the contrary, there are not enough histophathological data to permit the differentiation of Tsp from polar T cases.

XI/456(A) THE HISTOPATHOLOGICAL EXAMINATION OF SKIN BIOPSIES FROM AN EPIDEMIOLOGICAL STUDY OF LEPROSY IN NORTHERN MALAWI.

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Histopathological findings in skin biopsies in a total population survey in the Karonga District of Northern Malawi will be described. Using a 3 or 4 mm disposable punch, an attempt has been made to biopsy suspicious or doubtful lesions, as well as those newly diagnosed as leprosy on clinical grounds. From a total of 448 biopsies, 225(50%) showed definite evidence of leprosy and these were classified (Ridley–Jopling scale) as follows: TT – 32 (7% of total biopsies); TT/BT – 54 (12%); BT – 112 (25%); BT/BB – 3 (0.6%) BB – 4 (0.8%); BB/BL – 3 (0.6%) BL – 6 (1.3%); BL/LL – 3 (0.6%) and LL – 4 (0.8%); 4 cases (0.8%) were histologically Indeterminate. Sixty-seven (15%) showed pathological changes (mainly epithelioid granulomas), possible due to leprosy, but lacked specific criteria for diagnosis. The remaining 156 cases (35%) showed other dermatological conditions, or were non-specific.

Very few problems were encountered in the taking of biopsies, fixation, despatch by airmail or processing. Interpretation was aided by the full depth of all biopsies, resulting in the inclusion of a lower dermal nerve in many instances. This study provides the first comprehensive series of biopsies from leprosy suspects, based on a total population survey, in this part of Africa. Its implications for the histopathological pattern of leprosy in this part of the world will be discussed.

XI/457(P) EPITHELIOMA CUNICULATUM IN A PLANTAR ULCER

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A case of Epithelioma cuniculatum which is a rare type of verrucous epithelioma peculiar to the foot was found in a leprotic man on top of an old perforating plantar ulcer.

It is presented as a rare type of epithelioma occurring as a new complication for leprotic plantar ulcer which is not reported before to be complicated by any epitheliomatous changes.

XI/458(P) THE PATHOGENESIS OF THE SKIN LESION IN LEPROSY – WITH APPLICATION OF THE PERIODIC ACID-CARBOL PARAROSANILIN AND THE PERIODIC ACID-METHENAMINE SILVER STAIN.

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We have examined leprosy skin lesions of varying types with periodic acid-carbol pararosanilin and periodic acid-methenamine silver stains.

In the infection, the target organ is the Schwann cells. There may be two paths for the subsequent spread of bacilli: (a) from the Schwann cells of terminal (distal) nerves proximally to the same large nerves and (b) from the nerves to be distributed to surrounding tissue macrophages; via blood vessels, the bacilli may disseminate to be phagocytosed by the Schwann cells of other nerves and become distributed to surrounding macrophages.

Therefore, leprosy could be classified according to the bacillary distribution as silent, neural localized and disseminated.

Epithelioid transformation of macrophages and true granuloma formation are characteristic of human tuberculosis. In leprosy this is not true for all types of leprosy. Schwann cells showing epithelioid change have the ability to destroy the organism in tuberculoid, borderline and reversal reactions. In contrast, in lepromatous leprosy, the organisms are engulfed by Schwann cells and macrophages, which have a marked deficiency in their ability to destroy the organism.

In old cases, lymphocytes accumulate around nerves; in contrast, there are no lymphocytes in lepromatous cases.

Epithelioid transformation of macrophages is not seen in all types of leprosy.

XI/459(P) COMPARISON OF GRANULOMAS IN NERVES, SKIN AND LEPROMIN INJECTION SITES IN LEPROSY PATIENTS

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Skin and nerve biopsies were obtained from leprosy patients encompassing the entire spectrum. Modified Dharmendra antigen was injected intradermally at three sites behind the earlobe in another group of patients and normals. Biopsies were collected sequentially on 3rd, 10th and 21st post-injection days. IgG, IgM, IgD, IgA and the BCG cross-reacting components of *M. leprae* were studied by direct peroxidase and PAP technique; subpopulations of T cells and Dr antigens were examined using monoclonal antibodies.

Inflammatory exudates were examined and compared in both tissues with emphasis mainly on cellular reactions in or around dermal nerves. The localization of bacillary antigens in tuberculoid skin and nerves, particularly those demonstrating caseous nerve abscesses. The study also contributes towards delineation of reaction patterns in responders and non-responders to lepromin.

XI/460(P) EVALUATION OF CLINICO-HISTOLOGICAL CORRELATION IN THE CLASSIFICATION OF LEPROSY.

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102 cases of leprosy were studied clinically and histologically according to Ridley's scale: clinical and histological correlation was seen in 70.5 per cent cases. Ninety-one cases were Punjabis.

Of these, 63 cases were suffering from maculoanaesthetic leprosy; they were studied clinically and histologically according to Ridley's scale and correlation was observed in 74.6 per cent. Ridley's scale is therefore applicable in all types of leprosy. Maculo-anaesthetic leprosy should not be included in Tuberculoid, since some of these are Borderline lepromatous.

New and interesting clinical features were seen in eight Punjabi patients with bilateral glove-and-stocking anaesthesia and minimal skin infiltration. Clinical diagnosis was lepromatous-infiltrative, but histology report was three I, 4 BT and 1 BL.

Another interesting feature was the presence of large haemorrhagic bullae. In one patient, bullae were present on the hands and feet, and left deep ulcers and scars on healing. In another case there was sudden onset of generalised anaesthesia with widespread bullae on pressure points. This type of vasculitis in leprosy has not been reported so far.

Skin biopsy helps to determine the immunological status and the classification where specific tests are not available.

XI/461(P) RENAL INVOLVEMENT IN LEPROSY

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Renal involvement in 25 lepromatous and 25 non-lepromatous patients was studied by routine urine analysis, detailed biochemical investigations and renal histopathological study. The patients in whom renal tissue was not obtained were excluded. There was reversal of albumin-globulin ratio in lepromatous and non-lepromatous leprosy patients, more so in lepromatous cases. Creatinine clearance was reduced in 9 lepromatous patients and

2 non-lepromatous patients. Two patients had frank uremia. Renal biopsies were studied with special reference to evidence of leprosy, the presence of acid-fast bacilli and of amyloid deposit. Amyloidosis was seen in only one lepromatous patient. No acid-fast bacilli were demonstrated and no leproma-like lesion was seen in any case. Pathological features of nephritis of various types was seen in 40% of lepromatous and 12% of non-lepromatous cases. The follow-up of patients is continuing.

XI/462(P) MODELS FOR LEPROSY

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The lack of models for the behaviour of different diseases is probably due to an unconscious assumption of a general linear progression model for all diseases. However, many diseases, like leprosy or syphilis, have a non-linear behaviour pattern. The spectrum concept which dominates current thinking on leprosy is *par excellence* a linear concept. Graphic representations of this concept are critically examined as models for this disease, and not surprisingly, it is found that leprosy in real life deviates considerably from the predicted consequences of assumptions necessitated by the spectrum metaphor. It is evident that the linear logic of the spectrum concept is inadequate to describe the pattern of behaviour of leprosy in an individual.

An alternative three dimensional model selected from one of the simpler models of Catastrophe Theory (a branch of Topology in Mathematics), known as " Cusp Model" is found to describe the known behaviour of leprosy reasonably well. Unlike the spectrum models which are static and have very little information content, the Cusp model is a dynamic predictive model allowing for a variety of disease behaviour, like linear (continuous) and non-linear (discontinuous) progression, divergence (similar lesions progressing to different states under same conditions of change), and bimodality (manifesting as one of two different states under certain conditions). The Cusp model, though speculative (and probably too simple), provides a new insight into the behaviour of leprosy in an individual and appears rich in possible use in research and therapy.

XI/463(P) THE DISTURBANCES IN CATECHOLAMINE AND CYCLIC NUCLEOTIDE BALANCE IN MYCOBACTERIOSES AND ACUTE INFECTIONS.

N.K. Pervukhina, V.S. Burkin, L.A. Vinnick, Yu.V. Pervukhin, K.I. Nazarov, V.S. Sergeev.
Leprosy Research Institute, Astrakhan, U.S.S.R.

A comparative assessment of the sympathetic-adrenal system (SAS) state and some markers of cell immunity (concentrations and ratios of catecholamines (CA) and cyclic nucleotides (CN), cAMP, and cGMP, in urea, blood plasma and lymphocytes and the intensity of LTT) in patients with mycobacterioses (lepromatous leprosy, tuberculosis) and acute intestine infections (dysentery, "abdominal fever", alimentary toxo-infections) indicate disturbances in compensatory reactions and adaptative capacities of the patients. The long and rather benign course of the mycobacterioses was accompanied by activation of SAS with predominance of its sympathetic component, while in early acute intestine infections as well as in exacerbations, relapses and complications of leprosy and tubrculosis, the adrenergic component prevailed. In acute dysentery, the decrease, in activity of T-lymphocytes with preserved function of B-cells is accompanied by high lymphocytic levels of cAMP. In the mycobacterioses, B-lymphocytic function is preserved while T-cell activity is sharply decreased. cAMP levels in lymphocytes from the patients with mycobacterioses is decreased in parallel with normal (in tuberculosis) and increased (in leprosy) levels of cGMP that seems to be due to insufficient antigenic stimulation or to peculiarities of cell metabolism. The data obtained suggest the necessity of correcting the disturbed balance of CA and CN in the pathogenetic therapy of the patients.

XI/464(P) OBSERVATIONS ON THE NASAL MUCOSA IN TUBERCULOID AND LEPROMATOUS LEPROSY

Lata Mehta, C.J. Heather, M.J. Ridley, N.H. Anita.
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10 leprosy patients including 1 TT, 2BT, 1BB, 1 BL and 5 LL with infection from 1 month to 18 years were studied. Selected material was studied by light microscopy, immunoperoxidase semi-thin sections and by electron microscopy.

Two types of epithelial cells, clear or dark cells were observed in tuberculoid leprosy. Bacilli were present in nerves. Blood vessels were severely altered and lymphocyte infiltration enhanced. Changes in the basal lamina were notable, with oedema and exudate cells being prominent features. This was different to the appearances in LL where the basal lamina was atrophied and bacillary numbers high. Lysozyme was increased so also Igs but other inflammatory mediators were not detected. Cells similar to dendritic cells were seen by electron microscopy.

The findings are discussed in their importance in nasal immunity in leprosy.

XI/465(P) CLINICO-HISTOLOGICAL CORRELATION BETWEEN DIFFERENT TYPES OF LEPROSY

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For classifying leprosy – clinical, bacteriological, immunological and histological status are ideally correlated. Investigational facilities being meagre, leprosy is mostly classified and treated clinically in India. It is advocated that investigational facilities being made available, field workers may derive benefit, as close correlation is said to exist between clinical and other features. We investigated 270 leprosy cases to assess this assumption.

Results:
From 270 cases receiving a sulphone drug, 250 satisfactory biopsy specimens were classified and subsequently correlated with the clinical classification. The indeterminate, TT, BT, BB, BL and LL types of leprosy were clinically and histologically 5 and 82, 138 and 38, 27 and 30, 7 and 45, 12 and 30, 61 and 25 respectively. Clinically 199 were polar type; 63 being proved histologically. Histologically 82 and 105 cases were in the indeterminate and intermediate groups; clinically these being only 5 and 46. Polar and other groups presented clinicopathological correlation in 12% and 25% instances only.

Conclusions:
Indeterminate and intermediate forms, having nonspecific histology outnumbered the polar types which have specific histology. This histological conversion may be a result of treatment with sulphones, as observed by Khanolkar (1959).

An observed low clinicopathological correlation indicates that even when investigational facilities are available in under-developed countries, clinical assessment deserves priority.

XI/466(P) THE NATURE OF INFILTRATING CELLS IN CUTANEOUS LESIONS OF LEPROSY.

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Dermal lesions from 23 patients representing the full spectrum of leprosy were studied. The nature and quantities of inflammatory cells and their bacteria were determined by immunoflourescene and transmission electron microscopy.

The cutaneous infiltrates of patients with lepromatous leprosy (LL and BL) contained predominantly parasitized foam cells with large multibacillary vacuoles. Evidence of phagosome lysosome fusion was obtained. Intact and partially degraded *M. leprae* surrounded by an electron-lucent halo and embedded in an amorphous matrix were always found within membrane-bound vacuoles.

Only small numbers of scattered lymphocytes were found, mostly of the Leu 2a/OKT8 T-cell subset. In borderline patients (BL and BB) smaller numbers of bacilli were found in smaller vacuoles within macrophages. An increase in the numbers of lymphoid cells specifically of the Leu 5a/OKT4 T-cell subset was observed. At the tuberculoid pole of the spectrum (BT and TT), large numbers of T-cells with extremely long and complex filipodia were found closely associated with epithelioid and multinucleated giant cells. Many of the mononuclear phagocytes appeared non-viable and areas of necrosis were evident.

Eighteen months of treatment reduced the bacterial load and the numbers of cells in the cutaneous infiltrates. The numbers and relative frequency of the T-cells and their subsets appeared not to be affected.

XI/467(P) PORTAL OF EXIT OF *M. LEPRAE* THROUGH INTACT SKIN

Periaswamy V.
Gandhi Memorial Leprosy Foundation, Wardha, India

It has been accepted that *M. leprae* can exit through ulcerated skin of bacteriologically positive cases of leprosy. Investigations done by Periaswamy (1968) and Hameedulla (1982) revealed that *M. leprae* may be discharged from the intact skin also. The question arises as to how the bacilli from the dermis are transported to the surface of the intact skin.

There seem to be three probable routes through which *M. leprae* can come to the surface of intact skin, namely, ducts of the sweat glands, sebaceous glands and through hair-follicles. Sections stained for AFB showed that bacilli were not seen in the sweat and sebaceous glands. The possible route therefore, is the hair follicle. Hair follicles revealed *M. leprae* some-

times in clumps, not only in the sheaths of the hair follicles but also between the sheath and the shaft. The bacilli lying in the space between the sheath and the shaft are those liberated from the sheath and these get mixed up with the sebum and are carried by it to the surface.

XI/468(A) MORBIDITY IN LEPROSY – AN ATTEMPT AT A QUANTITATIVE STUDY

E. Vomstein, J. Kirubakaran, M.S. Nilakanta Rao
Leprosy Relief Rural Centre, Settipatty, South India

In this paper an attempt is made to analyse the morbidity in leprosy patients. Morbidity in this context means a deviation from a state of physical and mental well-being due to leprosy.

In chronic diseases like leprosy it is difficult to compute the morbidity status in the individual or community. However an attempt is made to work out figures which show the loss of man days, the deprivation of socio-economic status and psychological distortions. This analysis is made to show the loss of physical and mental stature of the patient.

For this purpose an equal number of patients belonging to the three major types of leprosy are selected at random and an analysis of the information during a period of ten years is made.

Even though it is well known that the patient is a loser on all fronts, quantification of the loss is seldom made. This paper aims at stimulating such studies which are likely to prove beneficial in greater understanding of a patient's sufferings and thus help in restructuring our approach to alleviate such sufferings.

SESSION XII

SOCIAL ASPECTS (A)

Chairman: Antia, N.H.

Rapporteur: Saylan

FRIDAY, 24TH FEBRUARY, 1984

Auditorium 08.30–12.00

Abstracts

A* : 468-483

SOCIAL ASPECTS (B)

Chairman: Askew, A.D

Rapporteur: Elzawahry

FRIDAY, 24TH FEBRUARY, 1984

Auditorium 13.00-16.30

Abstracts

A* : 484-498
P* : 499-502
T* : 503-510

*A : accepted for reading
*P : for poster presentation.
*T : for title reading.

XII/469(A) HEALTH EDUCATION – THE MASTER KEY TO LEPROSY ERADICATION

Margaret Owen
Leprosy Education Programme, Patna, Bihar, India

"The Leprosy Education Programme for Bihar" was a three year project of the Leprosy Mission. Its aim was to give widespread publicity to all sections of the medical profession and the general public. A small full-time team, led by an experienced doctor, was well equipped with suitable audio-visual aids.

METHODOLOGY was based on "Leprosy Weeks" in the main towns; 66 were visited, some several times. Fullest cooperation was given by health and administrative officers. Government paramedicals often staffed the exhibition, which was open to the public, while the team went out with entertaining programmes to schools, colleges, factories and villages. Two or three meetings would be held every day, especially for doctors, nurses, teachers and clubs.

FINDINGS: Leprosy education can be a popular programme. The purpose of creating awareness of leprosy as an ordinary curable disease was well fulfilled. Estimated attendances – Exhibitions 900,000, Special meetings 270,000. Many gained knowledge and understanding; some lost their fear; many more patients began treatment; many more doctors are treating leprosy. The stigma is reduced.

RECOMMENDATIONS: Similar Leprosy Education programmes providing entertainment as well as education should be run in each state.

Now story films, omitting the old scenes of leprosy and giving hope and ecouragement should be prepared.

HEALTH EDUCATION can be the MASTER KEY to open the door for leprosy eradication.

XII/470(A) IMPORTANCE OF RADIO AND TELEVISION IN THE DETECTION OF CASES OF LEPROSY

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Instituto Dermatologico Dominicano, Santo Domingo, Dominican Republic

The authors consider that the Radio and Television provide important channels of communication for the health education of the community in the matter of leprosy. It can make available information concerning the early symptoms of the disease and its treatment. Well oriented, full and continuing education of the public, through the radio and television may persuade people to seek medical help in good time. The results obtained will be reported; we showed during one year, four commercial television shows of 20 seconds length through five TV companies of the country and four radio emissions of 25 seconds length in 35 broadcasting stations in the whole country. Both commercials were made by a technical team in publicity and medical personnel of the programme.

XII/471(A) ON THE IMPORTANCE OF THE TEACHING OF LEPROSY AT THE NATIONAL UNIVERSITY OF SOMALIA R.D.

Khalif Bile Mohamud, Cumar Yusuf Hashi, Giovannia Tarabini-Castellani.
National University, Faculty of Medicine, Mogadishu, Somalia R.D.

The lessons derived from teaching of leprosy in the National University of Somalia, which we began in 1975, are the following:

1. A great interest in leprosy among the 4th year students. The teaching involved 20-24 hours of classwork including practical exercises. The students sit for an examination at the end of the course.

2. Training in epidemiological surveys and immunological measurements : the final year students are encouraged to pursue their studies and submit a thesis on some aspect of leprosy.

We have found that, as a result of our programme

1. Students become expert at making the diagnosis of leprosy and young physicians continue their good work in the hospitals and district consulting-rooms where they are appointed;

2. They are continuing their researches into an evaluation of the evidence for cell mediated immunity by studies of post-lepromin scars and of the conversion of lepromin-negative subjects by means of a mixture of lepromin A and BCG:

3. They contribute actively in epidemiological research with particular responsibility in primary and secondary schools.

Some of our former students have been appointed to important positions in the Ministry of Health.

Since 1982, we have undertaken a close collaboration between the University and the Ministry of Health since our principal teacher is also the leprosy expert at the Ministry and the Chief of the National Leprosy Control Programme is his Chief Assistant. It is apparent to all that teaching and the Control Programme work well together.

XII/472(A) THE IMPORTANCE AND VULNERABILITY OF SOCIO-CULTURAL FACTORS IN THE CAMPAIGN AGAINST LEPROSY.

Francis Girardin
Damian Foundation, Brussels, Belgium

A sociological research programme was undertaken in Togo – West Africa, studying 300 patients receiving intermittent treatment in the rural and urban areas. The study dealt with detection of the disease, the method of detection and the regularity of treatment. The results obtained showed how important the family environment is in the choice of treatment procedures (recourse to official health services or traditional healing methods); they also went to

prove the impact of socio-economic conditions on the regularity of treatment. The obstacles, whether socio-cultural or socio-economic, appear difficult to overcome. It is, however, possible to adapt the methods by which medical care can be implemented to local conditions. This, of course, requires a profound knowledge of the area and the standard of living of the patients. Recourse to the social sciences then becomes a necessity. Putting into practice the results obtained through research requires also that medical personnel be aware of the sociological aspects and capable of creating a sympathetic relationship with the patient.

In the final analysis, an improvement in the performance (which is poor at the moment) of the campaigns against leprosy can only be obtained at the cost of an increase in the quality of health care. The repercussions of this observation on the recommended strategies of a campaign against leprosy are discussed in the paper.

XII/473(A) STIGMA IN LEPROSY

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Department of Anthropology, University of Poona, Pune, India

A large number of leprologists and social scientists are attracted to the study of stigma in leprosy for obvious reasons. This area, comparatively little known, has been subjected to careful social science investigations on the basis of empirical data and presented in this paper.

The case study approach was employed involving the use of multiple techniques – interview schedules, informal interviews, depth interviews, probes, repeated contacts, participant – and non–participant observations.

Two tahsils of Poona district, Maharashtra State, India, were selected and 42 villages were completely covered under the study. In all, 110 case studies were built-up with all the data that could be gathered by the author. For doing so, the author personally contacted 632 people including the family members of the patients, their neighbours, relatives, friends and others from the villages. The data were then analysed systematically treating each case separately.

An attempt has been made to identify the causes of the social stigma in leprosy. The factors that lead to the emergence of varying degrees of stigmatization have been discussed in the light of factual data gathered from the field. The existence of a transitory phase in the process of exclusion of the leprosy patient from his social setting has been revealed. Finally, the stigma theory has been explored in the case of leprosy.

XII/474(A) EXPERIENCES OF ACCEPTANCE AND REJECTION AS FUNCTIONS OF HANSEN'S DISEASE, PERSONALITY FACTORS AND AGE

N.S. Chauhan, Upinder Dhar, Sheelendra Singh
Institute of Advanced Studies, Meerut University, U.P., India

Acceptance *vs.* rejection is one of the most important dichotomous dimensions of sociogenic needs, crucially determining the homeostasis of 'being' and remaining a contingent condition for growth or development of the social self. Acceptance promotes worth recognition and status. Rejection is aggressive exclusion with a feeling of hate and condemnation. This is an *'ex-post facto'* study having a 'Multigroup control group-Randomized' design. The two experimental groups are those of lepromatous and non-lepromatous patients. The control group relates to disease-free normal people. The study has '3 × 3 × 2' trivariate factorial experiments: four for the study of acceptance scores and four for rejection scores.

Hansen's disease elements are drawn from the Central JALMA Institute for Leprosy (Agra) and its Kusht Seva Sadan. Normal elements are freely drawn from the town population. Data are collected with the help of standardized tools. The final sample consists of 360 elements for each one of the eight experiments.

Results of the study show that personality factors and age, under the impact of Hansen's disease, exhibit four types of role variation i.e. role restriction, role reversion, role negation and new role resumption. The Hansen's disease in the process of overpowering personality ingredients not to play normal roles is less serious about 'acceptance *vs.* rejection' than 'identification *vs.* differentiation' dimension of sociogenic needs. The disease through its 'anti roles' works as an alien sub-system to demote acceptance satisfaction and to promote rejection experience as it does in case of identification *vs* differentiation. The findings are discussed in detail for each disease type, personality factor and age level.

XII/475(A) HANSEN PATIENTS IN A MILIEU OF SYMBOLIC "LEPERS" ON IGNORANCE, PREJUDICE AND SELF-PREJUDICE

L.Meisels-Navon
Tel-Aviv University, Israel

The research focusses on the decisive role of the institution for the treatment of leprosy in the shaping of society's and patients' attitudes towards the disease and demonstrates this by analysing the institutional social treatment policy at the Hansen Hospital, Jerusalem, which favours concealing the patients from public consciousness and changing the name "leprosy" to "Hansen's Disease".

The description of the findings follows the indentity-acquiring process of the patient, who comes to the institution from a world where - owing to the successful concealment policy of the institution – the stigma appears mainly in a symbolic form: the "leper" has become a stigmatizing symbol, disconnected from actual reference to "leprosy patients". In the institution the patient receives a double message: he is given the identity of a "Hansen patient", affected with a disease like many other diseases, but receives hints, interpreted by him as stigmatizing. Upon his release he hardly meets with actual stigmatizing reactions and nevertheless, as a result of the ambivalent message received at the institution, he develops a self-prejudice.

The findings show that one should not always accuse the outside world of prejudice, and stress the need for examining the message transmitted by the institution and for eliminating prejudices among patients. The paper clarifies the difference between ignorance and prejudice and proposes suggestions for an improvement of the institutional social treatment policy, which is relevant also for countries where the stigma bears a different character.

XII/476(A) MIGRATION AND LEPROSY CONTROL

Sister Senkenesh Gebre Mariam,
ALERT, Addis Ababa, Ethiopia

The rapid growth of the urban population presents a challenge to the control of leprosy; this problem has been investigated at ALERT's OPD under these six headings:

1. *Classification of Human Movement:* Short-term, long-term and permanent migration.

2. *Characteristics of Migrants:* Sex, age, education, occupation and disability grades.

3. *Reasons for Migration:* Push/pull factors, i.e. the forces which encourage the individual to leave his place (push), and those which attract him to the new place (pull).

4. *The Processof Migration:* Selection of destinations, distances, stages of migration.

5. *Process of Adjustment:* Presence or absence of social support. The role of leprosy settlements in the adjustment of the newcomer.

6. *Care of Displaced Leprosy Patients:* Patient/staff interactions, patients' treatment behaviour; policy of the institution towards this group and the effect of new approaches on the patient.

Method of Data Collection: All patients who expressed their unwillingness to return to their places of origin after diagnoses were referred to a special clinic set up for the needs of the group. Data were collected at the initial interview by means of a questionnaire. Subsequent changes in their life situation were recorded during the patients' monthly visits to their clinic.

XII/477(A) LEPROSY THE MOSLEM ATTITUDE

Haidar Abu Ahmed
Leprosy Control Programme, Ministry of Health, Khartoum, Sudan

Leprosy is a disease well known for its serious stigma. Inspite of all the scientific information available today about leprosy, the fear and the prejudices regarding leprosy and leprosy patients remain ingrained and persistent. In many societies leprosy is associated with guilt, rejection and isolation. These concepts were no doubt influenced by religious beliefs, local traditions as well as by the pathology of the disease.

It is known that disease control activities are not likely to be effectively carried out without an understanding of the values and beliefs of the communities affected. This is more evident in leprosy where there is an indigenous etiology for the disease in every country. It is lamentable that in most control programmes these important social and psychological aspects of the disease are overlooked and emphasis is laid only on early detection and treatment. Failure to appreciate the importance of the social and psychological factors has resulted in the failure of otherwise well conceived control programmes.

There is no reliable information about the Moslem veiws about leprosy. The beliefs, attitudes and practices prevailing in most of the Moslem countries and thought to have religious origin are in fact not so, but are the outcome of a complex of indigenous traditional beliefs. Most of these beliefs antedate Islam and are thus unrelated to real Islamic teachings.

An attempt is made to give the Moslem views about health and disease in general and the specific attitudes towards leprosy and the leprosy patient. These are mainly derived from findings in the Holy Qura'an and the Prophet's saying "HADITHS" and the historical perspective. This information, it is hoped, will be of help to leprosy patients, their communities and the leprosy workers.

XII/478(A) SOCIETY AND LEPROSY: PHILIPPINE EXPERIENCE: SOME PRELIMINARY NOTES

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The integration of the social sciences and pure sciences has long been a global interest but very few have attempted to work on this existing gap in the field of research. This limitation is the predisposing factor behind the conceptualization of this on-going investigation. This paper seeks to correlate the medical aspects (causation, transmission, symptomatology and treatment) of leprosy with the psycho-socio-linguistic facets (beliefs, knowledge, attitudes and practices) of the disease. The respondents for this study are divided into three sets, namely, the patients, the critical informants (who are unrelated to the patients but are occupying key positions in the community). Of the 213 respondents, 96 come from Barangay Guimod, Ilocos Sur while 117 come from Tala, Novaliches. An analytical comparison of the data have, so far, yielded results stressing poverty-related circumstances as the major cause of leprosy prevalence in these areas. It has also been shown that the respondents have overlapping notions of causation and transmission, and of prevention and treatment. These and the rest of the preliminary findings suggest that the present leprosy control programs be equipped with a stronger, concrete psycho-social foundation for greater efficiency.

XII/479(A) FOUR YEARS EVALUATION OF THE INTEGRATED SYSTEM IN THE MANAGEMENT OF LEPROSY IN-PATIENTS AT THE DR. SOETOMO PUBLIC HOSPITAL, SURABAYA

Indropo Agusni, Sunarko Martodihardjo, Mochammad Ibeni Ilias
Yayasan Kusta, Surabaya, Indonesia

The integrated system in the management of leprosy in-patients has been introduced in the Department of Dermato-venereology, Dr. Soetomo Public Hospital since 1978. An integrated care of leprosy in-patients means the admission of these patients together with non-leprosy cases in one ward without any differences in the medical care and services, and involving multi-departmental assistance if needed.

The aim of this effort is to support the idea that leprosy patients are no longer to be segregated and should be treated together with non-leprosy patients. The results of the treatment of 262 leprosy patients (154 male and 108 female) hospitalised in the Dermatological ward during the period August 1978 to August 1982 are reported.

The problem of leprosy stigma and the improvement of mental attitude of the personnel involved in this project are discussed. It is observed by experience that the selection of patients and priority to young people are important in the early steps of conducting the integrated system. Also a continuous motivation to the personnel involved in this work seems to be beneficial.

XII/480(A) LEPROSY POLITICS AND HUMAN RESOURCES-ACHIEVEMENTS AT NATIONWIDE LEVEL IN BRAZIL

Neusa Nunes da Silva e Goncalves, Aguinaldo Goncalves
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As a proposal for the formation and development of the control of endemic leprosy in this country was being elaborated, specific health steps within an hierarchic and integrated pattern of health services, we detected a real qualitative and quantitative lack of human resources in this area, as one of its serious bottlenecks.

Starting from this, the authors developed during 1982, at nationwide level, a systematic plan based upon the resources of the administrative and executive organs of Health Departmental System.

The experience consisted of the setting up of a scheme of encouragement and support to these departments for local level training; at regional level, four post-graduate courses were organized, through the National Department, in Amazonia, Mid-West, South and Southeast. The strengthening and or development of a referral system at state level were reached through the National Course of Clinical Dermatology; international qualifications were obtained,as a complement to joint action with the Pan-American Organization of Health.

This question is presented and discussed, emphasizing the basic points of examination of the whole situation, objectives, principles and strategies. The results obtained are presented in tabular and graphic form. They show the decisive roles of the student body coming from a network of services and universities, as multiplying and analytical agents of the proposed question and inserted into the whole context of the health field in Brazil.

XII/481(A) A STUDY OF THE BURDEN EXPERIENCED BY THE FAMILIES OF LEPROSY PATIENTS

M. Balasubramaniam, T.B.B.S.V. Ramanaiah, U. Sabesan, A. Koteeswaran, M. Rajasakthivel
National Institute of Mental Health & Neuro Sciences, Bangaloře, India

Since the dawn of mankind, leprosy has been considered as a separate disease entity and the patient is exposed to many stresses and strains due to uncongenial atmosphere in the family, and misconception and belief prevailing in the public.

Medical treatment alone does not alleviate the problems of the leprosy patients. The therapy has to be extended to their families on a broader perspective such as psycho-socio-cultural-economic areas.

An attempt is made in this direction to explore the burden experienced by the families of leprosy patients. A sample of 200 leprosy patients attending the Skin Department of the Government Rajaji Hospital, Madurai, was compared with an equal sample of patients with chronic skin problems like eczema and psoriasis, by administering the Family Burden Interview schedule covering such areas as: financial burden, disruption of routine family activities, disruption of family leisure, disruption of family interaction, effect on physical health of others and effect on mental health of others.

Data are collected, results discussed and few suggestions are made in the light of the findings.

XII/482(A) PATIENTS' UNDERSTANDING OF LEPROSY: A SERIES OF ACUTE DISORDERS

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Patients and medical practitioners employ different cognitive systems to understand and explain sickness. Medical anthropological studies have shown that conflicts between patient's and practitioner's explanatory systems can lead to problems such as poor compliance.

Illness beliefs of 61 leprosy patients at the McKean Rehabilitation Institute in Chiang Mai, Thailand, were assessed by Kleinman's Explanatory Model Format. This elicits patient's notions of etiology, labelling, appropriate treatments, and expected outcome. The patients used a wide variety of theories of etiology, and employed different lebels which often were associated with particular symptoms within the clinical spectrum of the disease. Leprosy was infrequently understood as a single chronic disorder. More commonly , it was perceived and experienced as a series of acute disorders which were not necessarily related to one another. The various theories of illness were instrumental in directing treatment choices, which often included therapies other than modern chemotherapy.

Despite the association between "leprosy" and "leprosy hospital", some patients at follow-up visits considered themselves to have new and unrelated problems. Patient education at follow-up visits should be given with the same concern for defining the problem and negotiating therapeutic goals as when the patient was first diagnosed.

XII/483(A) PSYCHOLOGY OF SENSORY LOSS

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Because the sensory system is among the first to myelinate, the fetus begins to respond to tactile stimulation approximately eight weeks after conception. Touch is our most developed sense at birth. Much of our response to our environment is determined by experience gained through touch. Recent studies in psychology show that touch continues to be extremely important, particularly in social interaction, throughout our lives.

Primate studies reveal that severe socialization problems arise when infant monkeys are not allowed to touch their mothers or peers. Deficits in neurological developments have been noted in tactically deprived infant monkeys. Human studies with institutionalized children and adults show that touch can improve their perception of a social situation and improve their willingness to socialize. With Hansen's Disease, sensory loss often results. To determine this effect 100 Hansen's Disease patients were interviewed. Their environment becomes more threatening and injury seems to arise spontaneously after sensation has been lost. Also, the Hansen's Disease patient's perception of his society changes with sensory loss. With sensory loss, the perception for the need for medical care is reduced in both patients and physician. An awareness of this insidious problem can help in more effective treatment of the effects of the disease.

XII/484(A) PSYCHOSOCIAL STRESS IN HANSEN'S DISEASE : A COMPARISON WITH PATIENTS WITH OTHER CHRONIC DISEASES.

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Stress has been shown to affect a variety of variables related to patients' responses to illness (e.g. susceptibility to disease, exacerbation of symptoms, compliance with medical regimen, etc.). The purpose of this project was to determine whether persons with Hansen's Disease experienced greater or less psychosocial stress than did persons with other chronic illnesses (e.g., arthritis, diabetes, etc.) or those persons who have no known illnesses. To measure stress in medical patients, most investigators have relied on checklists which indicate a frequency of stressful life events,as well as allow patients to rate their subjective experience of these events. The present study used such a checklist, as a measure of stress. Four groups, each with twenty subjects,were compared using the Life Events Survey:

1. Institutionalized patients with Hansen's Disease,
2. Patients with Hansen's Disease who were treated as outpatients,
3. Outpatients with chronic illnesses other than Hansen's Disease, and
4. Individuals with no known diagnosis of chronic illness.

Groups were equated for age, sex and language. Results suggest that institutionalized patients perceive themselves as having less stress than non-institutionalized individuals. In addition, stress levels reported by outpatients with Hansen's Disease closely resembled those reported by other chronic illness patients. Results are discussed in terms of their implications for the comprehensive care of persons with Hansen's Disease.

XII/485(A) PSYCHIATRIC MORBIDITY IN PATIENTS WITH LEPROSY

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Psychiatric morbidity in 200 untreated cases of leprosy was assessed. An equal number of patients with other skin problems was included as controls. Present-state examination was conducted to assess the morbidity. Depression and anxiety were the commonest findings in these patients. A correlation of these findings with the type of leprosy, the duration of the disease, the presence of deformities and the socio-economic status of these patients was made. The relevance of these findings, the prevention and management of these problems will be discussed.

XII/486(A) CAUSATIVE FACTORS FOR TREATMENT DROPOUTS IN A PUBLIC LEPROSY CLINIC

A. Koteeswaran, T.B.B.S.V. Ramanaiah, M. Balasubramaniam, N. Rajasakthivel, P. Jeyasingh
Madurai Medical College, Madurai, India

The major problem in a leprosy clinic is treatment dropout. Though sufficient regularity of treatment is emphasized, the patients do not abide by it due to various reasons.

The defaulter may develop severe physical deformities and also create problems to the "significant persons

To explore the causes for non-adherence to treatment, a sample of 150 patients attending the Leprosy Clinic of the Government Rajaji Hospital, Madurai, was studied. The patients are randomly selected,based on the following criteria:

(1) those patients who were asked to come for follow-up and who did not turn up for four consecutive sessions.

(2) those who have not taken any medical treatment during this period

(3) those who live within the corporation limits of Madurai city and its suburbs.

An interview schedule covering the areas such as family and financial aspects, level of knowledge and misconceptions about leprosy, opinion about the treatment and the hospital personnel was administered during home visits. They are compared with an equal number of regular attenders.

The two groups are compared and results discussed.

XII/487(A) SOCIAL ASPECTS OF LEPROSY CONTROL WITH SPECIAL REFERENCE TO REHABILITATION

R.S. Sharma,
Maharogi Sewa Samiti – Dattapur, Wardha, India

The reason why the progress towards complete control of leprosy in a large part of the world has been rather slow largely lies in the fact that the social aspects of the problem are not yet equally and effectively tackled along with the medical aspect. Massive, well-planned and organized efforts towards total rehabilitation-physical, economical, social as well as psychological – of its victim is therefore called for. The ultimate solution lies in completely overcoming rehabilitation which could be achieved through an extensive programme of mass-education, measures to prevent deformities, adoption of appropriate legislative measures and solving the problem and social evil of beggary. Till this is achieved, a massive programme of rehabilitation both institutional as well as domiciliary, to cover the entire dehabilitated population is necessary. Institutional rehabilitation should aim towards a total development of personality of its inmates through cooperative community work and living to achieve economic self-sufficiency and generation of self-confidence in addition to proper treatment. The Dattapur Leprosy Home embodying the philosophy and approach along Gandhian thought could be adopted as a successful model. Such institutions should not only adopt an integrated programme of hospitalisation and treatment, rehabilitation training and mental, spiritual and psychological development, but should link and integrate their total activity with the general programme of national reconstruction and social regeneration.

XII/488(A) EXPERIENCES IN ORGANIZING A HANDICRAFT WORKSHOP FOR THE ECONOMIC REHABILITATION OF PHYSICALLY & PSYCHOLOGICALLY HANDICAPPED FROM LEPROSY AND OTHER DISEASES

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Hubli Hospital for the Handicapped, Hubli, India

Many solutions exist to reintegrate the underemployed and the unemployed leprosy patients back into society.

At our institution, production of handicrafts was used as another method for economic resettlement. Handicrafts were produced both at a central workshop as well as in the homes of patients. No handicapped person stayed in hospital, once trained. Physically handicapped from leprosy, unemployed lepromatous patients and those handicapped from other causes were selected for training.

Method of organization – Stages:

I. *Research & Development*
   1. Designing a product that the individual could produce.
   2. Training supervisors to handle training and quality control.
   3. Establishing markets.

II. *Expansion:*
   1. Increasing the number of trained workers and their production capacity
   2. Reaching self-sufficiency.

Results:
1. 145 items have been identified needing the skills of 3 or 4 workers.
2. The markets are both local and foreign.
3. Sales increased from Rs.4,500 in 1976 to Rs. 689,000 in 1982, achieving self-sufficiency.
4. From 12 trainees in 1976, the number increased to 54 in 1982 of whom 27 were working at home and 17 at the workshop.

20 more are undergoing training. 16 of the 54 have physical handicaps from other diseases.

The inputs needed for further development of this idea will be discussed.

XII/489(A) LEPROSY THROUGH PRIMARY HEALTH CARE

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The experience of integration of leprosy into a general health programme based on primary health care in 30 villages covering a population of 30,000 will be described emphasizing how the problems of early detection of cases, regular treatment, stigma and rehabilitation have been tackled by the village health worker within the community.

XII/490(A) PEOPLE'S PARTICIPATION IN LEPROSY CONTROL

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There is a growing realization in the leprosy field that technological advances alone will not solve the problems, unless we succeed in involving the people in the eradication programme. But public participation too often, is wrongly understood as their participation on the lines we lay down, giving little chance to people to decide how and why they should participate.

The Gandhi Memorial Leprosy Foundation adopted a new approach in its Balarampur Control Unit by leaving the function of health education entirely to local persons who command the trust and confidence of the local rural people. Leprosy workers did no health education in that area.

The manner in which these persons were identified, the way they were given orientation in leprosy and in the problems of leprosy patients and the modus operandi of their working are discussed in the paper.

The period of this experiment is too short to draw conclusions but the initial response received through voluntary reporting, increased regularity and people's initiative in giving protection to leprosy patients from in-

stances of social harrasment are discussed in the paper. It is thus clear that if the problem is taken to the people and the initiative left to them to tackle it in their own way, the results are better and longer lasting.

XII/491(A) COMMANDOS AGAINST LEPROSY IN MEXICO–PRIVATE EFFORTS IN THE LEPROSY COMPAIGN

Roberto Arenas
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The campaign against leprosy in Mexico is accomplished through an official programme having dermatological centres and mobile units. The large area of the country renders the detection and control of patients very difficult.

The Mexican Association for Action Against Leprosy founded by Dr. R. Latapi has organized the "commandos against leprosy" which are administrative and tactical bodies made up of dermato-leprologists, local workers and physicians undergoing training in leprosy. These commandos travel to certain regions of the country and actively work against leprosy in several ways: they give free dermatological consultations; they visit the homes of leprosy patients, and offer health education. New cases are discovered by these activities and known patients are brought under control.

These activities are partly achieved with the support of the "Association Francaise des Fondations Follereau", whose president is Mr. A. Recipon.

The results of these activities during 1981-1983 are presented.

XII/492(A) THE SOCIAL REHABILITATION OF LEPROSY PATIENTS

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The problem of social readaptation of leprosy patients necessitated by recent advances in chemotherapy and physical rehabilitation, calls for radical changes to leprosy of society as a whole and much help on the part of governments.

The main legislative enactments concerning the rehabilitation of leprosy patients in the USSR are the following: free hospital and outpatient treatment; provision for disabled patients of prosthetic appliances and orthopaedic footwear; monthly allowances or disability pensions; reimbursement of travelling expenses connected with visits to antileprosy institutions; allowances for discharged patients; immediate provision of housing and help in employment. With regard to the employment of leprosy patients, it is necessary to avoid factors that would aggravate the course of the disease, such as: very cold temperatures, hard manual labour, long business trips that might interfere with regular treatment. For the effective social rehabilitation of leprosy patients, training of medical personnel, and educating patients and the general population about leprosy control – all these are of great importance. Writers and publicists play a real part in social rehabilitation of leprosy patients, emphasizing the achievements of modern medical science in the fight against leprosy in their writings.

XII/493(A) SOCIO-ECONOMIC FACTORS OF THE MIGRATORY PROCESS AND THEIR INFLUENCE ON THE PREVALENCE RATE OF LEPROSY IN THE STATE OF ACRE (AMAZON REGION) BRAZIL

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A retrospective study was undertaken in order to verify the influence of the migratory process and the associated socio-economic factors on the high prevalence rate of leprosy (10.0%) in the State of Acre (Amazon Region) Brazil. Historic documents, primary and secondary sources of information were collected on the beginnings of populating the area of this State (1877-1928). Special questionnaires have also been used to interview leprosy patients, fifty or more years old, including questions on their ancestral relatives with information about the localities they have lived in the past. They were applied on a sample of 138 leprosy patients of the State of Acre and on a sample of 228 leprosy patients of the State of Ceara (prevalence = 0.8%) situated in the North-Eastern Region, from which many batches of emigrating people have run away in the drying weather periods and have reached the Amazon Region for extracting caoutchouc from native trees.

After socio-epidemiological analysis the Author points out the socio-economic factors of the migratory process which have basically influenced the transmission of leprosy as a result of international and national forces of capitalism system in the exploitation of natural rubber in the Amazon Region of Brazil.

XII/494(A) THE ISLES SAW IT AND FEARED: LEPROSY'S IMPACT ON THE HISTORY OF HAWAII

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The history of leprosy in Hawaii presents the opportunity for a comprehensive study of the interaction between leprosy and society over virtually the full course of an epidemic. This history can be divided into five different eras.

The first (1866-1910) was a time of fear and hopelessness that drove those suffering from leprosy into hiding. The second (1910-1929) saw great strides in scientific knowledge of leprosy. The widespread use of chaulmoogra oil brought hope to the situation. Despite great improvements at the Kalaupapa Settlement, to the patients the third era (1930-1945) was "the dark age of leprosy". Hope in chaulmoogra oil had faded and leprosy was again regarded as incurable. The fourth era (1946-1968) witnessed repeated debates over the need for isolation and saw the discovery of a cure for leprosy. It was a time of renewed hope and long overdue change. The fifth era (1969-present), when outpatient treatment is the norm, has its own set of problems as changing immigration patterns result in an increase in new cases. The Kalaupapa Settlement has been declared a National Historical Park and attention is increasingly being focussed on the previous four eras because it is realized that there is much to be learned from them.

XII/495(A) DEVELOPING EFFECTIVE LOAN STRATEGIES FOR REHABILITATION FOR LEPROSY PATIENTS

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Leprosy is more than a serious worldwide medical problem. Persons affected by leprosy, in addition to the need to adjust to physical disability, may find themselves ostracized by the communities in which they live. Thus, it is important to emphasize the rehabilitation of the leprosy victims as well as the detection and treatment of the disease itself.

Clearly, the optimal strategy for rehabilitating leprosy patients is one which permits them, in so far as possible, to re-enter the social and economic mainstream of their local community as productive citizens. However, such strategy, while optimal may be very difficult to implement on a widespread basis.

One strategy that can be used to reintegrate leprosy patients into society is to provide them with loans to help them establish income-generating businesses. To be successful, however, a loan programme must fulfil at least two important objectives. First, it must develop effective criteria for identifying "good" risks among potential loan recipients. However, the primary aim of a leprosy rehabilitation programme is to render assistance to deserving individuals.

A leprosy rehabilitation programme must therefore endeavour to fulfil a second objective, namely, to convert persons who are "bad" risks into persons who are "good" risks. To achieve this objective, the loan programme will need to train and deploy its staff in order to provide adequate counselling and supervision of loan recipients.

It is only by developing a sound loan strategy – one which is capable of identifying loan recipients and in addition is capable of providing adequate counselling and supervision of less promising recipients – that social reintegration of leprosy patients can be implemented on a wide scale.

XII/496(A) REHABILITATION THROUGH SELF-EMPLOYMENT SCHEMES

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The objective of this paper is to study the rehabilitation of cases through self-employment schemes. Patients who were provided socio-economic rehabilitation during the period from 1979 to 1982 were included in the study.

In a country where unemployment is one of the major problems, self-employment ventures could help to provide a decent living. It is more suitable for leprosy patients who find it difficult to secure a job in Government or in private firms because of the stigma attached to the disease. For such persons, self-employment is a suitable method of business for their economic rehabilitation. Self-employment means that the particular line of business or activity which is appropriate to the environment (after taking into account the strengths and weaknesses of the person concerned and his environment), and which would offer a satisfactory source of income to the person.

This study analyses the various socio-economic and vocational factors of the patients before the disease, during treatment of the disease and after rehabilitation. The findings have been correlated with medical factors.

By rehabilitation, the patient's family ties are strengthened and his status and self-respect in the community restored.

XII/497(A) LEPROSY REHABILITATION AND RESETTLEMENT PROGRAMME

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Rehabilitation, including treatment, training and health education is a continuous process for leprosy patients, but often depending on the poor environmental and socio-economic conditions, it cannot be implemented effectively in urban areas. Hence, the alternative of voluntarily shifting the patients and the family for limited period to a Rehabilitation and Training Centre, where their follow-up and care can be ensured under proper supervision. It has been found that over a four-year period the following measures are necessary to produce successful results: 40 resident families, 50 patients are trained and employed.

a) Medico-social evaluation
b) Job description and training
c) Employment opportunities and job replacement
d) Sheltered or self-employment schemes
e) Domiciliary care of the aged and disabled

Resettlement is essential as patients must be integrated as useful members of society either into rural communities or absorbed into urban employment. The Sumana halli society has been able to resettle 12 families in various rural areas on a self-help, co-operative basis. Single individuals and selected families have set up small business units with bank loans while others have obtained employment in Government or local undertakings. SHRTC remains as a centre from which trainees move out in a small family groups to various locations, where their changed attitudes, improved knowledge and skills can be utilized for the benefit of society.

XII/498(A) GLOBAL LEPROSY CONTROL – IMPACT OF NEW IDEAS AND PRIORITIES

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Leprosy is a serious Public Health Problem of Third World Countries affecting nearly 15 million persons, and 1.5 billion people run the risk of contracting it. A quarter of the patients have physical disabilities and are often prone to unnoticed injuries. Nearly a quarter of the victims are children and majority of the patients are young adults.

Against this backdrop, we take a review of the global efforts to control the disease and help the sufferers.

Bio-Medical research has given more knowledge of the bacteria, mode of transmission, host response, social and economic factors keeping up the infection, newer ideas of therapy and possibility of primary prevention.

These will be discussed in detail with reference to the need to inter-relate this programme with wider actions of Health Promotion, Social Education and Economic improvement.

If we can collect enough comprehension and goodwill and apply technology to control leprosy, we will not only make the world a happier place to live in but will also leave a good example for the posterity.

XII/499(P) MOTIVATIONAL EDUCATION IN LEPROSY OF HIGH SCHOOL STUDENTS THROUGH HAND BILLS

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Hind Kusht Nivaran Sangh, Hyderabad, India

Hand-bills create little interest among the literate. However, in developing countries, if deployed for a proper group at a proper time in combination with an immediately following quiz contest carrying attractive prizes, it may serve well to induce the desired change of awareness at a cheaper cost.

On Anti-Leprosy Day 1983, with the co-operation of District Leprosy Officers, all the 10th class students of their districts were given a carefully prepared hand-bill on leprosy, including brief items which are of importance in control. Entry forms for the contest were made available from the following day. The students were asked to choose only one answer which was scientifically correct from among the 2-4 alternatives given at the end of each of the twelve statements (sentences) and were asked to complete the last part. Ten days were allowed for submission of entries through their headmasters. The District Leprosy Officers, after correcting the entries, furnished the number of students choosing each of the alternative answers to the (12) statements (sentences), without knowing that the figures would be analysed.

It is proposed to discuss the relevance of the answers to the handbill, and to evaluate the effectiveness of this method.

XII/500(P) INFORMATION AND EDUCATION ABOUT LEPROSY

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Thesis:
Information and education about leprosy must be incorporated into a general education programme. We have reached this conclusion following upon the introduction of the international leprosy emblem.

Status quo:
Leprosy is still considered as the depths of destitution and cannot be acknowledged as a generally accepted disease.

Means of attaining the goal:
Healthy people, especially those who are reponsible for education, must take an interest in the leprosy problem.

Our new series of informational leaflets, designed to be interesting for all, treats the subject of leprosy in a matter-of-fact and incidental way. At one and the same time the leprosy emblem is made known and spread as a symbol of trust and sympathy.

Young people will thus be made interested in the leprosy problem and they will provide the demand for more information.

A concerted campaign through all educational media should then follow and all educational and informational materials concerning leprosy should be made clearly recognizable by displaying the leprosy emblem.

Thus, will the ground be prepared for the sowing of the "seed of enlightenment".

Changing the status quo:
Potential leprosy sufferers of the future will be saved.

The fear of leprosy will be removed.

The treatment of leprosy will thus be incorporated into the general health programme.

The AHM proposes to display a poster series and a leaflet series in English, French, Spanish and German at the International Leprosy Congress.

We enclose the first poster in this series.

XII/501(P) ADJUSTMENTAL PROBLEMS OF LEPROSY PATIENTS

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Like most chronic diseases, leprosy may cause disability and prevent the patient from participating in normal social and working activities, and intertere even with his everyday activities.

It is obviously important to be aware of the adjustmental problems of the leprosy patients; a study was therefore undertaken to find out the adjustmental problems of 200 leprosy patients attending the Skin Department of the Government Rajaji Hospital, Madurai, and they are compared with an equal number of normal people by administering the Adult Form of the Bell's Adjustment Inventory which provides 5 separate measures of personal and social adjustment, viz., home adjustment, health adjustment, social adjustment, emotional adjustment and occupational adjustment.

The results are discussed.

XII/502(P) A STUDY OF ARREST AND RELAPSE OVER THREE DECADES IN A CONTROL UNIT

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Gandhi Memorial Leprosy Foundation, Wardha, India

This paper is a retrospective study of 64 (L & B) & 849 (N) arrested cases seen in the Sevagram Unit of the Gandhi Memorial Leprosy Foundation. It is based on data from 27 villages of the oldest unit of the Foundation, Sevagram, started in 1952. Work is done on the SET pattern. The Unit has well-maintained records and data. Thanks to the intensive survey, annual follow-up of all arrested cases in the last 30 years was possible. This study refers to 36 relapsed cases. Relapses in non-lepromatous types of leprosy leading to change of type enable the estimation of possible dapsone-resistance in leprosy.

The following factors are studied in this paper;

1) Age, Sex, Type and skin lesions;
2) Nerve involvement before and after relapse;
3) Study of stress and strain factor like pregnancy and parturition.
4) Effect of intercurrent diseases, like tuberculosis
5) Change of type after relapse;
6) Time elapsing from detection to arrest, and from arrest to relapse;
7) Problem of persisters and sulphone resistance;
8) Treatment before arrest and after relapse by monotherapy and multidrug therapy.

XII/503(T) RESTORATION OF "HUMAN STATUS" TO H.D. PATIENTS AND HUMANE HANDLING OF H.D. PATIENTS, AS A CONTROL MEASURE

Bhagwant Singh Dalawari
Vidarbha Maharogi Seva Mandal, Tapovan, Amravati (Maharashtra), India

Restoration of "human status", denied to H.D. patients because of stigma, should be assured by personal example of ONENESS with the patient instead of highbrow compassion. We should ensure involvement of the patient in the solution of his problems, understanding his disturbed state, giving him psychological help, replacing the unnecessarily torturing term "leprosy" (which keeps "leper" in use despite ILC's decision to the contrary) with "Hansen's Disease".

Dumping of patients in society without ensuring a life of dignity is no substitute for rehabilitation in treatment-cum-rehabilitation centres where patients with advanced disease and extreme disabilities, can earn their own living while under treatment. This psychological need must be understood, unless and until society has matured itself to accepting patients in society. Similarly children – patients and healthy children of patients – need protection from disease and anti-social elements must be assured.

The voice of patients must be heard in legislatures, and highly-placed people in Government and outside should display stigma-less attitude in such a way that one day a patient can say triumphantly "Others have tuberculosis, typhoid, etc. and if I have H.D., so what?". Only human and humane handling can bring this about. And only such an attitude can ensure voluntary reporting, leading to control of the disease.

XII/504(T) CHANGING FACES OF SELF-SETTLED COLONIES - A PRAGMATIC APPROACH

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German Leprosy Relief Association, Madras, India

There are innumerable self-settled colonies established by leprosy patients in India. They live in sub-human conditions and are denied all basic amenities. Children living in such colonies are denied healthy growth, education and natural development.

Rehabilitation of these patients has two distinct inter-related and inter-dependent aspects: the medico-surgical and psychological, and the socio-economic and educational.

As a first measure, a thorough medical, social and economic assessment should be made of these settlements.

The German Leprosy Relief Association initiated such assessment in self-settled colonies at Dhanbad in Bihar and Hyderabad in Andhra Pradesh involving approximately 1500 leprosy patients.

The study revealed the following:-

1. A well-knit community life is in existence
2. The potential for self-help and community development is very great.
3. Many patients have untapped ability to earn a living.
4. Many totally infirm patients need custodial medical care.

A viable programme of rehabilitation was launched and the results are encouraging.

Our ultimate objective should be to disintegrate the existing self-settled colonies by bringing harmonious social assimilation.

XII/505(T) SOME EXPERIENCES OF A VILLAGE HEALTH WORKER IN LEPROSY

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The experience of a Village Health Worker who is responsible for all aspects of the health of her village will be described with special reference to the problem of leprosy.

XII/506(T) REJUVENATION – THE NEED OF THE HOUR

Thomas Jayakar, D. Prabhavathi, R. Padmasini
Madras, India

We have interviewed 100 people to assess the reaction of different people in different walks of life to plan action for the control of leprosy, based on the feedback mechanism. In this pilot survey, professors, doctors, paramedical personnel, patients, their relatives, politicians and social workers were interviewed.

This is intended to find out the prevailing knowledge and views regarding mode of spread, treatment, prevention, control and overall views on leprosy in a cross-section of people and the acceptance and resistance that are likely to determine the social aspects of leprosy. It is a sample polling of opinion of the public of what is expected from the Government and medical authorities and also what the leprosy workers expect.

If this survey proves useful,we intend modifying it and extending it to larger number of people. Difficulties experienced in this pilot survey will be included in the conclusion.

XII/507(T) THE BEHAVIOUR CYCLE OF LEPROSY PATIENTS IN RURAL INDIA

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An analysis of observations, interviews and discussions of more than 500 leprosy patients revealed six basic stages of changed behaviour with several catergories of adjustment identifiable at each stage. It is recognized that within the interaction of two or more people the behaviour pattern is not a simple one, nor all positive, if it is directly influenced by affection, indifference or with other less attractive sentiments occasioned by the person being identified as a leprosy patient.

The patient strata were randomly selected from the rural area and their behavioural changes were carefully plotted during the course of their disease - starting from case detection, confirmation of diagnosis, long-term treatment, complications, disease arrest and lastly conforming with their own world through natural or artificial means.

XII/508(T) THE SOCIAL AND ADMINISTRATIVE ASPECTS OF CHEMOTHERAPEUTIC DRUG TRIALS IN LEPROSY

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This paper looks into the various social and administrative aspects which are encountered when doing drug trials, especially in leprosy. A comprehensive discusstion on how to undertake a double blind clinical trial is presented.

XII/509(T) MYTH, MAGIC AND TABOO: AN ACCOUNT OF SOME CASES PERTAINING TO THE SOCIAL ASPECT OF LEPROSY IN A TAMIL VILLAGE

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This paper gives an account of some case histories of leprosy patients in a Tamil village in South India.

It is written under the premise that the ecological, economic and the historically given socio-cultural environment of the village constitutes the basis of cognitive framework in the villager, which differs substantially from those of the urban middle class based leprosy controller. The paper attempts to seek answers to the following questions:

i) What is the framework of cognition within which health phenomena are percieved?
ii) What is the way in which leprosy is percieved within this framework?
iii) What implications does this framework have with reference to leprosy control programmes?

The paper is based on field information gathered in a village in South India where there were 18 leprosy patients out of a population of around 1150. Most of the data relate to events between 1970-79 in the village.

XII/510(T) REHABILITATION OF LEPROSY BEGGARS – AN EXPERIMENT

Suresh Soni
Shram Mandir Trust, Baroda, India

1. Why rehabilitation of leprosy beggars?
   They scarcely spread leprosy but they are human beings. They are compelled to beg, they do have self-respect. They had a life with dignity in a happy family – before they got the disease. On humanitarian grounds, they need to be rehabilitated.
2. History of Shram Mandir Trust
3. Why "Shram Mandir"?
4. What Shram Mandir is :
5. What makes us say that it is a successful experiment:
   Very few have left
   Many come from various parts of India
   They live happily
   Visitors
   Financial assistance received from many countries.
6. What has made it successful?
   Tremendous response of leprosy beggars
   Rs. 30 p.m. to totally crippled and aged, for personal expenses over and above food, cloth, etc.
   Independent houses for couples or two ladies or two gentlemen.
   Freedom, Involvement in decision making
7. Limitation: It is not ideal rehabilitation. They are not in their original families. But this is not possible
8. A request: All beggars must be rehabilitated.