XI INTERNATIONAL LEPROSY CONGRESS

ABSTRACTS

MEXICO CITY, 13—18 NOVEMBER 1978

**CONGRESS BUILDING, NATIONAL MEDICAL CENTER,
330 CUAUHTÉMOC AVENUE, MEXICO CITY**

ABSTRACTS OF CONGRESS PAPERS

The abstracts of papers presented at the Congress or read by title are photoreproduced directly from the book of abstracts furnished to each registrant at the XI Congress. This is done because it involves a considerable savings in printing costs over resetting these abstracts. It has been the practice in preparing the last three Congress Supplements to produce them this way, and it is believed that the presence of a few minor errors will not significantly interfere with their value.

Introductory Note

The program of each scientific session, which precedes the appropriate group of abstracts,lists the abstracts of invited papers and also shows the first and last numbers of abstracts of "free communications" and "poster communications." The Roman numeral of an abstract number refers to the number of the scientific session, and the Arabic numeral is the accession number given the paper at the Congress.

Addendums

1. According to information from the Mexican Organizing Committee, the following "poster communications" were not presented, although some of the persons mentioned below attended the Congress:

2. The abstracts for papers **IA 3** (Monzon, Session I), and **VII 227** (Morrison, Session VII) were not included in the original publication. We have, however, published a brief abstract by each author in this Supplement.

SESSION I
EPIDEMIOLOGY AND CONTROL

Monday, 13 November 1978
11:30-13:30
Auditorium 1
Chairman: **L. M. Bechelli (Brasil)**
Rapporteur: **J. Languillon (France)**

Invited Papers

Abstracts

IA/1 Laboratory aids in epidemiology and control.
R. S. Guinto (Philippines)

IA/2 Prospects pour le contrôle de la lèpre.
M. F. Lechat (Belgique)

IA/3 Atención primaria y control de lepra.
H. Monzon (Venezuela)

IA/4 The epidemiology and some implications of sulphone resistant leprosy.
J. M. H. Pearson (Ethiopia)

Free Communications

Monday, 13 November 1978
15:00-18:00
Auditorium 2
Chairman: **Dr. R. E. Pfaltzgraff (Nigeria)**

Abstracts
IA/5-IA/16

Free Communications

Abstracts
IB/17-IB/25

Poster Communications

Monday, 13 November 1978
11:00-18:00
Exhibition Area
Abstracts
I/26-I/52

EPIDEMIOLOGY AND CONTROL

IA 1

Laboratory aids in epidemiology and control

R. S. GUINTO

Leonard Wood Memorial,
(American Leprosy Foundation)
Cebu, Philippines

Leprosy eradication has been held back by an incomplete knowledge of its epidemiology and by the very limited measures currently available for its control. In recent years, however, innovative laboratory research has made important contributions to epidemiology and consequently to leprosy control. These laboratory advances will be reviewed in some detail in this report.

Leprosy control continues to rely almost entirely on secondary prevention achieved by chemotherapy, i.e., the reduction of infection by early detection and treatment of patients with bacilliferous disease. This report will stress the importance of laboratory support in trials of combined therapy for the prevention of dapsone resistance and "microbial persistence", major shortcomings of chemotherapy as a control measure. The urgent need of continued and intensive laboratory research into primary methods for the prevention of leprosy will be discussed.

IA 2

Prospects for leprosy control

M. F. LECHAT

Ecole de Santé Publique,
Université de Louvain, Belgium

Control of a disease depends on knowledge of its epidemiological characteristics and the health technology available. Although its mode of transmission is not elucidated, leprosy is considered as a communicable disease, with no extra-human reservoir, lepromatous patients constituting the main source if not the only source of infection, and apparently not everybody susceptible or likely to develop overt disease. This will determine the control strategies available. Appropriate treatment of the infective cases is one; it will supposedly lead to interruption of transmission, with reduction of incidence in the long term; such dapsone mass-therapy administered to outpatients has been largely used over the last three decades, with variable results. Other methods can be considered, whose effectiveness can be simulated using epidemiometric models. The present situation of leprosy in the world calls however for an adjustment of control methods, better adapted to local constraints, such as fast-acting therapy or vaccination. Sulphone resistance is a new determinant which will call for dramatic reconsideration of present methods of leprosy control.

IA 3

Primary health care and leprosy control

H. MONZON

Instituto Nacional de Dermatologia,
Caracas, Venezuela

IA 4

The epidemiology and some implications of sulphone-resistant leprosy

J. M. H. PEARSON

M.R.C. Leprosy Project, Addis Ababa, Ethiopa

The first proven cases of acquired sulphone resistant leprosy were reported in 1964. Since then they have been observed in increasing numbers in many countries where leprosy is endemic. These patients, being lepromatous, are infectious and therefore potential index cases for the spread of primary sulphone-resistant leprosy.

This paper will review available data on the epidemiology of both primary and secondary sulphone-resistant leprosy and comment on the implications for research, therapy and leprosy control.

IA 5

WHO activities in leprosy from 1973 to 1978

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World Health Organization, Geneva,
Switzerland

Guidelines on leprosy control. The WHO Expert Committee on Leprosy held its fifth meeting in October 1976. The Committee recognized, in particular, the importance of the problem posed by the resistance of *M. leprae* to dapsone, and to counter this recommended the use of a combination of two drugs in the treatment of patients with multibacillary forms of the disease.

Direct technical cooperation with countries. Activities have been redefined under two headings: (a) manpower formation, and (b) programme formulation of leprosy activities. The collaboration between WHO, governments, and voluntary as well as other international organizations, is being strengthened.

Research. Within the framework of the WHO Special Programme for Research and Training in Tropical Diseases, two programmes have been started: (a) in 1974 a programme for research in the immunology of leprosy (IMMLEP), and (b) in 1976 a programme for research on the chemotherapy of leprosy (THELEP).

Prospects. During the coming years, WHO will increase its efforts to improve the training of personnel engaged in leprosy control. With regards to research, particular efforts will be made to solve the problem of *M. leprae* cultivation by using the most advanced methods of microbiology.

IA 6

The use of information in addition to incidence rates in the evaluation of a vaccination trial against leprosy

L. M. IRGENS D. VAULA
R. SKJAERVEN

University of Bergen, Norway

In vaccination trials, epidemiological information should be obtained for two main purposes. First, the situation in the trial area is to be assessed with respect to present incidence rates and time trends. Second, the vaccine is to be evaluated in terms of difference in incidence rates between a vaccinated and a non-vaccinated population. In most areas where leprosy is prevalent today, it is a difficult task to obtain accurate information on the total number of new patients and the total number of inhabitants. Therefore, relevant information should be sought in addition to incidence rates, which may be inaccurate.

The present paper focusses on a model for evaluation of a vaccination trial based on such additional information obtained from The National Leprosy Registry of Norway. In this registry, epidemiological experience acquired during more than a hundred years of leprosy control is accumulated. The data, relating to 8231 cases from a mean population of approximately 1.8 millions, have been transferred to a computer register which has formed the basis for longitudinal epidemiological studies. It appears that associations exist between incidence rates in a period and personal data of the patients registered in the same period, such as age at onset, sex and type of leprosy. Based on such associations, an epidemiological index is constructed and implemented in a model for evaluation.

IA 7

The reason for the reduction of the protective efficacy of BCG in Burma

M. J. SHIELD J. L. STANFORD
G. A. W. ROOK

Middlesex Hospital Medical School, London

Many studies, in different parts of the world, have yielded widely varying rates of protection afforded to BCG against both tuberculosis and leprosy. When trials have failed, criticisms have been levelled at both the type of BCG used and the *modus operandi* of the trial itself. However, we have investigated the possibility that sensitization to certain environmental mycobacteria may enhance or detract from the protective efficacy of BCG. To explore this field, we have performed skin test studies with tuberculin-like reagents of high specificity. We found sensitization to certain organisms to be extremely common in Burma but absent in Uganda, and that this correlated with the low

(17%) and high (80%) BCG protection rates against leprosy in the respective countries. Nevertheless, amongst Burmese children below the age of four, who had only developed short sensitization to environmental mycobacteria, the protective efficacy of BCG approached that found in Uganda. Furthermore, we can show that sensitization to a *M. leprae* reagent amongst BCG-vaccinated individuals is influenced by sensitization to other environmental mycobacteria. Our field observations are now supported by experimental animal data. Both the field studies and animal work lend much credence to the idea that sensitization to environmental mycobacteria strongly influences the type of immunological response evoked by BCG vaccination.

IA 8

Value of dapsone as a chemoprophylactic against leprosy

S. K. NOORDEEN P. N. NEELAN

Central Leprosy Teaching and Research Institute, Chingleput, South India

The paper reviews the results of controlled double-blind studies on dapsone prophylaxis carried out at the Central Leprosy Teaching and Research Institute, Chingleput, South India, among child contacts of patients with lepromatous leprosy. The dose of dapsone in different studies varied from approximately 1 mgm per kg body weight per week, administered as a single weekly dose, to 4 mgm per kg body weight per week administered twice a week. The number of subjects per group varied between 320 to 360. The overall protection observed among contacts receiving prophylactic dapsone varied from 37% to 53% in the different studies. However, protection against development of lepromatous leprosy could not be evaluated, since no case of lepromatous leprosy occurred even in the control groups. The study showed that the degree of protection for various subgroups was not uniform, and that certain subgroups received relatively higher protection. The factor common to all subgroups showing high protection, in general, was their high risk of contracting leprosy as observed in the corresponding control groups. Long-term follow-up of contacts after the end of the period of prophylaxis indicated that there may be a "carry over" protective effect for dapsone prophylaxis.

IA 9

Leprosy in primary health care

A. GONZÁLES GALVÁN

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Primary health care gives an early opportunity of resolving the main health problems in rural, suburban and urban areas using a reasonable minimum of resources.

Primary health care provides the first contact, when medical services are offered and where the leprosy patient can first be cared for without having to wait for a specialist opinion. Furthermore, early diagnosis of Hansen's disease can be made and timely medical aid given to these patients.

It is in countries with scarce economic resources, and which in turn have large numbers of people with Hansen's disease, that most importance should be attached to first line treatment of leprosy.

This represents the entrance of Hansen's disease into the health services, and general measures of caring for the patient and his family are taken.

The treatment of leprosy patients in primary health care units in every country of the world should be an integral part of the national health service. The activities that are developed for the care of the patient with Hansen's disease should be integrated not only into the public health service, but also into other sectors which affect the development of the community, such as: education, agriculture, housing and communications.

IA 10

Immunogenetic aspects of leprosy. Possible association with genes of the major histocompatibility complex (HLA, Ch, GLO I, PGM_3)

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An association of a disease with genes of the major histocompatibility complex (MHC) may be evidence for an immunogenetic basis for the pathogenesis of the disease. Close linkage of

immune response (Ir) genes with genes of the MHC, especially those coding for the histocompatibility antigens (HLA), may explain such an association. Ir genes control the function of T- and B-lymphocytes for cellular and humoral immunity. In tuberculoid leprosy, the cellular immunity is nearly normal, while in lepromatous leprosy it is completely absent.

In order to investigate the immunogenetics of leprosy, 205 leprosy patients were classified clinically in five subgroups (TT, BT, BB, BL, LL) and typed for HLA antigens and other genetic polymorphisms located within the MHC on chromosome 6. From the same region (northern Thailand), 183 healthy unrelated individuals were used as controls. There was no significant difference between the overall group of leprosy patients or the three borderline classes and the controls. The two polar forms, tuberculoid and lepromatous leprosy, however, showed significant associations. HLA-A2 was decreased and HLA-B17 increased in tuberculoid leprosy; in lepromatous leprosy HLA-B7 was increased. When both polar forms were compared with each other, HLA-A2 was significantly higher, and HLA-B40 lower, in patients with lepromatous than in tuberculoid leprosy. A similar tendency could be observed for the distribution of the alleles of the red blood cell enzyme phosphoglucomutase-3 (PGM_3): the phenotype PGM_3 1-1 was increased among patients with lepromatous leprosy. This study permits some hypothetic explanations as to the influence of the MHC on the immune response in leprosy and may be useful for diagnosis and classification of the disease.

IA 11

Evidence to demonstrate HLA-linked control of susceptibility to tuberculoid leprosy

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Recent evidence indicates that the products of the HLA system have an important function in the immune response to infectious agents. Accordingly, genetic factors have been thought to influence the immune responsiveness and disease manifestations after infection with *M. leprae*. Leprosy families with the following characteristics were selected for study: a) at least two siblings affected with leprosy, b) at least two healthy siblings older than the youngest affected sib and c) both parents available for study. Parental HLA-haplotype segregation analysis revealed a significant deviation from random for siblings affected with tuberculoid leprosy ($p < 0.05$), who tended to be HLA identical. Further, B cell typing for the DR determinants suggested an association of DRW2 with susceptibility genes for leprosy, particularly the tuberculoid type and the recessivity of these genes. The latter finding was further confirmed when sera from normal mothers, or wives in these families and also in randomly selected couples, did not reveal any characteristic patterns with leprosy or leprosy type. The significance and implications of these findings will be discussed.

IA 12

On the genetics of susceptibility to leprosy

P. E. M. FINE E. WOLF
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There is some evidence that susceptibility and response type to infection with *M. leprae* may be determined by a genetic factor linked to the major histocompatibility locus in man. We report a test of this hypothesis carried out in the North Arcot District of Tamil Nadu, in South India, based on a study of 70 families with at least two affected children. A, B, and C locus typing was carried out on both parents, and on all affected children and all unaffected children older than the youngest case. Segregation analysis on these data revealed no evidence for an association within families in which one or both parents were affected, but marginal evidence for an association within families in which neither parent was affected. Possible explanations for this result will be discussed with reference to the social and epidemiological situation in the study area, and with reference to other published work on associations between HLA and leprosy. Attention is given to the general epidemiological problems posed by the

apparent familial aggregation of leprosy, and different methodological approaches which may be used to distinguish genetical from intra-familial contact factors are put forward.

IA 13

Risks of treating leprosy in a general hospital

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The Christian Medical College Hospital, Vellore, which has 1208 beds, is situated in an endemic area where the prevalence of leprosy is 2.8%. Leprosy patients occupy 2% of beds, and about 4000 are seen as outpatients every year. They share with other patients all medical, nursing, laboratory and other services.

The impact of such attitudes and practice on the prevalence of leprosy among staff and students is studied.

This hospital has a staff of 2669, including housekeeping personnel, technicians, nurses and doctors. There are 996 medical, nursing and paramedical students. Every employee and student is screened medically before entry into this institution and subjected to routine annual examinations. Of those who at initial screening had no evidence of leprosy, 23 developed the disease. Sixteen had tuberculoid, one borderline and six indeterminate leprosy. The prevalence rate thus is 0.6% which is less than ¼ of that found in the area.

Factors contributing to this low rate are discussed, with particular reference to age, sex, educational background, residential status and area of work. It is suggested that staff and students serving leprosy patients for whom no isolation is practised do not run any additional risk of infection.

IA 14

Distribution of leprosy in population groups at different risks — Estado Miranda, Venezuela

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Following the method known as 'Epidemiological Tracing', a total of 4700 contacts, residents of Estado Miranda, cohabiting or not cohabiting with known leprosy cases, were examined. The aim was to detect new cases and to carry out intradermal tests with a suspension of LCA antigens, taking readings every 48 hours, thereby establishing their sensitivity level to *M. leprae*.

The results obtained in both groups of contacts were compared with the corresponding results of a representative sample of the general population, 'non-contacts', resident in the same State, comprising 1600 people.

The enquiry showed the operational advantages of the method of detection used, in comparison with traditional methods, especially in regions of low prevalence, where the number of new cases discovered was ten times greater than that obtained in previous investigations.

The proportion of new cases found in the total group of contacts was 3.8 per thousand, corresponding to a rate of 14.7 among cohabiters, and to 2.8 per thousand among non-cohabiters.

Half of the new cases detected were found from among people of over 45 years old, mainly non-cohabiting contacts having open forms of the disease.

Furthermore, in 70% of cases it was found that, where it was possible to establish the most likely source of infection, this corresponded to open forms.

Where skin tests had been carried out, these contributed information in confirming the specificity of the antigen used, showing that the reactivity to this antigen in both groups of contacts, cohabiting and non-cohabiting, is definitely greater than that found in the general population. The differences in the proportion of positive reactors to the skin tests and the frequency of new cases varied according to:

a) whether or not contacts were cohabiters or non-cohabiters
b) whether residents were in areas of high or low prevalence.

This led us to conclude that this method may be of use in delimiting different risk groups.

IA 15

The Brazilian Phase III of prevention

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Successive National Congresses and Seminars concluded that Phase II of "leprosy" prophylaxis in Brazil (decades of case finding, ambulatory treatment, integration, education and rehabilitation) failed as flagrantly as Phase I (compulsory isolation). Counter-education and stigma have grown parallel to the expansion of the mass communications media, ashamed patients and contacts abscond and the endemic flourishes.

The principles of Phase III are:

1) Stigma is the principal enemy. The psychosocial problems are much more serious, attack *all* patients and extend to the healthy relatives — whereas *only a fraction* of patients suffer from important physical disturbances.
2) The solution of those problems is impossible while the disease is named "lepra", because of this word's ingrained and irremovable associations with filth, decay and loathsomeness, continuously aggravated by sensationalism.
3) The elimination of stigma will stop concealment, paving the way for the application of the medical and preventive policies of Phase II.

A new terminology has been adopted. Hansenology will be taught to school children. Prevention of disabilities by simple techniques, contraception and BCG will be extensively applied. Neutralization of stigmatizing activities, intensification of social-medical teaching, investigation and cooperation of the medical profession complete the new plans.

IA 16

Contribution to the clinical and epidemiological study of leprosy in Iranian children

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In all countries where leprosy is widespread, and in the known regions of endemicity, the cutaneous lesions of leprosy may easily be confused with those of other dermatoses.

In Iran, contrary to widespread opinion, leprosy is not exceptional in children who are in constant contact with their parents or with other leprosy sufferers, particularly those suffering from lepromatous forms of the disease.

In the course of a case-finding and epidemiological survey, we recorded several cases, confirmed clinically, bacteriologically and histopathologically, among children aged between 3 and 12, in different mountainous and agricultural regions of the country.

It is evident that the diagnosis and interpretation of clinical signs, particularly neurological, are vitally important in children. We have therefore chosen three short observations from among others to direct the attention of young practitioners to the need to examine closely and patiently these young children, particularly from the point of view of sensitivity to heat, pain and touch. In the majority of cases, the diagnosis of leprosy will be possible in the clinic, on condition that the examination is correctly carried out and that the doctor has an understanding of epidemiology, particularly in the regions where leprosy is endemic.

IB 17

Perspectives in urban leprosy control

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German Leprosy Relief Association Programmes in India.
Greater Calcutta Leprosy Treatment and Health Education Scheme, Calcutta, India

Urban leprosy control merits attention. Recent uncontrolled urbanization has led to a phenomenal rise of the urban populations, especially in developing countries.

In India, a quarter of the total population of six hundred million lives in crowded slums of townships where communicable diseases, including leprosy, thrive. The problem is worsened by rapid migration of rural populations to the cities.

Leprosy control should be linked with overall urban planning and urban health promotion involving the community. To achieve this, we need trained personnel and priorities in planning. Leprosy control should be promoted through a combination of medical, social and educational measures.

In metropolitan areas, it is necessary to

a) identify areas of inter-organizational co-operation

b) define priorities in public health terms
c) coordinate resources
d) amplify and relate leprosy control to basic community health and welfare measures.

The strategy of leprosy control rests on case-finding, easy and regular outpatient treatment services and health education. The programme must reach the total community.

The German Leprosy Relief Association has implemented leprosy control programmes in four important cities in India — Madras, Calcutta, Visakhapatnam and Bombay, covering a population of over four million. Out of a total 25,361 cases so far detected, 22,063 are receiving treatment. Nearly half of the total number presented of their own free will, 20% were diagnosed in a slum population survey, 25% in a school survey and 5% as contacts of known cases.

IB 18

Leprosy survey in industries

J. L. TIPHAGNE

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Aim: to show by concrete example that house surveys and village visits provide incomplete data regarding leprosy prevalence; these should be supplemented by examination of industrial workers.

A survey was conducted in 1977 in Mettur, an industrial town. It had hitherto been impossible to contact workers in their homes because of shift duties. It was decided to conduct a survey of workers in industry.

Initially there were objections from management, unions and workers. The latter feared victimization of leprosy patients, the former, interference with production. After many discussions, separately and together, and the involvement of local philanthropic bodies, all parties were convinced that neither labour nor production would suffer.

The support of the Mettur Youth Federation was solicited and their members, mostly unemployed graduates, volunteered to help in case detection. They were given a short intensive course in leprosy detection. A time-table was drawn up for each factory and the volunteers were sent in groups with an experienced paramedical worker to conduct the survey. Suspicious cases were seen by the doctor for confirmation and laboratory investigations.

In six industries, 2427 workers were examined, and 87 (3.6%) were found to have leprosy.

Many people learned about leprosy; the survey was inexpensive; there was no loss in production; management became sympathetic to leprosy patients, who now receive regular treatment in the factories. Workers bring suspicious cases. The Indian Association of Occupational Health has become interested and has sought our advice on conducting similar surveys elsewhere.

IB 19

Epidemiology of leprosy in South India

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In the course of an operational assessment of the Leprosy Control Programme, interesting epidemiological information was obtained from a Leprosy Treatment and Study Centre at Tirukoilur in Tamilnadu, South India. This centre caters for the needs of about 60 villages with a total population of approximately 80,000. Since 1955, when this centre was established, about 9000 cases have been registered and information obtained about their sex, age, type of leprosy, deformity status and bacteriological status at the time of detection, subsequent treatment regularity, and clinical and bacteriological status. This afforded an opportunity to examine the changing profile of the newly registered leprosy patients over the years. Population surveys were undertaken at approximately three-yearly intervals, and the coverages attained are extremely impressive. These surveys provide valuable information on secular trends in the prevalence of leprosy. Information on the subsequent progress of the patients is less complete, the factors responsible being migration of the order of 3% per annum, and mortality. Nevertheless, among those present, trends in treatment regularity and changes in clinical and bacteriological status have been examined. The findings provide valuable insight into the working of the leprosy control programme and of epidemiological changes in leprosy over a period of about 15 years.

IB 20

History of the official programme of leprosy control in Mexico

G. AYALA URIBE

National Programme of Control of Leprosy, Ministry of Health and Welfare, Mexico

The historic relation is shown between the official programme of leprosy control in Mexico since its foundation in 1930 up to the present day. The persons mentioned have been outstanding heads of this programme, and homage will be paid to their contributions at the XI International Leprosy Congress in Mexico City.

IB 21

New programme of leprosy control, Cuba 1977

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A. ABREU A. VALDIVIA
L. J. WERTHEIN

Ministry of Health, Havana, Cuba

In 1977 Cuba put into action a new programme for leprosy control designed to benefit all registered sufferers, whatever the clinical form of the disease.

The aim of this programme was to reduce drastically the prevalence and incidence of leprosy by treatment and by breaking the cycle of transmission so as to eliminate the disease in the near future. The main and secondary objectives are described, together with the steps taken to set up this new programme and the responsibilities of the different levels in the organization up to the outpatients in the Polyclinic. They took into account the role of the Polyclinic as part of the general health service, as well as the fact that large-scale organizations would also participate.

The statistical control model used for the programme is given. The fundamental characteristic of this programme is that the first-line drug used is rifampicin, which was given daily to 5000 known patients by the nursing staff.

Epidemiological factors are listed, the control of sources, and the chemoprophylaxis which form part of this programme.

IB 22

Leprosy control campaign in Somalia. Integration into the National Health Services

G. L. TARABINI-CASTELLANI
G. TARABINI-CASTELLANI

Campagna Periferica contro la Lebbra in Somalia, Mogadiscio, Somalia

This paper, after providing a brief survey of the leprosy endemic in Somalia, describes the criteria for leprosy control activities in the country. These activities, which until the end of 1977 were conducted by a private agency, are now undertaken in close cooperation with the National Health Authorities, which provide the necessary counterpart personnel to integrate the treatment of leprosy into their regular health programmes.

The paper deals with the psychological factors, the methods and techniques considered most appropriate and the selection and training of staff, and presents the organization chart devised for the purpose, as a basis for ensuring coordination and close cooperation between the agency and the National Health Authorities.

Leprosy control operations are supplemented by the dissemination of health education on leprosy at various cultural levels by means of lectures, posters and an audiovisual programme (slides with synchronized text): the latter are especially aimed at school-children and school teachers.

On integration, the subsequent checks on leprosy patients and their contacts become the sole responsibility of the national health personnel, in their respective districts.

IB 23

Social aspects and epidemiology of leprosy in Sri Lanka

D. S. P. SABAPATHY

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Leprosy has been diagnosed and recorded in Sri Lanka from the sixteenth century.

Sufferers have faced severe social stigma up to the present day.

The stigma and fear are especially strong among educated classes.

There has been a steady increase of cases from 1947 to 1977. The incidence among races appears to differ; but the same variation has continued during the last seven years. Endemicity in the nine provinces does not appear to depend on population density.

IB 24

Leprosy in Morocco

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R. ROLLIER

Casablanca, Morocco

Morocco, not including the Sahelian zone, has an area of 420,000 sq km and a population of 20 million. From 1 January 1950 to 1 January 1978 6000 leprosy sufferers were examined and recorded, of whom one-third were female and two-thirds male. Of these, 65% of the males and 55% of the females were suffering from lepromatous forms of disease.

After a period of 3 months' hospitalization, the patients receive ambulatory treatment and undergo a half-yearly follow-up examination. After 3 to 5 years, indeterminate and tuberculoid forms remain under observation but without treatment. The prevalence rates are extremely variable, ranging from 0.1% to 30%. No systematic method of case-finding has so far been established; only familial contacts are examined.

IB 25

Results of five years of integration of leprosy control into the Provincial Health Service of Phuket Island, Southern Thailand

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The Phuket province is one of the smallest and most hyperendemic with regard to leprosy of the 14 provinces comprising southern Thailand. It is an island with an area of 801 square kilometres where 103,362 inhabitants live in 3 districts with little mobility of population. The existing health structure covers every area, and the health workers are well motivated. Because of its strategic position in the region and its available health facilities, Phuket province was chosen in 1972 as the pilot province for integration of leprosy control into the provincial health services. In 1976, a stratified survey was conducted to assess the epidemiological situation and to evaluate certain aspects of the integrated control operations.

The results of epidemiological and operational assessment with their implications are reported and discussed in detail. The authors concluded that the result of 5 years' experience of integration of leprosy control in Phuket, showed that the overall prevalence had increased from 0.77 to 2.45 per thousand. Local health workers could detect 43% of the total registered cases; the remaining cases were found by a specialized leprosy survey team. The accomplishment of the three main targets of leprosy control, including treatment, contact examination and bacteriological smears, had gradually declined by 38% from 66% to 31%, indicating a great need for better supervision and motivation. It was also necessary to start adequate surveys before integration, followed by regular supervision and field guidance, to monitor the efficiency and effectiveness of leprosy control in the future.

I 26

Epidemiometric modelling for leprosy

M. F. LECHAT A. BOUCKAERT
C. VELLUT C. B. MISSON

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The current epidemiometric model of leprosy developed by the authors has been expanded to include acquired immunity, spontaneous healing, and infectivity during the latent stage. It has also been refined by introducing a realistic age distribution of the population with age-specific incidence and death rates. Structural modifications in the model makes it possible to predict the effect that secondary and primary sulphone resistance would have on long-term incidence and prevalence rates. The effect of rapidly acting drugs on the dynamic of the disease in populations, and the relative effectiveness of such measures as compared to others such as present therapy or (still to be developed) vaccination, have been studied.

I 27

Evaluation of mass anti-leprosy campaigns in Francophone Africa

M. NEBOUT

Ministère de la Santé Publique,
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In 6 states of West Africa, with more than 30 million inhabitants, there were 356,039 leprosy sufferers in 1976, as compared with 457,657 in 1971.

More than 144,000 patients were inactive, and of these more than half were untreated inactive, therefore on the way to being cured.

Moreover, an enquiry held in Upper Volta (by WHO) from 1975 to 1977 showed that the strict application of the criteria of healing defined by WHO would make it possible to declare immediately "free from control" more than 65% of the patients recorded in the sectors.

In 5 states of Central Africa with more than 13 million inhabitants, there were only 100,655 leprosy sufferers by the end of 1975, as compared with 191,900 in 1965; the prevalence has fallen from 1.77 to 0.78%. The total number of sufferers cured since the beginning of the campaign amounts to 80,689.

These impressive figures, based on eleven African States and relating to almost 45 million inhabitants, reflect the effectiveness of anti-leprosy campaigns.

The methods used are essentially offensive and are based on the mobility of the "polyvalent" services against transmissible diseases, which have assured the success of mass campaigns.

The remaining task is the maintenance of the structures and methods of the services against major endemics, which are useful tools, and not costly, and the only means of bringing about long-term success in the fight against leprosy. They have already proved successful in the fight against other transmissible diseases.

I 28

Operational classification in Hanseniasis control

C. D. V. BERNARDI J. FERREIRA
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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 identify precisely the clinical, bacteriological, histological and immunological aspects of the disease, we suggest an alternative simplified system of classification to be used in control programmes. 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 clinical and laboratory criteria that define each group are presented, as well as the correlation between this simplified system and the classic one.

I 29

Computer usage in Hanseniasis control

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The authors present the results of three years' experience in using a computer system to store data of Hanseniasis cases. Such data consist of clinical and personal particulars of diagnosed cases since 1933 (the date of the beginning of the control programme) in Rio Grande do Sul State, Brazil.

This data processing system improved routine dynamics and yielded prompt information for programme administration; information reviewed monthly is circulated to those responsible for field work in Hanseniasis control. There are, in fact, by-products of the system, such as a significant improvement in data quality.

By this method, separate occurrences in individuals can be correlated, a result that greatly facilitates epidemiological studies of this disease.

I 30

The role of arthropods in the transmission of leprosy

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This PL-480 supported collaborative study of Carville (USPHS) and the Jawarhalal Institute of

Postgraduate Medical Education and Research in Pondicherry, India, has been in operation since 1969. It was engendered by combining the diverse hypotheses about transmission of leprosy, the observations of Munoz Rivas on fleas (1942), and of Shepard on mouse footpads (1960).

Specific objectives were:

1. Determination of the arthropods in endemic areas that were likely to transmit leprosy by virtue of their habits.
2. Establishment of the rate of occurrence of viable *M. leprae* in arthropods and their distribution in their bodies.
3. Determination of the carrier rate and survival time of *M. leprae* in arthropods likely to be involved in transmission.

Findings and conclusions:

1. Leprosy bacilli occurred in 2 of 125 pool of *Anopheles*, 4 of 69 of *Culex*, 6 of 152 of *Cimex hemipterus*, 13 of 142 of *Pediculus humanus*.
2. Untreated LL patients always have bacteriemia, and laboratory-bred arthropods take up *M. leprae* in 70% of feedings. They survive in the gut of *C. fatigans* and *A. aegypti* for at least 48 hours, and for 26 days in *C. hemipterus*.

I 31

Demonstration of dapsone in urine and serum by an enzyme-linked immunosorbent inhibition technique

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Conventional methods for demonstrating dapsone are either insensitive or not practicable for general use in areas where leprosy is endemic. We have developed an immunoassay that is both simple and sensitive. It is an enzyme-linked immunosorbent inhibition technique (ELISIT) on micro-titreplates. The wells of the plates are coated with a protein-dapsone conjugate. Antibodies to dapsone, raised in a rabbit, specifically adhere to this dapsone coat. The adherence, however, is inhibited by the addition of free dapsone in fluids. Antibodies that do stick to the dapsone coat after a washing cycle, are identified by the addition of an enzyme-conjugated anti-rabbit IgG serum. Adherence of the enzyme conjugate is made visible by the coloured product of a suitable substrate. Even nanogram levels of both dapsone and mono-acetyl dapsone inhibit the adherence of rabbit antibodies to the dapsone coated wells, thus inhibiting the colour development.

The ELISIT, not requiring any complicated apparatus, is expected to be of great value in rural areas without sophisticated laboratory facilities.

I 32

The prevention of sulphone resistant leprosy

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MRC Leprosy Research Project,
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Since 1973 the number of patients with lepromatous leprosy receiving treatment in the Addis Ababa area has remained stable at about 1500. From this population about 50 per year showed clinically suspicious indications of sulphone resistance. In 1976 a trial that included some 800 lepromatous patients in Addis Ababa, was initiated: this trial attempted, by supplementary chemotherapy, to prevent the emergence of sulphone resistant leprosy. All patients continued to take dapsone 100 mg daily. Three supplementary regimens were tested, namely:-

a) Thiacetazone 150 mg daily for 12 months (this was administered with INAH 300 mg daily as a single tablet, called *Thiazina*)
b) Rifampicin 600 mg daily in months 1 and 7
c) *Thiazina* 1 tablet daily for 12 months plus rifampicin 600 mg daily in months 1 and 7.

Two hundred patients were included in each treatment group; the remaining 200 continued monotherapy with dapsone and acted as the control group. This paper will describe the implementation of the trial and analyse the preliminary results.

I 33

Acedapsone in the prevention of leprosy: field trial in three villages of high leprosy prevalence in Micronesia

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1659 non-leprous people in a Micronesian population experiencing an annual leprosy incidence rate of about 7/1000 were offered 15 DADDS injections during 1967—1970 for the purpose of preventing leprosy. Subsequent careful annual surveillance showed that there were no new cases during the 3-year DADDS campaign; then new cases occurred at the rate of about 2/1000/year, with a longer delay and a slower rise among those who received the full regimen of injections. A secondary wave of cases has appeared since 1973 among children born after 1968; this is probably due to post-campaign transmission from poorly controlled pre-existing cases of multibacillary leprosy in the population. Sulphone-resistance has not presented a problem. Recommendations are made for a balanced, long-term control programme with DADDS given only to contacts of patients with multibacillary leprosy.

I 34

Sulphone-resistant leprosy in Ethiopia

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During the period 1973 to 1977, some 400 patients with clinical evidence of sulphone-resistant leprosy have been seen and reviewed by the Medical Research Council Leprosy Project in the Addis Ababa Leprosy Hospital. Most of these patients had active lepromatous leprosy, despite a history of continued anti-leprosy treatment with dapsone. In confirming the suspicion of sulphone resistance, reliance was placed chiefly on a clinical trial in which dapsone was administered in full dosage under the closest supervision attainable under outpatient conditions: mouse footpad tests were performed in about a quarter of cases. The results of this 5-year programme, together with the findings in about 40 patients screened (by mouse footpad testing) for primary sulphone resistance, will be presented.

I 35

Incidence of hepatitis-B antigen positivity in Korean leprosy patients

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Sera from 80 leprosy patients were tested for hepatitis-B surface antigen (HBsAg) using solid phase double-antibody radioimmunoassay technique (RIA), and for serum glutamic-oxalacetic-transaminase (SGOT) and serum glutamic pyruvic-transaminase (SGPT) by the Karmen method. For controls, sera from 41 medical and nursing students were tested for HBsAG, and 1595 specimens of blood from the blood bank of the Catholic Medical Center were tested for SGOT and SGPT. Skin biopsies were used to establish histological diagnosis of the leprosy patients.

The frequency of HBsAg was 8.8% among the leprosy patients, slightly lower than the control group (9.8%). SGOT and SGPT levels were significantly higher in leprosy patients. There was no correlation found between the type of leprosy and HBsAg, but the frequency of HBsAg was higher in bacteriologically negative than in positive patients. No correlation was found between the sexes. Patients in their third and fourth decades showed a higher incidence of HBsAg than those over the age of 50. Resettlement villagers showed a higher incidence of HBsAg than outpatients. Incidence of HBsAg increased with the length of treatment. Patients on parental medication also showed a higher incidence of HBsAg than those on oral medication.

I 36

Incidence of HBsAg and Ag 'e'/Ac anti-'e' system in a hospitalized population of patients with Hansen's disease type L

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The high frequency of HBsAg carriers in closed communities and especially in sick people with changes in their immunological system, has been repeatedly mentioned in world literature. Moreover, attention is today concentrated on the coincidence or non-coincidence with HBsAg of a new system, called Ag'e'/Ac anti-'e', in the same patient. The said coincidence seems to be in strict relation to the infectious and contagious capacity, on the one hand, and to the potentiality for lesions in the carrier's own liver, on the other.

For this reason it is of interest to study these factors in a large population of lepromatous leprosy patients living in a hospital.

463 measurements were carried out on a total of 332 patients (198 males and 134 females). 201 (60.5%) (Group I) live in the Sanatorium; 131 (46%) are hospitalized for controlled periods (Group II). The control group consists of 37 people from the Sanatorium, not leprosy patients, who live in close contact with the patients.

In Group I, 16 patients were found to be HBsAg + (8%); in Group II, 7 + (5%) and in the Control Group 2 (5%).

1 Ag'e' (4%) and 3 Ac anti-'e' (13%) were found out of 23 Hansenian carriers of HBsAg.

HBsAg circulating in parallel was detected, by means of IEOP and enzyme-immune-assay.

The screening of Ag'e'/Ac anti-'e' system was carried out by electrophoresis.

I 37

Hepatitis B virus indicators in leprosy

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For 553 patients with leprosy, several indicators of HBV virus were investigated: HBs Ag, anti-HBs, anti-HBc, HBe Ag, anti-HBe.

A significant difference in the prevalence of HBs Ag between patients with leprosy (25.5) and controls (12.0) was found, but not between LL and TT, males and females, institutionalized and outpatients.

From the measurement of five indicators, it appears that all the patients with leprosy had been infected by hepatitis B virus, and that the impaired cell-mediated immunity which characterizes LL patients did not play a significant role in the evolution of their hepatitis infection.

I 38

The e-antigen (HB_eAg) in leprosy

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The incidence of hepatitis B antigen is far higher among patients with lepromatous leprosy than among patients with tuberculoid leprosy or among controls; this association has been previously ascribed to a genetic predisposition, but further data showed a higher rate association with lepromatous leprosy only in those countries (tropical and developing) where the antigen is very common.

A new antigen, e-antigen, which is distinct from HB_sAg, is also associated with hepatitis B virus; it is found among highly infectious HB_sAg carriers and appears to be a valuable marker of the potential infectivity of HB_sAg-positive serum. Prior to the present study, no data were available on the carrying of the e-antigen and e-antibody by patients with tuberculoid or lepromatous forms of leprosy.

One hundred and forty-two sera from leprosy patients, 86 with lepromatous leprosy (L) and 56 with tuberculoid leprosy (T), were examined by immunodiffusion, for the presence of e-antigen and e-antibody.

The test for e-antigen was negative in all leprosy patients; the e-antibodies were found in only 9 patients (6%), all carriers (except one case with T) of hepatitis B antigen (HB_sAg). The HB_sAg test (RIA method) was positive in 24% of L cases and in 11% of the T cases; the anti-HB_s was present in 47% of the L cases and in 59% of the T cases.

The results suggest the possibility that the higher rate of the hepatitis B antigen in leprosy patients is not associated with depression of cellular immunity and that leprosy patients who are positive for the surface B antigen represent a very low infectivity risk and can be considered as chronic asymptomatic carriers of HB_sAg.

I 39

Programme of leprosy control in the Dominican Republic (1973—1977)

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The writers made an evaluation of the programme of leprosy control in the Dominican Republic during the period 1973—1977. This was planned, directed and carried out by the Dominican Institute of Dermatology, a private concern, with the agreement of the Secretary of State for Public Health.

For the purpose of carrying out this programme, the country was divided into 4 regions, and in each of these a Dermatology Unit was set up, headed by a dermatologist/leprosy specialist, who was assisted by paramedical and office staff. Each unit relies on dermatological clinics run by adequately trained field auxiliaries who carry out the programme in rural areas and in very distant provinces, and who also carry out the control of contacts in cities. During this time 2184 new cases of leprosy were discovered in the dermatological examination of 242,328 new patients, 34,441 examinations of contacts and 153,491 people examined during population censuses. At the end of 1977 there were 4290 cases of leprosy on the current register, with a control of 92.6%. The occurrence of leprosy was also studied by province, sex, and age group.

I 40

Past, present and future of leprosy in Nicaragua

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This abstract reflects the three fundamental stages of leprosy control in Nicaragua. Relying on historical facts, it shows the situation of the leprosarium in an urban zone and the neglect of the health factor until 1976. Reasons are given for the present change from a leprosarium to a National Dermatological Centre. In this way ambulatory treatment is given to those having skin infections, especially ambulatory control for the leprosy patient. Plans are put forward for a programme integrated with the Ministry for Public Health for leprosy control through decentralization and mobile units in the endemic areas.

I 41

Control of leprosy in Morelos, Mexico

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Morelos, a federal entity of the Mexican Republic, has a territorial land area of 4941 km^2 and an estimated population of 950,605 in 1978. There are 211 verified cases of leprosy, and 799 contacts, that is one leprosy patient in 4463 of the population.

The leprosy patients are found in 57 localities, and are of the following clinical types: 136 lepromatous, 27 tuberculoid, 2 dimorphous, and 46 indeterminate. There is a predominance of diffuse lepromatous.

Classified by the degree of severity of the lesions: 67 early, 59 moderately advanced and 85 advanced.

There is a slight male predominance: 120 males to 91 females, two are under 15 years, and 209 over 15 years.

Programmes for detection are in operation, with 42 centres and 33 public health dispensaries employing 135 doctors and 123 nurses.

Our target population has been the school age-group (6—12) estimated to be 180,666 for 1978.

The control of leprosy patients and their contacts is carried out in our units with the following personnel: 12 social workers, 9 laboratory technicians, 12 dentists, and 2 chemists.

released from treatment. No relapses were observed. The present report elucidates the reasons for short-term resumption of therapy and stresses the importance of follow-up studies after termination of treatment (control for the occurrence of relapses).

I 42

Leprosy in the United States (1967—1976)

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A total of 1168 cases was reported in the continental U.S. during 1967—76. The average number of cases per year was 119, and the average age of the patients was 37 years. This represents an increase in the number of cases of 27.6 cases annually, as compared with the previous twenty year report 1949—1968, when 1820 cases were reported.

The significant aspect of this review was not only the increase in the number of cases, but that there was a definite change in the ratio of native and foreign born patients, shifting from a 1:1 ratio for the previous 20 year report to a 1:3 ratio for this present report.

The problems accounting for this change as it relates to the foreign born newly reported cases are discussed, correlating them with the deficiencies of the National Registry, with proposals to improve the overall activity of the registry for improved control of the disease.

I 43

Leprosy eradication project in Malta — report after 6 years

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Following our report, published in 1977, on the state of our project after 5 years, a report is now given on its state after 6 years. The results continue to be positive. Further patients could be

I 44

Leprosy in Greece (1928—1977). An assessment of the main epidemiological characteristics of leprosy in the last 50 years

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From the records of the Clinical Center for Hansen's Disease in Athens, which has just completed 50 years as the only leprosy institution in Greece, detailed information on all treated leprosy cases (2384) has been obtained and evaluated. The assessed data indicate the following:

1. A decline in the incidence rate from 2.7/1000 in 1928 to 0.04/1000 in 1977.
2. A gradual shift from LL and BL forms to TT.
3. Islands and coastal regions contribe 63.8% of the patients.
4. The onset of the disease shifted from the age-group 21—30 in 1928 to age-group 51—60 in 1977.
5. 28.3% of all treated patients have a member of the family or a relative suffering from leprosy.
6. 87.6% of the patients come from a low social, educational and economic class.
7. There was a high incidence (31.8%) of hepatic disorders; 29.2% systemic hypertension, 26% renal disorders, and 18% respiratory disorders.
8. The occurrence of disabilities was 42.9%; the gravity (WHO rating) varied from 0.17 to 3.0, and depended mainly on several factors (time elapsed between onset of disease and treatment, clinical form, number of leprosy reactions).
9. The death rate was 18%.

I 45

Preliminary study of leprosy in Saudi Arabia

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This study was carried out in the Hadda Leprosy Hospital in Saudi Arabia with the aim of defining certain problems, including clinical aspects, forms of the disease, and residential areas of the patients.

The number of patients in the Hadda Leprosy Hospital is a small fraction of the total number suffering from leprosy in Saudi Arabia. Out of 144 inpatients in the Hadda Hospital (the only leprosarium in the country), 72 are Saudi and the majority of the remainder are from Yemen.

Of the Saudis, 75% are from the south-western region of the country, indicating a relatively high prevalence of the disease in this area.

This study is intended to be the first step towards an epidemiological field survey, since no previous field survey has been made.

I 46

School surveys in Bombay

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Of 415,497 students examined, 2012 were found to be suffering from leprosy, the detection rate being 4.8 per 1000. The age and sex of the students were related to the occurrence of leprosy. The disease was more common among male students in the age group 10 to 19 years. Rate of infection among students speaking some south Indian languages was significantly higher than among others. Only 2.1% of the cases were bacteriologically positive, about 97% had no deformity, and over 78% were at an early stage. In a significant number (61%) the single lesion present (presumably the initial lesion) was on the covered parts of the body.

I 47

Prevalence rate of leprosy in some urban slums — experience in Bombay

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Rapidly proliferating slums in populous industrial cities of developing countries pose special problems in arresting communicable diseases, especially leprosy. Bombay has a population of 6.5 millions with 847 slum pockets consisting of over 260,000 huts, in which people live in unhygienic conditions. Intensive field operations have revealed the existence of hyper-endemic foci of leprosy in some slums.

3812 members of 729 families (family size: 5.2) living in an area of about one square furlong were counted; 3178 of them (83.4%) were examined.

In addition to the patients detected during this mass survey, self-reported cases living in the area and those detected during school surveys were re-identified. The prevalence rate was 24.8 per 1000: 50 adults and 29 children had leprosy.

Though the total prevalence rate is high, most of these (60 out of 79) had a non-contagious form of leprosy. However, there were 12 lepromatous or BL patients, and seven active borderline-tuberculoid cases, a prevalence rate of 5.9 per 1000. The smear-positive cases represent a prevalence rate of 3.1 per 1000.

Assuming that the tuberculoid and indeterminate cases are epidemiologically unimportant, the high prevalence of active disease in a community of over 3000 living under poor hygienic conditions in an area of one square furlong poses a challenge for planning an eradication programme.

I 48

Comparative operational study of two methods of population survey in rural areas of Thailand

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In 1976 and 1977, two epidemiological surveys were undertaken by the authors in rural areas of two provinces of Thailand, using a system aimed at covering at least 95% of the population to be examined. The object of the survey is not only the epidemiological assessment of the leprosy control programme but also to study the effectiveness of two methods of evaluation

surveys, using house-to-house surveys and gathering all the villagers together.

The first method of house-to-house survey was conducted in Phuket province in 1976, while the second method of gathering together all the villagers was undertaken in Mahasarakam province in 1977. The prevalence rates of leprosy before conducting the survey were 2.2 and 2.3 per thousand respectively.

In rural areas of Phuket, out of a total population of 62,564 living in 10,268 households, 32,308 people from 5301 households were surveyed at random (sample size: 51%); a total of 31,350 people was examined (97%) and 31 new leprosy cases (8 L, 23 NL) were detected (0.99 per thousand).

In Mahasarakam, from a total population of 28,542 from 4884 households in 73 substratal villages (30% sample of population), 27,649 people were examined (97%) and 66 new leprosy cases (12 L, 42 NL) were detected (2.4 per thousand).

The methods used in each survey are described in detail and the implications of the figures and facts discussed. The importance of such surveys in highly endemic areas is stressed. The results of surveys for detecting tropical dermatoses, BCG- and smallpox-scars, will also be discussed.

I 49

Some results from 20 years of leprosy control work in the Mahasarakam Province of North-Eastern Thailand

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With regard to leprosy, Mahasarakam province is one of the most hyperendemic in Thailand, although a leprosy control programme has been in operation for 21 years. The first evaluation survey in 1977 revealed that from a total of 28,542 people who were screened in 73 villages (an approximately 3% sample and 97% coverage), 27,649 people were examined (examined rate 96.8%) and 66 new cases (12 L, 42 NL) were detected with the detection rate of 2.4 per thousand. The overall point prevalence has fallen by 52% from 5.6 in 1966 to 2.7 per thousand in 1976, indicating the valuable effect of the control services. The annual detection rate of new cases has also fallen by 24%, from 0.21 in 1966 to 0.16 per thousand in 1976. The annual detection rate of new lepromatous cases has declined 25% within the 10 years of this operation. Annual contact examination has also revealed a fall in the annual detection rate of new cases of 88%, from 41 to 4.7 per thousand in 1976. Since the result of a survey in the sampling villages showed that the prevalence had increased from 2.6 to 4.9 per thousand, this indicates the necessity to improve and speed up the case-finding programme. Improvement in the operational measures for maintaining surveillance of cases released from control, and out-of-control cases, and investigation on persisters, drug-resistant relapses should be undertaken.

The results of operational assessment with its implications are also reported and discussed in detail.

I 50

Leprosy in the Karimui: a genetic investigation into its susceptibility

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The total population of the Karimui sub-district of the Eastern Highlands of Papua New Guinea has had clinical examinations for leprosy. These examinations have been performed 13 times since 1962 by one of the authors (D.A.R.). All leprosy cases have been confirmed by histopathological examination.

The people of the Karimui are derived from an isolate, the Daribi, who originally migrated from the south coast. Their unique social and environmental milieu allows for an attempt to partition some of the genetic variation in the susceptibility to leprosy. First this study defined the population and identified the ascertainment biases. The familial nature of the disease along with the possibility of defining aetiological heterogeneity was investigated by analysing family histories, through third degree relatives.

Pedigrees were obtained from 547 individuals affected with leprosy. Forty five percent (246) of these individuals had at least one other

affected family member (with any form of leprosy) in their first three degrees of relation, i.e. familial type. Among the individuals with lepromatous leprosy (BL, BL/LL, LL) a significantly increased number (30/37; χ^2 = 18.27) were in the familial segment of this leprosy population. The overall segregation ratio for all forms of leprosy within families presenting an individual with lepromatous leprosy was 0.43. There were several families in which the disease was observed in several generations and several half siblings were affected.

Non-lepromatous leprosy conformed to two family types: 1) non-familial (81%) and 2) familial. Among the familial group there were cases of half siblings affected and several generations of affected individuals, but the segregation ratio was merely 0.25.

The possible role of the following will be discussed: 1) genetic factors in susceptibility to leprosy; 2) genetic heterogeneity within a segment of the leprosy population; and 3) allelic restriction in the determination of population frequencies of leprosy and its variable age of onset in a segment of the non-lepromatous leprosy population.

I 51

Leprosy in Western Samoa

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Leprosy has been known in Western Samoa since the last quarter of the 19th century. During the 1920's leprosy patients were sent to a leprosarium in Makogai Island, Fiji, where they were kept for several years before returning to Samoa; this policy ended during the 1950's.

In 1954, Dr. N. R. Sloan visited Samoa and concluded that the prevalence was 1.6 per 1000 population (63.5% lepromatous, and 36.5% tuberculoid and indeterminate). 12.5% of all cases were below 15 years of age. In 1964 Dr. R. Wardekar, WHO consultant, estimated the leprosy prevalence to be 2.2 per 1000 population.

In 1975 a random sample Tuberculosis/Leprosy Survey was conducted with the assistance of WHO and 19,601 persons were examined; the following information was obtained: leprosy prevalence of 3 per 1000 population; lepromatous rate 42%; positive cases 46%; cases below 15 years of age 14.8%.

As leprosy appears to be one of the major health problems in the country, the government, with the assistance of WHO, started in late 1977 an integrated leprosy control programme.

I 52

The present situation in Okinawa Islands

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The ratio of the total population of Okinawa to the mainland of Japan is 1/100, but the ratio of newly registered patients in Okinawa is 2/3. In 1968, ten years ago, the number was 173, but in 1977 the total was only 41.

The two National Leprosaria hold 920 inpatients. The non-governmental leprosy association has three outpatient clinics, permitted only in Okinawa; they treat 499 registered patients.

An immunological investigation of the contacts is being undertaken.

Prejudice and stigma are common among the older people; and the indifference and lack of interest among young people in Okinawa is worse than in India. The overcoming of these attitudes will be the most important aim of our future work in Okinawa.

SESSION II
EXPERIMENTAL LEPROSY

Tuesday, 14 November 1978
9:00-13:00
Auditorium 2
Chairman: **C. H. Binford (USA)**
Rapporteur: **G. Munoz-Rivas (Columbia)**

Invited Papers

Abstracts

II/53 Quantitative aspects of experimental infection of armadillos with *Mycobacterium leprae*.
W. F. Kirchheimer, R. M. Sanchez, J. P. Pasqua, T. Walsh (USA)

II/54 Indigenous leprosy in the nine-banded armadillo (*Dasypus novemcinctus*).
W. M. Meyers (USA)

II/55 Nude mice for research in leprosy.
K. Kohsaka (Japan)

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EXPERIMENTAL LEPROSY

II 53

Quantitative aspects of experimental infection of armadillos with *Mycobacterium leprae*

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T. WALSH

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One objective requiring knowledge of quantitative aspects of experimental leprosy in armadillos is an integral part of our attempts to study fundamental aspects of leprosy, such as validity of the genetic hypothesis and the mechanism of resistance (susceptibility). In validating our susceptibility tests, based on inability to develop hypersensitivity to *M. leprae*-protein, we arbitrarily give "resistance" a quantitative connotation, hoping that at a dose of *M. leprae* infectious for only 10% of armadillos, the assumed cell differences in susceptibles and resistants become measurable. Dose-response experiments show that the desired bacterial dose falls below 10^5 intracutaneously inoculated *M. leprae* A.

Another quantitative aspect concerns production of large numbers of high quality leprosy bacilli in as short a time as possible to supply WHO and others with Lepromin A and infected tissues to IMMLEP and NIAID. In our experience, the most suitable way to accomplish this is by intravenous inoculation of several hundred million *M. leprae* A. Rates of infection (disseminated leprosy) approach under these conditions 100% in less than two years. Approximately 50% of armadillos carry billions of *M. leprae* per gram of liver, spleen, lymph nodes and subcutaneous lepromas in about 12 months. Even with such overwhelming doses, an occasional unusually resistant armadillo is encountered.

II 54

Indigenous leprosy in the nine-banded armadillo (*Dasypus novemcinctus*)

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In 1975 Walsh *et al* reported the discovery of a leprosy-like disease in seven armadillos (*D. novemcinctus*) recently captured in Louisiana. This prompted further surveys of armadillos captured in Louisiana, Texas, Mississippi and Florida. A total of 50 armadillos with a similar disease, hereafter called "indigenous leprosy", have now been identified. They were found in 11 sites in Louisiana and one site in Texas.

Five of the 50 animals had nodules in the skin and the remaining animals had no gross clinical evidence of disease. Smears of ear snips from 46 animals and nasal smears from 23 animals contained acid-fast bacilli (AFB). Autopsies were performed on all AFB-positive armadillos and histopathological evaluations were made on tissues from 41 of the animals. Histopathological changes were similar to those seen in armadillos experimentally infected with *M. leprae* from leprosy patients. There were lepromatous infiltrations of various organs and tissues and AFB in phagocytes in nerves.

The AFB obtained from lepromas were not cultivable, their acid-fastness was extractable with pyridine and they produced a pattern of Mitsuda reactions in leprosy patients similar to that elicited by *M. leprae*. These confirmatory studies and other evidence indicate that the AFB causing indigenous leprosy in armadillos is *M. leprae* or indistinguishable from it.

II 55

Nude mice for research in leprosy

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Nude mice (BALB/C-*nu/nu*) were infected with *M. leprae* obtained from a lepromatous patient, and they were kept under SPF condition in Vinyl(plastic)-isolator. The nude mice could survive for about two years, and they developed lepromatoid lesions with swelling of the footpad at the inoculation site and cool parts of the body with infection by *M. leprae*. Histopathological examination and several identification tests (including lepromin test and D-dopa oxidase activity test) were carried out on the acid-fast bacilli, which proliferated in the nude mice, and it was confirmed that the lepromatoid lesions and generalized infection with peripheral nerve involvement in the nude mice were caused by both infection and proliferation of inoculated *M. leprae*. The successive passage of *M. leprae* which had proliferated in the lesion of the first infected nude mice into other nude mice was confirmed experimentally. The reproducibility of animal transmission with nude mice was also proved. *M. leprae* obtained from five different patients were successfully transmitted into the footpads of nude mice. The maximum yield of *M. leprae* was 1.1×10^{10} in a footpad in the 8th month after infection.

II 56

The nude mouse as an experimental lepromatous leprosy model: the enhancing effect of thymus cells in infected nude mice

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We have previously reported that lepromatous lesions were seen macroscopically in experimentally injected hind- and/or fore-paw sites of nude mice which had been inoculated with many wild (from patients), normal or nude mice-passaged strains of *M. leprae*. Macroscopically, lesions were observed only on the injected foot, but microscopically, disseminated lesions were seen in the liver, lung, spleen, nerves, bone marrow, testis, nose, ear, tail and the uninoculated foot.

This study was carried out to investigate whether thymus cells would be effective in nude mice after foot inoculation. Thymus cells were inoculated into nude mice 5 to 7 months after they had been inoculated with *M. leprae*; the foot lesion was more developed macroscopically and histopathologically, as compared with that of untreated nude mice, from the point of view of foot thickness (over 2.0 mm) and bacillary counts in a foot (more than 10^{10} bacilli).

From a consideration of these findings, it seems most reasonable to conclude that thymus cell grafting in infected nude mice was useful for obtaining numerous bacilli at an early stage after foot inoculation, as an experimental lepromatous leprosy model.

II 57

Experimental leprosy in *Dasypus sabanicola*

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Studies of the experimental inoculation of the armadillo *D. sabanicola* with *M. leprae* and of the morphological and immunological characteristics of this species are presented.

In the experimental transmission, inocula from lepromatous patients and from earlier infections of leprosy in armadillos were used at a concentration of 5×10^8 to 3×10^9 acid-fast bacilli. Animals were inoculated simultaneously by the intradermal and intravenous routes. In 1976, intra-cardiac inoculations were introduced with satisfactory results.

Independent of the route of inoculation, the earliest appearance of systemic disease was observed between nine months and one year; the slowest infection was observed four years after inoculation.

Typical and atypical systemic manifestations have been observed in *D. sabanicola*, as well as localized manifestations. Histological aspects of each of the different types of leprosy lesions in this species are presented.

II 58

Experimental leprosy in nine-banded armadillos imported into UK from USA

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Our experience and procedures since 1974 for successfully establishing experimental leprosy in nine-banded armadillos imported from USA will be presented. By using the intravenous route for inoculation and a dose of not $< 10^8$ *M. leprae*/animal, we have obtained some 60% of heavily infected animals by 12-24 months. Bacteriological data on the yields of *M. leprae* from the liver, spleen and lymph node will be presented.

The value of methods for monitoring the progress of the infection, including nasal smears, bacteriaemia, biopsies of ear skin and anti-mycobacterial antibodies, will be discussed. The antibody studies are part of a collaborative programme with Professor M. Harboe (Oslo) and are also being used as a method for identifying armadillos, as caught from the wild, that may already have a mycobacterial infection.

II 59

Inoculation of *Mycobacterium leprae* into 3 species of autochthonous armadillos in Argentina

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The results of the inoculation of *M. leprae* into 3 species of autochthonous armadillos in Argentina are reported.

The 3 species — *Zaedus pichy*, *Chaetophractus villosus* and *Dasypus hybridus* — received repeated intradermal and intracardiac inoculations of bacilli.

The inocula were obtained from untreated lepromatous patients and were prepared according to Dr Storrs' technique with 10^8 bacilli per ml in the resulting suspension.

In the first two species, tuberculoid granulomas developed at the site of the intradermal inoculation 5 months after the first inoculation. Further tuberculoid granulomas appeared 40 days after a subsequent inoculation. In *Dasypus hybridus* we did not observe the development of lesions, even when the identical technique was followed. After these results were obtained, *Dasypus novemcinctus* was included in the investigations. Immunological research in the 4 species is being undertaken. All the animals are being kept for the purpose of obtaining comparable immunological models.

II 60

Study into the susceptibility of armadillos to infection by *Mycobacterium leprae*

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Two species of armadillo (*Chaetophractus vellerosus*, *Euphractus sepcinctus*) were inoculated with a suspension of *M. leprae*.

C. vellerosus was divided into 11 groups composed of 5 to 8 armadillos in each, and *E. sepcinctus* into 4 groups of 3 animals in each.

The number of bacilli injected ranged from 10^4, 10^6, 10^8 up to 10^9. The methods of inoculation used were the intradermal (ear lobe), subcutaneous, intraperitoneal or intravenous, and the dose was administered from one to five times during the course of 6 months. Approximately 60% of the animals injected presented with visible granulomata at the end of 6 or 8 months. Some granulomata enlarged and others diminished with the passage of time.

Bacteriological and histopathological examinations of several organs were carried out from 6 to 30 months after inoculation. The appearance of granulomata does not seem to depend on the number of bacilli, the route, or the frequency of inoculation. The present results seem to indicate that susceptibility of armadillos to infection by *M. leprae* might be genetically determined.

II 61

Effect of vaccine from ICRC bacilli against *Mycobacterium leprae* infection in mouse footpad

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In the search for a vaccine in leprosy, the possible candidates are *M. leprae* from armadillo and cultivable mycobacteria and their combinations with BCG to induce specific immunity. The strain C-44-ICRC bacilli isolated from lepromatous nodules has been shown to possess a close antigenic relation with *M. leprae*.

A vaccine was prepared from a culture of strain C-44-ICRC by γ-irradiation (140 K rads). Two batches of mice (CBA) were injected subcutaneously with 10^7 organisms per mouse. Each batch was divided into 4 groups with an equal number of untreated mice. One group was challenged with 7.5×10^3 fresh *M. leprae*/ footpad, 7 days after vaccination and other groups after 1, 2 and 3 months.

The growth of *M. leprae* in all the 'control' mice followed the normal growth pattern, yielding 8×10^4 to 2×10^6 orgs/F.P. during 7 to 10 months. In vaccinated mice challenged after 7 days and 1 month, early yields were higher ($\times$ 2.5) than in the untreated mice. This indicated an enhancement phase. However, the numbers dropped sharply ($\times$ 0.6 to $\times$ 0.2) at 9 and 8 months respectively, followed by a rise. In other groups (2 and 3 months), the growth was suppressed without initial enhancement.

The results clearly demonstrate that irradiated ICRC bacilli induce protective mechanism against *M. leprae* infection in the mouse footpad, developing 6 weeks after vaccination. The pattern of growth in vaccinated mice suggest specificity of action. These data also establish the feasibility of the mouse model for anti-leprosy vaccines.

II 62

Experimental transmission of a feline non-tuberculous mycobacterial skin disease resembling leprosy

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Since 1970, more than 35 cases of a non-tuberculous mycobacterial skin disease have occurred naturally in cats on the West coast of Canada, particularly in the Vancouver area. The agents are non-culturable and the histological features of the disease resemble human leprosy, i.e. both the lepromatous and the tuberculoid forms have been observed.

Experimental infections with material from diseased cats caused large subcutaneous and generalized lesions in rats after 9 to 12 months post inoculation, and cutaneous lesions in cats after 9 to 15 months, regardless of whether or not the material was passaged through rats or cats repeatedly. In one feline case, a nasal granuloma was also observed.

Fluorescent antibody studies show that the agent gives a positive reaction with *M. leprae*, *M. lepraemurium*, *M. smegmatis*, *Nocardia brasiliensis* and diphtheroid bacteria described by Delville.

Although the identity of the agent has not been established, the disease might be a very useful model for the study of human leprosy.

II 63

Skin lesions, granulomatous hypersensitivity and cutaneous nerve damage induced by sensory peripheral nerve as antigen

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Systemic skin lesions resembling those of non-lepromatous leprosy have been induced in 16 out of 26 Dutch Bantam rabbits using human sural nerve plus Freund's adjuvant.

Ten rabbits previously injected with human sensory peripheral nerve (sural or dorsal roots) have developed a state of granulomatous hypersensitivity i.e. when skin tested with 10% sural nerve they have developed epithelioid cells organised into tubercles. Ultrastructurally these epithelioid cells show in their cytoplasm abundant and dilated rough endoplasmic reticulum filled with an electron dense product. In two of these rabbits, epithelioid cells have been found in the cutaneous nerves and there is degeneration of unmyelinated fibres.

Thus all the essential features of the skin lesions of non-lepromatous leprosy have been reproduced on our experimental model. These experiments suggest that the skin lesions in the human disease are auto-immune responses to sensory nerve rather than direct responses to *M. leprae*.

A specific diagnostic test for leprosy, similar to the Kveim test for sarcoidosis, is now possible, using sensory nerve as the antigen.

II 64

The non-myelin human nerve antigen producing granulomatous hypersensitivity in rabbits

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The antigen of human sensory peripheral nerve involved in the production of the granulomatous hypersensitivity response in rabbits with its associated degeneration of cutaneous unmyelinated fibres is not a component of myelin. Very high skin-test doses of myelin are negative. Skin testing of crude subcellular fractions of the non-myelin component of nerve strongly indicates that antigen is present in the low speed, so-called nuclear, fraction. Membranes may be obtained from the well-washed nuclear fraction of dorsal roots by means of a discontinuous sucrose gradient, and these are positive on skin test. Consistent with this is the observation that the detergent 2% deoxycholate (which dissolves membranes) can extract antigenic activity from the sural nuclear pellet. After removal of deoxycholate, the extract is positive on skin test at doses of less than 1 μgm total protein. Like the Kveim antigen, the antigen of the nuclear fraction is resistant to extraction by organic solvents, the residue retaining full activity. Thus, it is unlikely to be a lipid or glycolipid. Since the mitochondrial and microsomal sub-fractions are negative, and the active membrane fraction is less dense than the nuclear envelope, the antigen is possibly a protein or glycoprotein component of Schwann cell plasma membrane.

II 65

Electrophysiological studies of experimental sensory polyneuritis in rabbits

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An acute sensory polyneuritis occurs in patients with non-lepromatous leprosy. To test the hypothesis that this polyneuritis may be an auto-immune response to sensory peripheral nerve rather than being directly due to *M. leprae*, rabbits were injected in the footpad of one hind limb with different types of human peripheral nerve (sural, dorsal and ventral roots) plus Freund's complete adjuvant. Electrophysiological studies were carried out in the sural nerve of the opposite hind limb. In 3 experiments, preliminary sensory testing was conducted by placing the injected rabbit among 5 controls. The 2 examiners independently tested the 6 rabbits for response to pinprick. In all cases the animal not responding or showing a reduced response to pinprick was the injected animal. Electrophysiological studies on the sural nerve showed slowing of conduction in the fastest myelinated fibres; the A delta fibres appeared normal.

Of the two groups of unmyelinated fibres, the faster appeared to be normal, but the action potential of the slower was reduced in size and was more diffuse.

The treatment caused damage to the fastest myelinated and the slowest unmyelinated fibres.

These experiments may be useful in elucidating the pathogenesis of sensory nerve damage in leprosy.

II 66

Experimental allergic neuritis

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It has been reported earlier that basic myelin protein from human peripheral sensory nerves when injected into the footpads of rabbits, produces a neuritis simulating leprous neuropathy, and that it can serve as an experimental model. An attempt was made to reproduce the observations made. Human sural nerve myelin proteins were injected into footpads of rabbits, rats and mice. No specific comparable lesions were noticed.

Furthermore, basic myelin protein obtained from sural nerves of monkeys and dogs was injected into different groups of CBA mice.

II 67

Nerve damage in leprosy — a quantitative study

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In order to study nerve damage in leprosy, a quantitative study was undertaken in human as well as experimental models. Sural nerve biopsies were obtained from patients with early lepromatous leprosy. Experimental lepromatous leprosy was induced in mice by footpad techniques after thymectomy and total body irradiation. The nerves were processed for electronmicroscopy and light microscopy; single nerve teased preparations were made; fibre diameter and internodal lengths were measured and statistically analysed and will be correlated with the degree of nerve damage manifested. The results are presented and discussed.

II 68

Infectiousness of human leprosy bacilli in mice

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Investigators have reported success in the experimental transmission of leprosy to mice that had been treated by various immunosuppression techniques.

In this paper five different methods of immunosuppression are discussed, (1) $Na^{131}I$-injection, (2) radiation, and (3) $Na^{131}I$ added to radiation, all administered to pregnant mice to immunosuppress their foetuses, and then to their littermates, (4) anti-lymphocyte serum (ALS) administration, (5) nude (nu/nu) mice, with normal mice as control. Acid-fast bacilli (AFB) were evident nine months after the injection with leprous bacilli on stamp-smear samples of the testes of the inoculated sites. AFB(+G) in globi was compared with the positive results in each leprous strain.

Group A leprous strains showed approximately 10% infectiousness in both the suppressed and the non-suppressed mice. Group B leprous strains in suppressed mice alone was about 40%, but the positive rate was different for the various suppression methods above and in the several strains of mice. The remaining mice in Group C showed no infection in either the suppressed or non-suppressed mice.

However, in these groups, the strains of the leprosy bacilli were all pathogenic for nu/nu mice.

II 69

Indigenous leprosy in armadillos (*Dasypus novemcinctus*)

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In 1974 a disease resembling experimental leprosy in the armadillo was first detected in an armadillo that had been recently captured in Louisiana. We have now seen 60 armadillos with a similar infection. These animals came from 12 sites, 12 to 325 miles from New Iberia, Louisiana.

The lesions in animals with indigenous leprosy were similar histopathologically to experimental leprosy and were characterized by infiltrations of histiocytes that contained large numbers of acid-fast bacilli (AFB), including globi. Nerves were invaded by the AFB.

The AFB causing these lesions were non-cultivable on Lowenstein-Jensen medium and their acid-fastness was extracted by pyridine. Lepromins prepared from tissues of infected armadillos gave a pattern of reactions in leprosy patients that paralleled those to human lepromin.

Detailed epizootiological and histopathological studies of indigenous leprosy in armadillos may provide valuable information on modes of transmission of leprosy in nature.

II 70

Spontaneous leprosy in a chimpanzee

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A five year old male chimpanzee captured in Sierra Leone was inoculated with bovine leukemia virus. Two months later the animal developed a dermatitis and eventually nodules on the ears and face. The skin of the hands and feet became diffusely thickened and ulcerated. Histologically the nodules were composed of foamy macrophages with some lymphocytes and neutrophils. Acid-fast organisms were seen within the macrophages, small dermal nerves,

a branch of the radial nerve at the level of the carpus, circulating monocytes and in nasal exudates. The animal was Mitsuda- and tuberculin-negative.

Tests to identify the acid-fast organisms included inoculation of rats, mouse footpads, and artificial media; the DOPA-oxidase test; extraction of acid-fastness by pyridine; and lepromin testing in leprosy patients. Results of these procedures indicated that the organism was either *M. leprae* or indistinguishable from *M. leprae*.

The chimpanzee died (anesthetic-related) 33 months after the first clinical signs were seen. Tissue collected at necropsy showed lesions of leprosy in subcutaneous lymph nodes, nasal septum and turbinates, epiglottis, lung, liver, spleen, kidney, eyes, major nerves of the forelimb and skin.

II 71

The histopathology of experimental leprosy in the armadillo: *Dasypus novemcinctus*, Linn., and *Dasypus sabanicola*, Linn.

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In late 1974, twenty *D. novemcinctus* (9-banded) armadillos were imported from the United States to the United Kingdom where they were inoculated intravenously and subcutaneously with *M. leprae* from patients with untreated lepromatous leprosy.

There were 4 deaths in the early months, but of the 16 survivors, 9 showed gross evidence of infection within 11 months of inoculation. Histopathological examination of a wide range of tissues revealed large numbers of bacilli, many in apparently viable form (MI 20-40%), in skin, peripheral and dermal nerves, nasal tissues, bone marrow, endothelial lining cells of vessels, tendon, synovium, viscera (including lung), eye and tongue. These findings, from the first armadillo colony established outside the Americas, confirm the widespread nature of the experimental infection without a cell-mediated response on histopathological examination.

In early 1976, 5 *D. sabanicola* (8-banded) armadillos, imported from Venezuela, were similarly inoculated. Excluding one early death, 4 animals sacrificed at 2 years revealed a heavy infection, with a *low* MI, but still with no evidence of a cell-mediated immune response.

The histopathological findings will be presented in confirmation of the extraordinary susceptibility of 8- and 9-banded armadillos to experimental infection with *M. leprae*, and the wide distribution of bacilli in many different tissues and cells.

II 72

Armadillo classification and relation to humans

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The nine banded armadillo, *Dasypus novemcinctus* L. is highly susceptible to human leprosy. However, there may be differences in susceptibility between species and sub-species within the Dasypodidae family. Evidence to date shows that 3 of 5 species of the genus *Dasypus* develop disseminated leprosy, but there are 7 other armadillo genera on which little or no information is available.

The research potentials of armadillos in leprosy as well as studies on other human abnormalities are substantial. A consideration of the armadillo's relation to man makes this family of even greater research interest. Armadillos are mammals of the cohort Unguiculata, order Edentata. Primates are also members of this cohort. All orders of this group are probably descended from a primitive insectivore. Other commonly used laboratory animals such as rodents, rabbits, and dogs are members of other cohorts. Thus, the armadillo is more closely related to primates phylogenetically than other commonly used research animals.

Like humans, *D. novemcinctus* possesses a simplex uterus, hemochorial placenta, and pelvically located ovaries whose interstitial glands do not possess stromal tissue or medullary cords. Gonadal adrenal tissue is invariably found in the ovaries. The armadillo adrenal possesses a foetal zone histologically and developmentally similar to that of humans and other primates. Similarities in the development of the hypothalamo-hypophysial neurosecretory system between the armadillo and the human foetus add one more feature to make the

armadillo attractive as a comparative animal model.

II 73

Inoculation of hedgehogs (*Erinaceus europaeus*) with *Mycobacterium leprae*

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Following the report on the infection of armadillos with *M. leprae*, we suggested conducting the same experiments with hedgehogs. These nocturnal hibernators originated during the Cretaceous Period. Their body temperature in summer is ca. 35-36°C, in winter ca. +1°C. Not much is known about their immunological properties, which may be primitive. We have carried out controlled breeding of two generations of hedgehogs free from parasites. A suspension of *M. leprae* from patients with untreated lepromatous leprosy was inoculated into these as well as into trapped animals. Thirteen months later two animals developed dimorphous granulomas with intracellular acid-fast bacteria at the site of the inoculation. A third animal, with more granulomas on the belly, is now hibernating, 20 months after inoculation. It is not quite clear whether the bacteria are persisters or newly grown in the granuloma. This investigation shows that hedgehogs perceive *M. leprae* as a pathological organism. The research will continue.

II 74

Serum glycoprotein studies in armadillos experimentally infected with *Mycobacterium leprae*

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Various investigators have reported increased levels of serum glycoprotein in a number of pathological conditions including malignancies, rheumatoid arthritis, disseminated lupus erythematosus and certain bacterial infections. It has been postulated that this increase is associated with inflamed or otherwise altered tissue.

Inasmuch as the armadillo is now employed as an experimental animal in leprosy research, a study of the serum glycoprotein (expressed as protein-bound hexose) in the experimental disease was undertaken.

Protein-bound hexose and total protein determinations were made on sera collected from two groups of armadillos: (1) non-inoculated and (2) armadillos experimentally infected with *M. leprae*. In the latter group, determinations were made on sera collected at intervals dating from time of inoculation until the animal was sacrificed. In addition, the organisms present in liver and spleen from infected armadillos were counted to determine the degree of dissemination in these organs.

Raised protein-bound hexose levels and increased hexose/protein ratios were found in the sera from infected armadillos when compared with non-inoculated armadillos. These results suggest that a correlation may exist between the serum protein-bound hexose level and the degree of activity of the disease process in armadillos experimentally infected with *M. leprae*.

II 75

Distribution of pseudocholinesterase types in patients with leprosy

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Pseudocholinesterase types (dibucaine number) were determined in 115 patients with lepromatous leprosy and 133 controls of similar ethnic extraction. Among the former, one homozygous and 21 heterozygous individuals with the atypical enzyme were found, while in the control group only 7 heterozygous persons were encountered. The differences were statistically significant (p0.01). These results agree with those published by Thomas and Job on 721 Indian patients with leprosy, and support the hypothesis that the presence of atypical pseudocholinesterase plays a role in susceptibility to this disease.

II 76

Chemotaxis in Virchowian Hanseniasis (lepromatous leprosy)

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H. M. BRASCHER
J. VARGENS NETO

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Recently, special attention has been directed to chemotaxis in several diseases. An investigation was carried out into Virchowian Hanseniasis (VH). Boyden's technique, modified by Snyderman and Pike, was used. It was found that in four cases of VH:

1. the monocytes were "lazy"; that is, their migration towards casein was slower than in normal monocytes;
2. the serum level of chemotatic factor inactivator (CFI) was high in cases of VH (41% of inactivation in VH, while only 1% was found in TH and IH).

Attention is drawn to the possible role of monocytic chemotaxis in the pathogenesis of Hanseniasis.

SESSION III
CLINICAL ASPECTS

Tuesday, 14 November 1978
9:00-13:00
Auditorium 1
Chairman: **F. LATAPI (Mexico)**
Rapporteur: **K. RAMANUJAM (India)**

Invited Papers

Abstracts

III/77 The polar concept.
F. E. RABELLO (Brazil)

III/78 Lesiones tempranas. Casos "1."
J. E. CARDAMA (Argentina)

III/79 The Saidapet story. Findings of a 19 year follow-up of children with untreated leprosy.
K. RAMANUJAM (India)

III/80 The spectrum of leprosy — the intermediate zone.
A. C. MCDOUGALL (Great Britain)

III/81 Reactional episodes.
R. C. HASTINGS (USA)

Free Communications

Abstracts
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Poster Communications

Exhibition Area
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CLINICAL ASPECTS

III 77

The polar concept: as it stands today

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According to the immune-responses, the fairly well limited spectrum of clinical forms embodies two definitely opposed groups — namely immune-negative L (V — Virchowian) and immune-positive T, leaving a group I "indeterminate" or incipient with respect to the immunological response.

These groups are by definition unstable and changeable, constituting the dynamic aspect of this conceptual approach, the Zone of Instability.

In marked contrast with these groups, forms exist that are characterized by their rigid stability and mutual incompatibility — the polar types L(V) and T (so-called polar LL and TT).

A most important phase of the disease is to be found in group I (here renamed Incipient) comprising up to 50-70% of all cases of the disease: the "Endemic Matrix", in the pre-granulomatous area of the Zone of Instability.

These incipient forms, a valuable tool in field work, are at present well defined on clinical, histological and immunological grounds.

In disagreement with what was proposed in Madrid 1953, we suggest that the so-called "group" B or D should be deleted. These forms are actually and by definition included, for the most part, in the immune-negative L(V) group, a series of histotypes being labelled B, BB and BL — which are less than 10% of all forms of the disease.

III 78

Early lesions

J. E. CARDAMA

Buenos Aires, Argentina

a) General introduction. History, definition, existence as a concept and in leprosy practice. Importance in epidemiology.
b) Clinical, immunological, histological, bacteriological features, etc.
c) Importance of early lesions as "matrix" of all other clinical forms.
d) Crucial importance of treatment in this stage.

III 79

The Saidapet story. Findings of a nineteen year follow-up of children with untreated leprosy

K. RAMANUJAM

Schieffelin Leprosy Research and
Training Centre, Karigiri, South India

In the thirties, little was known about leprosy amongst children. Cochrane held the view that childhood leprous lesions were often abortive. The basic data on child leprosy were lacking. This situation led to the establishment of the Silver Jubilee Children's Clinic by Cochrane at Saidapet, India, in the year 1937.

The objectives of this unit were to study the manifestations of leprosy in children, to assess clinically the relative seriousness and prognosis of the various types of leprosy, and to discover what happens to child leprosy if untreated.

Between 1937 and 1956 a total of 1147 children with definite and suspicious signs of leprosy were admitted. The children were subjected to careful documentation. They were not given any treatment. Such untreated children numbered 690. They were called up for re-examination at periodical intervals. The documentations were repeated when necessary.

FINDINGS:

Type distribution: The most frequent type of leprosy was the minor tuberculoid, 42.1%. Next came the maculo-anaesthetic (macular tuberculoid), 31.8%. Lepromatous and major tuberculoid cases constituted 10.3% and 9.9% respectively. 4.2% suffered from the incipient lesions of childhood.

Evolution: Spontaneous healing was maximal in the major tuberculoid cases, 88.7% and they remained 'polar'. In the minor tuberculoid variety the rate of healing was 78.4% and there was transformation to major tuberculoid and to lepromatous in 0.6% and 1.2% of the cases respectively. The regression in the maculo-anaesthetic group was 55.4%, and 9.4% of them turned lepromatous and a few into minor and major tuberculoid and borderline leprosy. Cochrane's assessment of the incipient lesions of childhood as a potentially malign form of the disease was amply borne out by 54.3% of these cases turning lepromatous over the years.

III 80

The spectrum of leprosy — the intermediate zone

A. C. McDOUGALL

Slade Hospital, Oxford, England

Those forms of the disease between the poles of lepromatous and tuberculoid, variously called intermediate, borderline or dimorphous, will be described. Our increased knowledge of the immunological processes behind the clinical appearances in these forms of leprosy has done much to resolve some of the previous confusion in terminology. There is, however, still room for improvement, particularly in field work, where the classification at the outset may be of practical importance in relation to the likelihood of 1) adverse reactions, 2) disability/deformity, 3) deterioration towards the lepromatous pole, and 4) to the total period of drug treatment needed to achieve cure of the infection.

In contrast to patients with lepromatous leprosy (where the lesions are largely the result of the sheer accumulation of bacilli and macrophages in the tissues), patients with borderline (dimorphous) leprosy often present because of cellular reaction to the presence of leprosy bacilli, sometimes in relatively small numbers. Factors determining the patient's level of 'reactivity' and the point in time at which this occurs, following inoculation, are still poorly defined. Our knowledge of the mechanisms at work in "D" leprosy will be advanced only if we insist on interpreting the clinical, histopathological and immunological findings in close relation to a full medical and social history from each patient, including his drug intake. We must also acknowledge the need to do this on several occasions, often over a period of many years.

III 81

Clinical aspects — reactional episodes

R. C. HASTINGS

USPHSH, Carville, La., U.S.A.

Reactional episodes or lepra reactions (or simply reactions) are thought to be clinical manifestations of allergic or hypersensitivity reactions to antigens released from non-viable *M. leprae*. Fundamentally two types of reactions occur in leprosy. Type I or reversal reactions can occur in patients with T lymphocytes sensitized to *M. leprae* antigens, hence they are seen in borderline and tuberculoid patients. The basic immunopathology is that of a delayed hypersensitivity reaction (Type IV hypersensitivity — Gell & Coombs). The typical clinical picture is the development of acute erythema and oedema of pre-existing borderline-tuberculoid skin lesions and parallel inflammation of previously involved peripheral nerves.

Type II or erythema nodosum leprosum (ENL) reactions can occur in patients with high titres of anti-*M. leprae* antibodies, hence they are seen in lepromatous and borderline-lepromatous patients. The fundamental immunopathology is thought to be a multi-focal Arthus reaction, usually with evidence of circulating immune complexes in severe cases (Type III hypersensitivity — Gell & Coombs). Clinically ENL is characterized by the development of crops of tender erythematous skin nodules and is associated with fever and varying degrees of inflammation of a variety of other tissues and organs containing *M. leprae*.

III 82

Clinical and histological studies of the nose in treated lepromatous leprosy

R. P. E. BARTON
A. C. McDOUGALL R. THEODORE

St. Mary's Hospital, London, England

The initial clinical, bacteriological and histological findings in the nose of a series of

patients with early untreated lepromatous leprosy were presented at the Tenth International Leprosy Congress at Bergen in 1973 (Paper 6/47). Further details have subsequently been published.

The original group of patients has been kept under observation over 5 years. Their progress is reported. A further larger group of lepromatous patients on dapsone treatment for periods of between 3 months and 8 years has also been studied in detail and the findings are presented.

The importance of the nose in the initial assessment of lepromatous leprosy is now generally accepted. In this paper the significance of careful attention to the nose in lepromatous patients on dapsone therapy, whether regular or irregular, is argued. Clinical, bacteriological and histological evidence is given.

III 83

Involvement of the respiratory system in leprosy

B. KUMAR S. KAUR S. K. MALIK
R. N. CHAKRAVARTY M. P. SINGH

Postgraduate Institute of Medical Education and Research, Chandigarh, India

Involvement of the respiratory system was studied in 25 leprosy patients selected at random. The history pertaining to the respiratory system was recorded. Nasal and sputum smears were studied for AFB. AFB culture of sputum was made, and two views of chest X-ray taken. Anterior and posterior rhinoscopic and detailed laryngoscopic examinations were carried out. Under general anaesthetic, biopsies were taken from the following structures: epiglottis, false vocal cords, right upper and lower bronchus.

AFB were seen in 58% of patients with lepromatous, and in 12% with borderline leprosy. Bronchial smears were positive for AFB in 12% of patients. AFB were not found in any epiglottis or false vocal cord biopsies. One specimen each of the upper and lower bronchus showed AFB.

III 84

The effect of different therapeutic regimens on the acetylcholine sweat function test (SFT) in tuberculoid leprosy

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N. PARISIS J. CAPETANAKIS

Skin and Veneral Diseases Clinic, University of Athens, Greece

Anaesthesia, anhidrosis and hypohidrosis are among the principal manifestations of tuberculoid leprosy.

In assessing the effectiveness of different therapeutic regimens (rifampicin, clofazimine, dapsone), the SFT (Parikh) was performed and the cutaneous sensation was observed before, during and after one year's treatment of the tuberculoid lesions of 32 patients.

The results indicate that after one year's treatment in 14 out of 18 patients with rifampicin and in 3 out of 7 patients with clofazimine, a satisfactory improvement in the SFT and the thermal and touch sensation was achieved, while in the 2 out of 7 patients under dapsone treatment only a slight to moderate improvement of the SFT and the thermal and touch sensation was observed.

III 85

Characteristics of dimorphous leprosy in the Dominican Republic

D. MARTINEZ R. RICART

Instituto Dermatologico y del Programa de Control de la Lepra, Santo Domingo

The writers review 300 cases of dimorphous leprosy registered in the records of the Dominican Institute of Dermatology. These were studied from the clinical, immunological, bacteriological and histopathological points of view; also by sex, race, age group, time from onset, signs of lepromatous reaction, neuritis, and the presence of disabilities.

They also reviewed the treatment prescribed for these patients, the duration of treatment before clinical quiescence, sources of contagion, etc. They show the increase in the annual occurrence of these cases, that 3.4% were new patients during 1973 and 26.8% during 1977. The writers classify the cases into borderline-

tuberculoid, borderline-dimorphous, and borderline-lepromatous, according to the clinical, immunological, bacteriological and histopathological characteristics found in the dimorphous spectrum.

III 86

The effect of leprosy in mothers on their children before and after birth

M. E. DUNCAN

MRC Leprosy Project, Addis Ababa, Ethiopia

In a prospective study, 114 women with leprosy and 36 without leprosy were followed throughout pregnancy and for up to 2 years after delivery. The babies of lepromatous mothers weighed significantly less than those of non-lepromatous or healthy mothers, whether or not leprosy bacilli were present in the mother's skin smears. The placental weights followed the same trend. Lepromatous leprosy might be suitable as an "experimental model" for studying placental insufficiency.

The babies of lepromatous mothers gained weight rapidly after birth, implying that their low birth weight was due to a placental factor: but after 6 months of normal growth while being breast-fed, they began to do badly. They failed to gain weight at the normal rate, several became marasmic, and many were unduly susceptible to skin, respiratory or gastrointestinal infections. This trend of "failure to thrive" was not seen in babies of non-lepromatous mothers.

III 87

Tuberculoid relapse in lepromatous leprosy

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When lepromatous patients relapse while still receiving dapsone therapy (due to the emergence of dapsone-resistant strains of *M. leprae*), their relapse lesions retain lepromatous (LL or BL) characteristics, including those graded as histoid or hyper-active. The same is usually true of those patients who relapse after stopping treatment after receiving many years of apparently successful dapsone therapy. However, we have observed small numbers of the latter type of patient who after stopping treatment have relapsed with tuberculoid lesions, clinically and histologically classified as borderline-tuberculoid (BT). Examples will be described, and the clinical and immunological significance of the findings will be discussed.

III 88

Renal damage in leprosy

V. K. LOGINOV Z. A. SLUVKO

Leprosy Research Institute, Astrakhan, USSR

For detailed elaboration of the picture of renal damage in leprosy, 80 patients (mainly with lepromatous leprosy) were studied with the help of functional tests. Kidney damage occurred even in the early stages of disease, glomerular filtration and concentration function being specially vulnerable. This was proved by comparison of the urea and creatinine concentration in blood and urine, amylase and diastase activities, clearance rate, calculation of the Ambar constant and concentration coefficient by creatinine and glomerular filtration rates. The severity of functional renal disturbances was related to the course and duration of the disease and the occurrence of exacerbations. In cases of longstanding leprosy, renal function declined owing to the accompanying disturbances of the tubular apparatus.

Some toxic effect on renal function was found to be due to long-term treatment with sulphones only or the giving of sulphones and other antileprosy drugs. The data obtained suggest that it is necessary to control the renal function in patients undergoing sulphone therapy and to administer nonspecific drugs that improve the function of the glomerular apparatus and prevent the appearance of secondary pyelonephritis.

III 89

Inflammatory arthropathy in leprosy

J. ALCOCER R. HERRERA

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Hospital General Centro Medico La Raza, Mexico

Bone involvement is common in leprosy, but little attention has been given to joint changes in that disease. It is for this reason that this investigation was undertaken.

Eighteen patients with leprosy were studied prospectively (12 with lepromatous, 3 with indeterminate, 2 with tuberculoid and 1 with dimorphous leprosy) by clinical examination, X-rays, joint scan with ^{99}Technecium and, in four cases, synovial biopsy.

Fourteen patients had joint symptoms. On examination, 17 patients had pain and inflammation of joints, especially the hands, wrists, knees, ankles, elbows and feet. Four patients had acute polyarthritis during erythema nodosum leprosum with histological changes of non-specific synovitis.

X-ray changes were mainly in bone. In 14 scans there was increased joint uptake of the radioactive substance, attributable to synovial inflammatory changes which correlated clinically with the joint involvement, principally in the lepromatous cases. Bone changes predominated in tuberculoid and indeterminate leprosy.

Careful clinical examination and joint scanning show that inflammatory arthropathy in leprosy is more common than reported hitherto and that it is independent of the neuropathy.

III 90

The histoid nodules in lepromatous leprosy

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General Hospital, Mexico

Although since 1960 Rees presented in London the first Wade's observations on the existence of lepromas with histological features of histiocytofibromas, the histoid variety of lepromatous leprosy was described in 1963.

These lesions occur in patients with old, sulphone-resistant leprosy: subcutaneous or cutaneous, rounded, shiny, well-defined nodules formed of spindle-shaped histiocytes arranged in whorls with numerous bacilli.

Two patients with this kind of lesion are presented. The first one: 42 year old man who had had irregular dapsone treatment and several relapses, presented with many nodules with clinical and histological aspect of fibromas but with very few bacilli. Three months' treatment with rifampicin produced flattening of most lesions, but neither histological nor bacteriological changes.

The second case: 24 year old man without previous treatment, with many large nodules resembling fibromas, histologically formed by both spindle-shaped and foamy histiocytes and numerous bacilli. Three months' treatment with rifampicin produced slight clinical improvement.

The authors think that any lepromatous patients could have histoid and ordinary nodules at the same time, but specially those who present complete or partial dapsone resistance. The histoid nodules can be present in patients who have not had treatment.

III 91

Leprosy and the Bureau Barrière syndrome

J. J. GALLI A. G. VINCITORIO

Parana E., Republic of Argentina

The differential diagnosis between Hansen's disease and the ulcerative acropathy of Bureau Barrière is discussed. Each zone has its own pathology; the coast of Argentina is an endemic leprosy zone and has a high incidence of alcoholism.

The diagnosis of these infections has often been confused. Therefore an exhaustive analysis of the differences in clinical presentation of the two infections was undertaken.

III 92

Fundamentals of the term "Facies Antonina"

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The term "Facies Antonina" is given to signify certain facial changes in patients suffering from the late stage of tuberculoid leprosy. In this investigation we are concerned with the clinical symptomatology, briefly distinguishing it from the "Facies leonina" of lepromatous leprosy. The linguistic origin of the term will be examined. By comparing "Facies Antonina" with 15th century paintings, an astonishing analogy becomes evident. On the basis of these findings it appears that the term discussed has been derived from certain paintings of the Renaissance period.

III 93

Eczema is another important complication of leprosy

S. GHOSH S. CHAUDHURY
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School of Tropical Medicine, Calcutta, India

Eczematoid lesions affecting some parts of the body, particularly the lower extremities, are frequently seen among leprosy patients. A review of the literature revealed that the etiopathogenesis of this condition has not yet been properly investigated. It was, therefore, thought worthwhile to investigate this dermatological condition in all aspects.

A sample survey was undertaken to find out the incidence of eczema among 234 leprosy cases, comprising an equal number of lepromatous and non-lepromatous types. 27 cases were found to be suffering from eczematoid lesions in the lower extremity in one limb or in both.

The probable etiological factors responsible for this condition were thought to be (1) allergic reaction to sulphones (2) anhidrosis and (3) anaesthesia.

These cases were then investigated clinically, histologically and chemically in an attempt to discover the factor responsible for this condition.

Most interesting were the histopathological findings — there were specific changes in the arterioles, atrophy of dermal glands due to non-specific factors. Clothing habits of this part of the country also have an important bearing on this condition.

III 94

Ichthyosis in Hansen's disease. Histological, clinical and smear studies in localized ichthyosis

R. ANNAMALAI

Government Stanley Hospital, Madras, India

Ichthyosis, or dry skin, may be genetic in origin or acquired. The genetic type of ichthyotic skin disorders is not included in this study.

In the acquired type of ichthyosis, the affected area may initially be localized, and later may become generalized.

In the 200 cases studied, the common site of involvement was the anterolateral skin surface of the lower third of the leg or legs. Associated findings were: loss of hair, colour changes in hair from black to golden in other areas of the body, such as the upper extremities, pigmented knuckle-pad, minimal traumatic fissuring or deep traumatic fissuring of feet, unilateral oedema of the feet, varying degrees of sensory loss over the affected ichthyotic skin, asymmetrical thickening of nerves, recurrent vesicular eruptions of palms and feet, hyperhidrosis of palms and feet, eczematous reactions in some. In a few, an associated vitiligo was noted.

H and E histological sections showed:

1. Fenestration of collagen;
2. Tuberculoid granuloma around neurovascular elements;
3. Tuberculoid granuloma around appendages.

Alcian blue stained histological sections showed:

1. High content of acid muco-polysaccharides;
2. Collections of mast cells.

H and E histological sections or radial nerve showed:

Tuberculoid granuloma.

Smear for AFB was negative in most cases.

The majority of cases showed the early stages of tuberculoid leprosy. In a few, ichthyosis was due to myxœdema or diabetes mellitus. A therapeutic trial with dapsone gave excellent results in cases of leprosy.

Regrowth of hair occurred in 6 months after therapy with 100 mg dapsone daily. Sensation returned after a year. Pompholyx, which recurred monthly, resolved. Deep traumatic fissuring resolved after 3 months.

III 95

Occupational allergic eczema in doctors' assistants caused by sulphetrone

N. A. TORSUEV V. N. POGORELOV

Donetsk, USSR

Four doctors' assistants, aged between 30 and 60, developed, several weeks or months after they began giving intramuscular sulphetrone injections to leprosy patients, a bright erythematous rash on the dorsal surface of the fingers, palms and wrists. The rash was accompanied by burning and itching. One or two days later, oedema of the face and a conjunctivitis

appeared, and shortly afterwards the shoulders and dorsal region, which had never been in direct contact with the injected suspension, were affected. The rash consisted of small erythematous papules, followed by vesicles containing transparent fluid: these vesicles subsequently crusted over, and became infiltrated. In the interdigital folds there were painful excoriated areas. The general state of health was not impaired. The assistants ceased giving sulphetrone, and were given a course of desensitization together with external symptomatic therapy; the eruption disappeared. When contact with sulphetrone was restored, all four patients developed a severe relapse which lasted three to four months. Patch tests with 50% sulphetrone solution were strongly positive in all four patients.

III 96

Involvement of the liver in leprosy reactions

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J. C. DE ALMEIDA PERNAMBUCO
I. BASTAZINI C. J. TONELLO

Hospital Lauro de Souza Lima, Sao Paulo, Brazil

The liver is one of the organs most affected in leprosy, but there are few references to its involvement in leprosy reactions. However, the functional and histopathological picture of that liver condition has not been clearly described.

The following liver function tests were performed in 25 patients with acute leprosy reactions: serum bilirubin and transaminase, prothrombin time and activity, electrophoresis of plasma proteins, HBsAg and anti-HBsAg antibodies, BSP retention test. Skin and liver biopsies were carried out.

Similar investigations were done in 25 patients with active lepromatous leprosy without reactions.

The liver is involved in acute leprosy reaction, with histological lesions similar to the skin lesions and suggestive of reactions to immune complexes. There are foci of specific inflammatory infiltration in regression and areas of hyperplasia of the reticuloendothelial system with neutrophil extravasation and deposition of fibrinoid material. The adjacent liver tissue may show signs of necrosis with loss of trabeculation.

These lesions were intense in seven, moderate in ten and absent in eight patients with leprotic reactions. Similar lesions were not found in patients with lepromatous leprosy not in reaction.

Four patients had mild jaundice and a slight increase in serum transaminase; they belonged to the reaction group. The BSP retention test showed significantly greater abnormalities in those patients with leprosy reactions who had major histological changes.

Levels of gamma-globulin were significantly lower in patients with reactions. This finding is interpreted as due to consumption of antibodies by deposition of immune complexes during the reaction.

III 97

Arthritis in lepromatous Hansen's disease

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A prospective study was undertaken in Hospital Lauro de Souza Lima (Bauru, Sao Paulo, Brazil) of 25 patients with lepromatous Hansen's disease with arthritis, the objective being to describe the clinical, laboratory, histopathological and evolutive characteristics of the articular involvement of the leprotic reaction, erythema nodosum leprosum (reactional arthritis).

Thirty-two samples of synovial fluid and 20 biopsies of the synovial membrane were obtained from 14 patients. Bone biopsies were taken of three cases with radiological manifestations (erosions).

Articular manifestations may precede, accompany or follow the appearance of erythema nodosum leprosum or polymorphous lesions, but, in almost half the cases, they are absent. Arthritis generally has a sudden beginning and can be monoarticular, oligoarticular and polyarticular, symmetrical or asymmetrical. The

laboratory picture is similar to that of erythema nodosum leprosum reactions without arthritis, and radiological alterations such as osteoporosis, erosions, periostitis and soft tissue swelling can be observed. The synovial fluid may be non-inflammatory, inflammatory or septic and leprosy bacilli were observed in 9 samples (6 cases).

The study of the synovia showed cases with acute fibrinous or fibrinous-purulent synovitis, and bone biopsies of these cases showed osseous necrosis with intense inflammatory reaction. The paper discusses the differential diagnosis with various rheumatic diseases and one hypothesis is offered to explain the physiopathology of reactional arthritis. Also the paper describes the evolution and treatment of arthritis in lepromatous Hansen's disease.

III 98

Squamous cell carcinoma as a complication of plantar ulcer in leprosy

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R. N. FLEURY

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In the Hospital Lauro de Souza Lima, during the last 6 years, 10 cases of squamous cell carcinoma were seen adjacent to plantar ulcers in patients with leprosy. Because of its rarity (only 1.9% of carcinoma of the skin occur in the foot), the existence of very few cases reported in the leprosy literature and the unique features of these tumours, the present enquiry was undertaken. All the tumours occurred in plantar ulcers of long duration, and in one case there was a chronic suppurative osteomyelitis deep in the ulcer. The lesions had a cauliflower aspect and were ulcerated in the centre, spreading superficially and deeply. In one case there were inguinal lymph-node metastases. The histological diagnosis was difficult, despite repeated biopsies, since the neoplasm was well-differentiated and difficult to differentiate from pseudo-epitheliomatous hyperplasia. In this respect this neoplasm is similar to verrucous carcinoma of the oral cavity, giant condylomata acuminata of Buschke-Loweinstein and to the epithelioma cuniculatum described by Becker.

III 99

A case of leprous dactylitis of all fingers in borderline leprosy

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C. J. G. CHACKO

The Leprosy Mission Hospital,
Vadathorasalur, South India

A 25 year old male patient with borderline-lepromatous leprosy presented with swelling of all 10 fingers following 4 months of anti-leprosy treatment. The clinical description of "banana fingers" was apt. X-ray of the hands showed multiple punched-out shadows in the bones, presumably occupied by the granulomas. A punch biopsy from the fingers confirmed the presence of granulomas in the bone. Both the skin biopsy and the bone histology were consistent with the borderline type of leprosy. This is a well-documented case of extensive lytic lesions in bone due to leprous osteomyelitis in a case of borderline leprosy. Granulomatous infiltrations of bone, including sarcoidosis and tuberculous dactylitis, have to be considered in the differential diagnosis of this condition.

III 100

Stable tuberculoid leprosy

T. ZAMBRANO D.

Centro Dermatologico Ladislao de la Pascua,
Mexico

Stable tuberculoid leprosy is the benign form of the disease and comprises cases which recede, which are non-infective and which commonly occur in children and in the elderly.

The patient is a woman aged 80 years from Mexico D.F., with a dermatosis present for one year.

This dermatosis affects the scalp, trunk and extremities. It consists of plaques 1 to 15 cm in diameter, infiltrated, erythematous, circular and oval, with well-demarcated borders, with fine scales on the surface and with central atrophy and anaesthesia. There are no other pathological data.

Bacilloscopy negative; lepromin reaction positive. Histological report: granular infiltrate around vessels and in connective tissue.

The plaques faded after four months of treatment with diaminodiphenylsulphone 25 mg daily.

III 101

Stable tuberculoid leprosy

M. MALACARA E. AVALOS

Centro Dermatologico Ladislao de la Pascua, Mexico

Stable tuberculoid leprosy is the benign form of the disease; it is not transmissible and may recover spontaneously. A case with these characteristics is presented.

The patient was a woman aged 48 years, from Teloloapan Gro., Mexico (endemic area). She had had a dermatosis for 4 months, consisting of five violaceous erythematous plaques. These were asymmetrical, infiltrated, well-demarcated, 3 to 5 cm in diameter and dysaesthetic. The ulnar nerves were swollen and painful. Investigations showed: bacilloscopy of nasal mucosa and cutaneous lymph negative; Mitsuda reaction positive (15 mm nodule with central necrosis); 10 mm reaction in skin to trichophytin, PPD, candidine and varidase; reduction in T- and B-lymphocytes; positive MIF test to lepromin and PPD; raised CH_{50}, C_3, C_4 and immunoglobulins. Histopathology characteristic of tuberculoid leprosy.

Six months later the lesions had receded.

In this patient there was a good correlation between clinical, bacteriological, histopathological and immunological findings.

III 102

Schweninger-Buzzi type of anetodermia in Hanseniasis patients

L. MARGARIDO A. ROTBERG

Instituto de Saúde-Biblioteca, Sao Paulo, Brazil

Out of 600 adult Virchowian patients, 14 showed anetodermic lesions Schweninger-Buzzi type i.e. 2.3% significantly higher than in general population. Males more affected than females 2.9% against 1.5 which contradicts previous reports.

SESSION IV
MICROBIOLOGY

Tuesday, 14 November 1978
15:00-18:00
Auditorium 1

Chairman: **J. H. HANKS (USA)**
Rapporteur: **J. DELVILLE (Belgique)**

Invited Papers

Abstracts

IV/103 Studies on *Mycobacterium leprae* from infected armadillos.
P. DRAPER (Great Britain)

IV/104 *Mycobacterium leprae,* other mycobacteria and a possible vaccine.
J. L. STANFORD, M. J. SHIELD, G. A. W. ROOK, (Great Britain)

IV/105 Acido-résistance de *M. leprae* et problémes soulevés par sa culture.
J. DELVILLE (Belgique)

IV/106 Cholesterol, a growth factor for mycobacteria from leprous tissues.
L. KATO (Canada)

IV/107 Neuron invasion gene of *M. leprae.*
L. BARKSDALE (USA)

Free Communications

Abstracts
IV/108-IV/115

Case Presentations

15:00-18:00

Centro Dermatologico Pascua — by previous enrollment — 32 leprosy cases, mostly of the "diffuse" form were seen by 450 physicians. This presentation was arranged by Dr. Roberto Arenas.

Poster Communications

Exhibition Area

Abstracts
IV/116-IV/138

MICROBIOLOGY

IV 103

Studies on *Mycobacterium leprae* from infected armadillos

P. DRAPER

National Institute for Medical Research, London, England

The discovery that the nine-banded armadillo is susceptible to leprosy has increased greatly the amounts of *M. leprae* available in the laboratory. A heavily-infected animal may provide up to 1 gram dry weight of bacteria. Methods have been devised to extract the bacteria from infected tissues (liver, spleen and lymph-nodes) with quantitative yields. There remains some doubt as to how much the bacteria are affected by the separation procedures, and the search for 'gentler' methods for separation continues.

The main impetus for this work has been the need of the World Health Organization IMMLEP programme for quantities of suspensions of purified bacteria and cell-free extracts. It has been possible at the same time to obtain much new data on the chemistry of *M. leprae*, especially of its cell and lipids, which are produced in our laboratory as side-products of the cell-free extract.

Aspects of the separation processes used for obtaining pure bacteria, and of the chemistry of the walls of *M. leprae*, will be presented.

IV 104

Mycobacterium leprae, other mycobacteria and a possible vaccine

J. L. STANFORD M. J. SHIELD
G. A. W. ROOK

Middlesex Hospital Medical School, London, England

A number of relations have been claimed between the leprosy bacillus and certain other bacteria. The bases for these claims are one of two kinds. Either the strain has been isolated from tissues of leprosy patients, or skin-tests with tuberculins prepared from cultivable species have been shown to produce results very similar to those obtained with *M. leprae* reagents. Most of the cultivable organisms isolated from leprosy patients have been readily recognizable as species that have little in common with *M. leprae*. Their presence is due to tissue or laboratory contamination, or perhaps coexistence with *M. leprae* in immunologically defective tissues. In most cases the species isolated have been very different from species resembling *M. leprae* in skin-tests. Although the species giving tuberculin reactions like those to *M. leprae* are not noticeably similar to the leprosy bacillus in other respects, their recognition has led to some important immunological and epidemiological discoveries. As an example, results will be presented showing how killed organisms of selected species can be used to enhance the protective efficacy of B.C.G. If, following B.C.G. vaccination, the 80% protection from tuberculosis observed in Great Britain and from leprosy observed in Uganda can be made universal by such a simple and safe procedure, then we need look no further for an effective vaccine.

IV 105

Acid-fastness of *Mycobacterium leprae* and the problems raised by its cultivation

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The classical definition of *M. leprae*, acid-alcohol-fast bacteria, does not always correspond to the objective observation of the leprosy lesions. Staining by the method of Ziehl-Neelsen, indeed, fails frequently (especially in tissue sections) to detect the causative agent of leprosy. Other techniques are, however, able to detect non-acid-alcohol-fast organisms in all leprosy lesions.

If one agrees that *M. leprae* has not yet been cultivated, one must also agree that the characteristics of *in vitro* grown *M. leprae* are not known. Since *M. leprae* may exist in a non-acid-alcohol-fast phase in leprosy lesions, especially before the appearance of the acid-alcohol-fast bacteria, one may not claim that *M. leprae* must grow *in vitro* as an acid-alcohol-fast bacterium.

Careful observation of leprosy lesions and the examination of sections stained by different techniques leads us to formulate the hypothesis of the existence of a developmental cycle in *M. leprae*.

Long-lasting and careful observation of our *M. leprae* cultivation trials enabled us to note elongation of bacilli with loss of Zielh-Neelsen acid-alcohol-fastness, followed by development of diphtheroids, and, after a very long time, reappearance of typical acid-alcohol-fast bacteria and disappearance of the diphtheroids.

These facts permit the conclusion that one may not *a priori* exclude the possibility of cultivating *M. leprae* in a non-acid-alcohol-fast phase.

IV 106

Cholesterol, a growth factor for mycobacteria from leprous tissues

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Suspensions of *M. leprae* isolated from human and armadillo leprous tissues were inoculated into culture media containing yeast extract, glycerol and cholesterol, enriched with sheep serum. Cholesterol was the essential substance to obtain isolation cultures as well as subcultures. No growth occurred in the absence of molecular cholesterol or cholesterol-containing substances such as animal sera, serum albumin or egg yolk. Lipid-free sera did not promote growth, and the rate of multiplication was proportional to the cholesterol content of the sera. The optimal concentration of cholesterol in the media was 0.1 to 0.5 mg/ml, but growth occurred only when serum was added to the liquid or solid media. Cholesterol uptake by the inoculated mycobacteria occurred rapidly and in considerable amounts. The sterol was not a source of energy neither was it a source of carbon. Cholesterol accelerated not only the *in vitro* growth of mycobacteria from leprous tissues, but also shortened the growth-time of such slow growers as *M. africanun, M. tuberculosis* and *M. bovis.* These species grow within a week on semi-solid media containing cholesterol.

Cholesterol is present in macrophages and, based on the presented results, cholesterol is proposed as a growth factor for the *in vitro* primary cultivation of mycobacteria derived from hosts.

The nature of the strains cultivated from leprous tissues and their role in leprosy is not clear; neither is the mechanism known by which cholesterol facilitates the growth of the cultures isolated from leprous tissues or the slow-growing pathogenic species of the genus mycobacteria.

IV 107

Concerning the NI (Neuron Invasion) gene of *Mycobacterium leprae*

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M. leprae is described in Bergey's Manual (1976) as an obligately parasitic mycobacterium exhibiting pyridine-extractable acid fastness, capable of limited multiplication in non-immunosuppressed but generalized infection of immunosuppressed mice with a generation time of 20-30 days. (The host range of *M. leprae* has since been extended to include the nine banded armadillo, *Dasypus novemcinctus,* and perhaps one or two other species of *Dasypus.*) Three properties not listed are the "predilection" of *M. leprae* for peripheral nerves, the production by *M. leprae* of a phenol oxidase and the need of *M. leprae* to grow in "cooler parts of the body". These signal properties of *M. leprae* must be under genetic control, either directly or pleiotropically. It is convenient to designate the controlling genes as DOX (DOPA oxidase), HODep (host dependence), PeAF (pyridine extractable acid fastness), Ts (temperature sensitivity; i.e., need for "cooler parts of the body"), DT (division time) and NI (capacity to penetrate nerves). A typical mycobacterium has been chosen and the degree to which certain other mycobacteria vary from it considered. *M. leprae* is outstanding in its variance from

average. When each of its unique properties is evaluated in relation to the putative NI gene, certain conclusions seem inevitable regarding the probability of such a multivariant parasite originating from any of the known mycobacteria.

IV 108

Evaluation of bacteriaemia in leprosy patients

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Thirty-five leprosy patients have been screened for bacteriaemia by haemolysis (HL), leucocyte adherence (LA) and buffy coat (BC) methods, and the results have been compared. HL-method has yielded a higher number of acid-fast bacilli (AFB) in patients with bacteriaemia. In addition, in the present study the skin over the anticubital fossa has been taken into account while blood sampling by venipuncture, and therefore in 19 lepromatous cases two blood samples from each patient have been collected and AFB per ml of blood has been compared between samples. This study shows that skin over the anticubital fossa does not play any significant role in contaminating blood samples during venipuncture. The results will be presented and discussed.

IV 109

Mycobacterium leprae, a pleomorphic organism with a non-mycobacterial, cultivable, precursor phase

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It has been speculated that *M. leprae* has a complex life cycle. An L-form cycle was described by Chatterjee. Another phase of this pleomorphic organism may be a non-acid fast, non-bacillary form, morphologically a coccoid to cocco-bacillus. While the L-form and classical mycobacterial phases are non-cultivable in artificial media, the non-acid fast coccoids are cultivable with difficulty. These can be isolated from leprous lesions of man and infected mice. Primary isolation is difficult; maintenance requires enriched media. These organisms, after many passages, transform into a scotochromogenic mycobacterium producing an orange to orange-yellow pigment, with a characteristic odour, do not produce niacin, hydrolyse Tween 80 or reduce nitrate, and have poor catalase activity (less than 20 mm by the semiquantitative technique). While the coccoids have a strong DOPA oxidase activity, the mycobacterial converts are only weakly so.

When inoculated intraperitoneally into thymectomized mice, a generalized infection is produced, and non-cultivable mycobacteria can be recovered from footpads and elsewhere (in direct smears). Coccoid organisms may be isolated from tissue homogenates.

Antigens from isolates give results that are roughly comparable with lepromin at 24 hours, but provoke no late response.

It is suggested that these organisms may be the cultivable and infective forms of *M. leprae*.

IV 110

Rational chemotherapy of leprosy

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The emergence of drug-resistant strains of *M. leprae* is becoming a serious problem in the treatment and control of leprosy. Sulphone-resistance in leprosy has been known for several years. Recently, rifampicin-resistant strains of *M. leprae* have been reported. Rational chemotherapeutic agents that act directly on an essential metabolic activity in *M. leprae* would provide the most effective answer to the problem of leprosy caused by such drug-resistant bacilli. We have already demonstrated the occurrence of a characteristic form of the enzyme *o*-diphenoloxidase in *M. leprae*. The enzyme was present in organisms separated from infected human skin nodules, spleen and testes; from mouse footpads; and from the skin nodules, spleen, liver and lymph-nodes of experimentally infected armadillos. Now we have observed that the bacilli retain the enzyme even after repeated passages in the armadillos.

We reported previously that inhibitors of *o*-diphenoloxidase suppressed multiplication of *M.*

leprae in mouse footpads, indicating that the enzyme activity is of metabolic significance in the bacilli. In these experiments, the inhibitors were administered directly at the infection sites. The most potent of the compounds tested was diethyldithiocarbamate (DDC). Subsequently, we have treated with DDC experimentally infected animals orally as well as intravenously. It is concluded that *o*-diphenoloxidase is a constitutive enzyme in *M. leprae* and that specific inhibitors of the enzyme would be of chemotherapeutic value at least in cases where the leprosy bacilli are resistant to conventional forms of treatment.

IV 111

Mycobacterium leprae and the diphenoloxidase activity

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Our earlier studies have shown that *M. leprae* recovered from lepromatous human tissues lacked *o*-diphenoloxidase activity. The occurrence of this enzyme in *M. leprae* derived from armadillo tissues was investigated. The whole cell suspensions of *M. leprae* exhibited consistent oxygen uptake. When 3,4-dihydroxyphenylalanine (DOPA) served as a substrate, metabolically active cell suspensions failed to oxidize DOPA and thus did not enhance oxygen consumption over the endogenous activity. Incubation of DOPA with cell suspension did not show an increase in absorption at 540 nm which has been reported for an intermediate of DOPA oxidation. Although mushroom tyrosinase actively oxidized DOPA and several phenolic compounds, the enzymatically active particulate fraction of *M. leprae* was unable to oxidize these compounds and was completely deficient in *o*-diphenoloxidase activity. These results suggested that the enzyme *o*-diphenoloxidase is not a characteristic property of *M. leprae*.

IV 112

Cultivated *Mycobacterium leprae* and its antigenic reactions

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It is known that bacilli in culture may vary in biochemical composition and antigenicity as well as virulence as compared with the same strains derived from parasitized host tissues. Not unexpectedly, cultivated *M. leprae* have shown similar variations requiring comparative studies between organisms derived from *in vitro* and *in vivo* sources. Immunofluorescent specific antibody identification studies of *M. leprae* indicated that the reacting antigens were largely surface antigens, and monitoring these during culture growth indicated that the reaction was stronger in early than in late cultures. Accordingly, Mitsuda-type lepromin from culture strain HI-75 was compared with reaction to standard lepromin at four weeks in five TT-BT and ten LL patients. The former reacted similarly positive to both antigens, while the latter gave no reaction at four weeks. When the HI-75 lepromin was given to another group of eight LL patients and reaction evaluated within 48 hours, it was found that an Arthus-like reaction developed in all. Initial attempts at masking this reaction by absorption with LL serum were unsuccessful. However, on the assumption that the Arthus-inducing antigen was probably of polysaccharide nature, HI-75 lepromin was prepared from bacilli treated with enzyme disruption of polysaccharides. This antigen failed to elicit Arthus-type reaction in LL patients. The same antigen produced strong Fernandez type reaction in TT and BT patients only. The reaction was so uniformly strong (3+) as to suggest that the treatment had unmasked protein antigens generally held to be responsible for the lepromin reaction.

IV 113

Electroncytochemical study of cytochrome oxidase and peroxidase of *Mycobacterium leprae M. lepraemurium, M. tuberculosis, M. kansasii* and *M. balnei*

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The data in the literature concerning the oxidation-reduction enzymes of *M. leprae* are conflicting. For clarification of this, the comparative electroncytochemical study of *M.*

leprae and other noncultivable and cultivable mycobacteria appears to be promising.

Since 1975 we have studied cytochrome-c-oxidase activity and peroxidase activity in cells of *M. leprae, M. lepraemurium, M. tuberculosis,* strain H37Rv, *M. kansasii* and *M. balnei.* The incubation media with additives of cyanide and sodium azide were used as controls.

The osmiophilic product of oxidized diaminobenzidine (DAB), indicating the areas of cytochrome-c-oxidase activity was seen within both electrondense layers of plasma membrane (PM) and mesosomes of *M. leprae, M. lepraemurium, M. tuberculosis, M. kansasii and M. balnei.* The degree of reaction intensity on mesosomes was higher than that on plasma membrane.

In some instances we observed a more marked deposit of reaction product in outer layers of PM and inner layers of mesosomes in cultivable mycobacteria.

In *M. leprae*, which were studied directly in host tissues, the reaction product was less marked on PM and associated more frequently not with the whole membrane but only some parts of it. The product of reaction to peroxidase in both cultivable and noncultivable mycobacteria was situated in mesosomes and in both osmiophylic layers of PM. Reaction on mesosomes was more marked. In tissue cells, deposits of oxidized DAB were demonstrated in mitochondria. Thus, cytochrome-c-oxidase and peroxidase activities were demonstrated in mesosomes and PM in cells of all the mycobacteria studied. It was noted that cytochrome-c-oxidase and peroxidase activity was lower in *M. leprae* and *M. lepraemurium* than in *M. tuberculosis, M. kansasii* and *M. balnei.*

IV 114

Examination of North American armadillos for mycobacteriosis

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Between 1 January 1974 and 31 December 1977, 393 laboratory examinations for mycobacteriosis involving 373 individual wild-caught nine-banded armadillos (*Dasypus novemcinctus*) were made at Carville. Complete autopsies with histopathological evaluation were done on 188 of these armadillos. Blood buffy coat smears, histopathological ear skin clip examinations, and where indicated biopsies and smears from external lesions were done on 205 of these armadillos. Two hundred and eighty-two of the 373 feral armadillos were caught in Louisiana, 78 were imported from Florida and 13 from Texas. No leprosy-like disease was found in any of these 373 armadillos. Seventy-five of the 135 autopsied armadillos from Louisiana were caught by personnel from the Louisiana State Wildlife and Fisheries Commission in the French Acadian region where Walsh *et al.* (1975) reported a 10 per cent prevalence of "natural" leprosy in armadillos. Duplicate specimens of these 75 armadillos were examined by the Epidemiology Investigation Service of the National Center for Disease Control, Atlanta, Georgia, also with negative results.

In highly leprosy-endemic parts of South America, where many cases of leprosy receive no treatment, no leprosy-like disease was found in 569 feral armadillos (May 1977) by local investigators.

From the French Acadian region of Louisiana where armadillos allegedly acquired leprosy from patients, no new human cases were reported from 1967 to 1976. Independent verification of the claim (confirmation so far is restricted to materials supplied by Walsh *et al.*) would make mandatory inquiries into the possible ways this situation might have arisen.

Culturable mycobacteria, like *M. scrofulaceum* and *M. peregrinum*, have been isolated from armadillos at Carville and *M. avium, M. bovis* and *M. intracellulare* from *Dasypus novemcinctus* and *D. sabanicola* in Colombia.

IV 115

Continuous *in vitro* growth of *Mycobacterium lepraemurium*

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In 1972 Nakamura described a novel system in which Mlm (*Mycobacterium lepraemurium*) achieved one cycle of growth *in vitro*. This organism is an interim model for *M. leprae*, and for 69 years was an obligate intracellular microbe. The keys to success were: (a) empirical

adjustment of ORP and (b) supplementing a synthetic base with seven compounds that compensate metabolic deficiencies. Growth at 30° ceased after six weeks; serial transfers did not succeed.

Optimization of the Nakamura system increased growth rates 3.3 fold, i.e., to 8x the rates in susceptible mice. The terminations of growth and loss of growth potential after 6 weeks were due to chemical instability of the supplements. This obstacle was eliminated by substituting stable compounds. Serial transfers permitted each inoculated cell to generate 10^7 new cells. The temperature was still restricted to 30° and growth potential declined during serial transfers.

Incubation at 38° increased elongation of the cells and greatly repressed the growth rates. This growth inhibition was alleviated by yeast extract and tryptic digests of casein. Growth rates were now 10x those in mice. During serial transfers of the cell to new medium each 4 or 8 weeks (total period 24 weeks), cell populations expanded 20 million times without loss of growth potential. Thus, growth is now continuous at the body temperature of the natural hosts. The cultures do not yield mutants that are becoming adapted to growth *in vitro*.

IV 116

Immunological evaluation of the ICRC bacillus — an *in vitro* isolate of *Mycobacterium leprae*

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Efforts to cultivate *M. leprae*, the causative organism of human leprosy, have been undertaken by various laboratories throughout the world, but have met with little success. Some acid-fast bacilli have been cultivated *in vitro* from lepromas and have been claimed to be *M. leprae*, but in reality turned out to be mycobacterial species other than the leprosy bacillus. One such organism was isolated in Bombay, India, in 1958 and was designated the Indian Cancer Research Center (ICRC) Bacillus by the investigators concerned. Preliminary studies conducted by these investigators indicated the possibility that this organism was *M. leprae*, but studies conducted elsewhere on the same organism appeared to contradict the initial observations.

Our studies were undertaken to determine the exact position of this bacillus in the spectrum of mycobacterial species and also to try to determine whether the ICRC bacillus was in fact *M. leprae*. Methods of evaluation consisted of determinations of the antigenic mosaic of the organism, the sharing of antigenic determinants with other mycobacteria and other relevant immunological studies.

Results obtained so far will be discussed from the point of view of the status of the ICRC bacillus in the mycobacterial species and its significance in relation to the impact of such claims on the ongoing research in the field of leprosy.

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IV 117

Growth of ICRC bacilli — strain C-44 in footpads of mice

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Shepard demonstrated that *M. leprae* multiply in the footpads of mice. The pattern of growth — limited multiplication and a plateau — was shown to be a characteristic feature of *M. leprae* and distinct from that of other mycobacteria.

The ICRC bacilli — strain C-44 (1969) — were grown from *M. leprae* isolates of a lepromatous nodule, in tissue culture conditioned medium. The strain is one of 15 strains, isolated from lepromatous nodules and established in culture in Dubos medium. In this study, strain — C-44 bacilli maintained in tissue culture conditioned medium — from P_{10}, P_{21} and P_{25} were injected into the footpads of CBA mice at a dose of 7.5×10^3 organisms per footpad by Shepard's method. The growth of AFB was estimated by standard smear counts from footpad harvests.

In two groups of normal mice, the organisms multiplied and reached a peak of 2×10^7 between 6 and 7 months followed by a plateau, a characteristic similar to that of *M. leprae*. In T/900r mice the growth reached 1×10^6 at 5 months and continued to rise to 4×10^9 at 12 months. A few irradiated mice showed foot-drop

after 10 months. Histopathologically, the infiltration of AFB was localized to striated muscle tissue in normal mice, while in irradiated mice, the AFB disseminated to other organs, causing granuloma in liver, and a few were detected in nerves. The pattern of growth of ICRC bacilli, C-44, in the footpads of mice was thus identical with that of *M. leprae*.

IV 118

New experimental model for leprosy

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Cuba is nearing the end of a new Programme of Leprosy Control, using microscopy to evaluate the bacteriological improvement in the patient's condition.

It was necessary to make a careful study of the bacteriological controls, introducing the technique of inoculation into mouse footpads, as a continuation of the investigation into leprosy.

At the first stage lymph was taken from the elbows of patients whose Bacterial Indexes were codified 4-5 and whose Morphological Indexes were 70 and 100.

A pool of buffered physiological solution was made, using Shepard's method of bacilli counting and preparing a final concentration of 7×10^6 bacilli per ml.

F_1 hybrid rats were used, and 0.2 ml of the prepared suspension was then injected into hind footpads.

After 6 months, in 50% of animals inoculated, the bacilli multiplied by 2×10^8.

With the bacterial suspension obtained from the footpads of these animals, a final concentrate of 7×10^6 bacilli per ml was prepared, and a second group of hybrid rats inoculated. After 6 months, in 100% of animals inoculated the bacilli multiplied by 2×10^8.

The pyridine extraction method was used in the first as in the second stage of the work, to identify the alcohol-fast bacillus which was assumed to be *M. leprae*. A new experimental model for investigation of leprosy, with highly satisfactory bacillary multiplication, is obtained using the F_1 hybrid rat. This does not call for the use of special techniques such as thymectomy and radiation nor for immunosuppressive drugs.

IV 119

Electron transport and ATP generation in host-grown *Mycobacterium lepraemurium*

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Spectrophotometric observations indicated the presence of flavoproteins and cytochromes of the *b*, *c*, $a + a_3$ and *o* type in cell-free extracts of *M. lepraemurium*. The cell-free preparations catalysed phosphate esterification coupled to the oxidation of various substrates. The oxidation of added NADH, generated NADH and succinate yielded P/O ratios of 0.72, 1.08 and 0.48, respectively. Ascorbate was oxidized but without resultant ATP formation. The oxidative phosphorylation associated with all the substrates was uncoupled by the conventional uncouplers. NADH oxidation and the coupled phosphorylation was quite sensitive to flavoprotein inhibitors as well as to antimycin A and Cyanide. Although the ATP formation linked with the oxidation of succinate was not affected by rotenone and amytal, it was markedly inhibited by thenoyltrifluoroacetone, antimycin A and Cyanide. These data in conjunction with the spectrophotometric observations indicated that oxidation of NADH is mediated through the complete electron transport chain. ATP formation coupled to succinate oxidation appears to be generated only at phosphorylation site 2 i.e., between cytochrome *b* and *c*. The results suggest that *M. lepraemurium* is metabolically competent to obtain energy through oxidative process like other cultivable mycobacteria. With such a functional respiratory mechanism, it should be possible to grow *M. lepraemurium* in culture media, with appropriate substrates added.

IV 120

Ultrastructure of lepromatous leprosy — morphological analysis of the development of therapeutics

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The ultrastructural changes found in patients with lepromatous leprosy were studied. The patients had been given different treatments: hyperbaric oxygen, rifampicin, a phosphate cocktail of tetracycline, diamino-diphenyl-sulphone and diamino-diphenyl-sulphonamide with N (2,6-dioxo 3 peperidil) thalidomide.

With hyperbaric oxygen and phosphate of tetracycline, rapid involution was observed; at the clinical level there were pseudoxanthomatous nodular lesions which ultrastructurally consisted of large vacuoles. Within these vacuoles were cytoplasmic remnants and bacilli in an advanced state of degeneration.

With rifampicin and diamino-diphenyl-sulphone, involution as rapid as before was found, but without large vacuoles in the cellular limits. Marked limiting sclerosis was also found.

Successive changes in the cytoplasmic formations throughout the development of this process are described. Of special interest is the lack of cytoplasmic organelles, especially mitochondria, exhibiting a serious cellular metabolic change.

The discovery of intracytoplasmic bodies composed of involutions of the endoplasmic reticulum limited by a membrane, supports the hypothesis of Brieger and Allen on the formation of lysosomes arising from involuting cytoplasmic organelles in cells during autolysis.

IV 121

Electron microscope studies of *Mycobacterium leprae* during the course of its breakdown in human lepromatous tissue

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In order to establish the morphological index and a bacteriological count in electron microscopy, it is essential to determine what comes from degenerating bacteria and what from the cells that contain them. Numerous studies have tackled that point. It has been found that the destruction may produce the picture either of plasmolysis with more or less total erosion later of the capsules, or else a pseudomyelin picture.

The author stresses the occurrence of a third type of appearance, consisting of the alternation of very thin light and dark concentric lamellae with a width of 25 to 30 Å. Apart from chemical factors, the configuration and the size of the mesosomes in the bacilli affected may play a part in determining all these appearances.

In the lepra cells not containing accumulated lipids, the author has observed vacuoles containing paracrystalline or granular elements measuring 70 A and forming rows about 39 Å apart. These aggregates are suggestive less of a metabolic load than the structures described by the present and by other authors in old mycobacteria from human lepromata.

On the basis of electron microscope pictures, some suggestions are made about the significance of certain classical cellular inclusions.

IV 122

Ultrastructural study of *Mycobacterium leprae* obtained from a human leproma

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An electronmicroscopic study related to *M. leprae* obtained from a human leproma before treatment has been done. Groups of bacilli or non-grouped bacilli were observed inside the cytoplasm of macrophages; they appeared as rounded bodies or as bacillary forms with a high electron density. The electron transparent zone (E.T.Z.) has been observed and also several components of bacterial cell surface as filaments that go across the cell wall and the E.T.Z.

Phagolysosome-like structures and "foamy" structures were seen in typical lepra cells containing many bacteria. A frequent finding was mitochondrial breakdown as well as myelin figure formation inside the mitochondria or

inside cytoplasmic vacuoles. The small quantity of "dense bodies" is noteworthy. Results are discussed.

IV 123

The early cellular response to *Mycobacterium leprae* — an ultrastructural study

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The ultrastructural changes that occur in leucocytes in the early weeks of exposure to *M. leprae* were studied by inoculation of the bacilli into the peritoneal cavities of mice and recovery of the peritoneal cellular exudate at periods ranging from 10 minutes to 14 weeks.

Phagocytosis of the bacilli had taken place by 20 minutes, and occurred by a process of simple engulfment of the micro-organisms by cytoplasmic processes and incorporation into phagosomes. Shortly thereafter, lysosomal aggregation around these structures and apposition against them took place and was soon followed by the appearance of lysosomal material within the phagosomes.

Macrophages and occasionally neutrophils and eosinophils were seen to engage in phagocytosis of the bacilli. *M. leprae* were found within macrophages up to 14 weeks after intraperitoneal inoculation, but until then the lysosomal enzymes appeared to be incapable of producing any morphologically detectable deleterious effect on the bacilli. The bacilli remained within the phagosomes throughout this period and were not seen free in the cytoplasm of the host cell. The previously described electron transparent zone seen in the phagosomes of lepra cells around *M. leprae* was not observed; however, multiple droplets of unidentified lipid-like material were seen in macrophages between two and four weeks after their exposure to *M. leprae*.

IV 124

Ultrastructural study of the cells in the peritoneal exudate of mice exposed to *Mycobacterium leprae*

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Only a few studies have been made of *M. leprae* using the electron microscope. Draper studied the intracellular localisation of *M. leprae* and *M. lepraemurium* in peritoneal macrophages following a natural infection *in vivo*.

In this study the authors used adult Wistar rats subjected to an aseptic inflammation by the method of Epón films for the electron microscope study of single-layer cell preparations from the peritoneal cavity. At 24 hours an intraperitoneal injection was made of a suspension of bacilli from skin lepromata of an untreated patient. The films were removed from the cavity at different intervals after the injection. The material thus obtained was prepared for study under the electron microscope.

The results agree with the host-parasite interaction which occurs during infection of the peritoneal cavity of the mouse.

In the first 24 and 48 hours there was a marked predominance of mononuclear phagocytic cells, and neutrophils were also present.

There were different structures of the phagocytized material with little electron-transparent material around it, possibly made up of bacilli and of cellular remains in the inoculum.

Phagocytic vacuoles were frequently seen from the first day, following the incorporation of material by phagocytosis.

There were multilaminar structures in the cytoplasm of almost all the mononuclear cells.

There were cells with intermediate features between the phagocytes and the fibrin-producing cells.

IV 125

Cultivation of *Mycobacterium leprae* from a human skin biopsy

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A 39-year old male patient presented at a Hong Kong leprosy clinic with nodular skin lesions which had been present for approximately one year. He reported that eight months previously he had received two months' medical treatment for leprosy elsewhere. Routine skin smears showed a bacteriological index of 2.3, and clinical and bacteriological examinations were characteristic of borderline-lepromatous leprosy.

Part of a skin biopsy was aseptically homogenized and washed in phosphate-buffered saline (PBS). The pellet remaining after ultracentrifugation contained abundant acid-fast bacilli which were resuspended in PBS, and aliquots were inoculated into flasks of Skinsnes' medium with hyaluronic acid, and Kato's medium with sheep serum as well as Dorset, Lowenstein-Jensen, and blood agar media. All cultures were incubated at 34°C.

No growth was observed at any time on routine media. After 12 weeks, smears from Kato's medium revealed coccoid organisms showing variable carbolfuchsin staining. Thereafter, both the turbidity of the cultures and the number of coccoid and elongated acid-fast organisms increased. These organisms are being evaluated with fluorescent antisera and standard serological and biochemical tests for specific identification of *M. leprae*, which will be reported together with subsequent cultivation attempts from treated and untreated lepromatous patients and normal skin.

IV 126

Comparative skin test trial with a non-acid-fast organism isolated from leprous tissues to establish its immunological identity with *Mycobacterium leprae*

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A non-acid-fast pleomorphic organism (coccoid and bacillary) has been repeatedly recovered from leprous tissues: it has a tendency to transform into acid-fast bacteria in the footpads of mice. Antisera raised against these organisms specifically and consistently stained *M. leprae* in immunofluorescent staining. Suspensions of whole bacterial bodies of three such strains, two (IKS and WiD) isolated in India and one (86) in Ethiopia, have been used as skin-test antigen in a double-blind comparative trial with lepromin, on 100 known leprosy reactors and non-reactors in Jhalda, an area of high prevalence in West Bengal, India. The subjects were cases and contacts of leprosy, whose ear-lobes contained acid-fast bacilli in some instances. Antigen No. 86 from Delville's laboratory came closest to lepromin in the early (24 hours) reaction (significant at 95% confidence level), while the two others from Chatterjee's laboratory were less close. Release of the cytoplasmic antigen by disruption of whole cells may improve the reactivity, and a further trial is planned with disrupted organisms. Some tests with ultrasonically disrupted antigen from one of the strains has given reactions comparable with lepromin. These data will be discussed. It is suggested that these pleomorphic organisms are the cultivable precursors of *M. leprae*.

IV 127

Viability of *Mycobacterium leprae* outside the human body

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Because of our inability to culture *M. leprae* in artificial media, it was not possible to check the viability of the organism in the tissues or in contaminated material. However, with the advent of the mouse footpad model, this difficulty has been overcome, and it is now possible to apply this technique to establish the viability of *M. leprae*. In the study conducted, nose-blow material and skin homogenates from patients with lepromatous leprosy were dried in the shade for different intervals of time, and then inoculated into mouse footpads. In the first instance, the bacilli were found to be viable after drying for 9 days. The work has since been extended, and organisms have been left in different atmospheric conditions for much longer periods before being inoculated into mice. The results will be presented and discussed.

IV 128

Application of periodic acid-carbol pararosanilin stain and periodic acid-methenamine silver stain for staining leprosy bacilli in leprous skin lesions

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In 150 biopsies of treated patients with tuberculoid, borderline and lepromatous leprosy, tested with periodic acid-carbol pararosanilin stain and periodic acid-methenamine stain, there is a significantly

greater number of bacilli than in sections stained with classic carbol fuchsin.

It is noteworthy that with those two methods there are many bacilli in the epidermis, free zone, hair follicles, blood vessels, nerves, muscles and connective tissues, besides the infiltrate in dermis, where the bacilli were not detected with carbol fuchsin stain.

It is suggested that under the action of an antileprosy drug, some leprosy bacilli, especially in lepromatous leprosy lesions, may lose their acid-fastness and become chromophobic; chromophobic bacilli can regain their staining properties after periodic acid oxidation. Under the chromophobic form, leprosy bacilli can survive in healing and healed lesions, and may be a cause of relapse.

IV 129

Demonstration of *Mycobacterium leprae* in tissues from bacteriologically negative treated lepromatous leprosy patients

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M. leprae are readily demonstrated in biopsy specimens from patients with active lepromatous leprosy by the Fite-Faraco (FF) staining method. Serial biopsy specimens taken during the course of effective chemotherapy regularly reveal decreasing numbers of AFB, and eventually none can be detected by the FF method. The Leprosy Registry at the Armed Forces Institute of Pathology contains many cases with serial biopsy specimens taken during treatment. These cases were studied to detect organisms that could not be stained by the FF technique. Histopathological sections were stained by hematoxylin and eosin, and FF methods, and by a prolonged Gomori's-methenamine-silver (GMS) technique. In sections of tissue obtained before treatment, well-stained acid-fast bacilli (AFB) were seen in FF and GMS stained sections. With effective chemotherapy, as would be expected, the bacilli became granular, and eventually lost their acid-fastness completely. When comparable sections of these specimens that contained no AFB were stained by the GMS method, large numbers of organisms were frequently detected. These persisting carcases are probably a continuing source of *M. leprae* antigens long after the patient is considered bacteriologically negative by routine studies of skin smears and sections of biopsy specimens.

IV 130

Cell-biological studies on the acid-fast organisms isolated and cultivated from leprosy patients

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The cultivable acid-fast organisms from leprosy-infected materials were studied microbiologically.

Most materials were repeatedly washed in sterile saline solution and aqueous solution containing 8.0% of NaOH, and inoculated into an egg-yolk medium and incubated at 33°C for 3-5 weeks. The colony of cultivated organisms was coloured grey or orange-yellow.

The frequency of isolation of cultivated acid-fast organisms from these materials was 0%, 17.5%, 25.0%, 25.0% and 86.7% in the case of ear-lobe leproma, subcutaneous leproma, nasal mucosa, nasal crusts and nasal washings respectively.

The biological properties of the organisms were not very different from those of atypical mycobacteria.

The organisms did not produce progressive lesions in any parts of the experimental animals inoculated subcutaneously, intraperitoneally and in footpads of rabbits, guinea-pigs and mice, macro- and microscopically.

However, in the case of inoculation into mice footpads, acid-fast organisms similar to leprosy bacilli were observed in the inoculated sites, and the number of these organisms seemed to multiply.

Attempts were made to cultivate on egg-yolk media the organisms collected from the infected footpads of mice, but there was no growth of acid-fast organisms.

IV 131

Freezing and storage of *Mycobacterium leprae* in liquid nitrogen

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The use of liquid nitrogen as a means of preserving biological material is now being applied to suspensions of *M. leprae*. Previous attempts to preserve these organisms at low temperatures have resulted in serious reduction or total loss of viability. In this study, we have investigated the effect of freezing rate, prolonged storage in liquid nitrogen, and thawing rate on the viability and subsequent growth of *M. leprae*.

Some loss of viability of *M. leprae* was detected, and this was found to be associated with the freezing process, rather than with storage or thawing. Slow freezing (1°C/min. to —70°C, then immersion) was found to be less deleterious to the organism than quick-freezing (direct immersion in liquid nitrogen), with a loss of viability of 90% (compared with 98%). The growth pattern of *M. leprae* was unaffected, except for a delay in the appearance of growth caused by loss of viability. Our experiments indicate that very little killing of *M. leprae* occurred during storage in liquid nitrogen, and that the rate of thawing of bacillary suspensions had little effect on the viability.

IV 132

Studies on cell culture of *Mycobacterium leprae* and *Mycobacterium lepraemurium*

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The authors succeeded in cultivating *M. lepraemurium* in Balb/c 3T3 recloned cell line (A31). The increase of the number of intracellular bacilli was 440-fold over a period of 40 days in one series, and 130-fold over a period of 42 days in another series. The average generation time of *M. lepraemurium* in A31 cells was 5.3 days which was the fastest growth of the organisms *in vitro*. The intracellular bacilli were transferred without loss of the number of organisms by host cell transfer. The growth of intracellular bacilli was inhibited by streptomycin 100 μg/ml, INH 5 μg/ml and rifampicin 5 μg/ml. Streptomycin was removed on day 40, and cultivation was continued in a streptomycin-free medium; the intracellular bacilli began at once to multiply, but INH- and rifampicin-treated bacilli did not multiply.

M. leprae in A31 cells showed elongation of organisms, and the increase of the number of bacilli was 4-fold after 50 days. The authors are now attempting to keep the host cells in better conditions for longer periods and to obtain the growth of *M. leprae in vitro*.

IV 133

Taxonomic features of *Mycobacterium lepraemurium*, an obligate intracellular microbe for 69 years

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Continuous growth of Mlm (*Mycobacterium lepraemurium*) *in vitro* occurs without loss of growth potential and without relaxation of the original growth requirements. For the first time, it has become possible to define the multifactorial deletions and deficiences in a host-dependent microbe. Prolonged growth at 30° in a semi-synthetic medium required compensating >16 metabolic defects. Continuous growth at 38° required compensating >18 such defects. These observations suggest that characterization of host-dependent microbes may depend upon *what they cannot do*, not upon what they *can* do.

The present data on Mlm refute two currently urged views regarding the etiology of rat and human leprosy: (a) that the agents are not acid-fast and (b) that rapidly growing mycobacteria with the features of *M. scrofulaceum* are the agents of these diseases. In experiments which demonstrated continuous growth, the total number of cells inoculated and grown exceeded 10^{12}. Additional billions have been grown during the past five years. Although there has been abundant opportunity for non-acid-fast bacteria or rapid growing mycobacteria to emerge, the constant necessity of compensating >18 taxo-

nomic markers in Mlm indicates that the genetic markers in Mlm are as stable as those in growth competent microbes. Examination of ten physiological and biochemical characteristics of six selected species of mycobacteria has revealed that *M. avium* is most closely related to Mlm and that *M. scrofulaceum* is the most distant relative.

IV 134

Cultivation of *Mycobacterium lepraemurium* in flask system

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Kurume University School of Medicine, Japan

On the basis of the fact that *M. lepraemurium* (Hawaiian strain) quantitatively multiplies in ND-5 medium, cultivation of *M. lepraemurium* in the flask system was adopted in order to obtain sufficient quantities of *in vitro* cells for biochemical and immunological studies.

The compositions of culture media are as follows: the two basal media are Kirchner in NC system, and Dubos in ND system; α-keto-glutarate is incorporated as an additive in sub-system 5, while for sub-system 15, it is oxaloacetate. Other additives are cytochrome c, hemin, l-cysteine HCl, adenosine, and NADH.

The results obtained indicate that the size of flask remarkably influenced the yields of *M. lepraemurium*, i.e., the bacilli multiplied more abundantly when the cells were grown in a "100 ml" Erlenmeyer flask (net 128 ml) containing 42 ml, of ND-15 medium than in a "50 ml" flask (net 64 ml); physiological and morphological features were demonstrated in the case of ND system only, observed by electron micrography.

During the experiments, it was also found that l-malic acid as well as succinic acid stimulated the growth of bacilli.

IV 135

Cytochromes of *Mycobacterium lepraemurium*

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We have 8 strains of *M. lepraemurium*: Douglas, Fukuoka-1, Hawaii, Keishicho, Kumamoto, Kurume-42, Odessa and Osaka-1. These strains were cultivated on 1% Ogawa yolk medium. The oxido-reductive difference spectra of cytochromes in whole cells of the cultivated 8 strains were compared to that of *in vivo* grown Hawaii strain. The same spectra were found, that is, cyt b_1 at 561 mμ and cyt a_2 at 630 mμ. Cyt c and cyt a were not observed in these bacilli. The oxido-reductive difference spectrum of cytochrome in whole cell was measured by the split beam spectrophotometer Chance under frozen state by liquid nitrogen. A shoulder of Soret peak of cyt a_1 at 590 mμ and cyt a_2 at 460 mμ was newly observed in the frozen state. An undescribed peak at 490 mμ was seen in cultivated organisms. Cyt c and cyt a were not found even in the frozen material. On the other hand, cultivable acid-fast bacilli have the cyt c and cyt a. The cultivated *M. avium* Kirchberg strain has cyt c, cyt b_1, cyt a and cyt a_2, but the *in vivo* grown Kirchberg strain has only cyt b_1. Easily cultivable acid-fast bacilli produce adaptively the cyt c and cyt a in cultivated state. Therefore cultivation of *M. lepraemurium* may be very difficult.

IV 136

Large acid-fast bodies found in leprosy materials

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In human lepromatous tissue and infected armadillo livers, large acid-fast bodies (average diameter, about 40 μm) were found.

This large body differed from the "lepra cell" in the following ways:

1) it was covered with thick, mucoid and acid-fast substance resistant to alkali digestion.

2) it had a characteristic interior structure. A fertile large body developed a honeycomb matrix composed of hexagonal units. The matrix substance had special optical and staining characters.

3) it was found in material which was free from tissue components after purification by counter-current distribution in polymer two-phase system, or by Dr Draper's method.

Some kinds of acid-fast large bodies were found in infected mouse footpads.

In the case of murine leprosy, similar observations were made, and in colonies of a cultivable variant of *M. lepraemurium* grown on Ogawa's egg-yolk medium, acid-fast large bodies were observed, even after many subcultures.

IV 137

Skin adnexa in leprosy and their possible role in dissemination of *Mycobacterium leprae*

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Skin biopsies from 20 patients each of tuberculoid, borderline and lepromatous leprosy were examined using H. & E., P.A.S., van Gieson and Fite Faraco stains with a view to finding bacilli and their exact location in relation to the skin adnexa.

Of the 20 lepromatous patients, 8 had acid-fast bacilli in sweat glands, 2 in sweat ducts, 4 in sebaceous glands, 9 in hair follicles and 12 in blood vessel walls. All patients showed acid-fast organisms in nerves and arrector pili muscles. In the borderline group, 5 patients had bacilli in sweat glands, 2 in sweat ducts, 7 in hair follicles, 3 in sebaceous glands and 7 in blood vessels. Bacilli were present in nerves in 11 and in arrector pili muscles in 8. In the tuberculoid group, bacilli were present in nerves in 3, arrector pili muscles in 2, and blood vessels in 3.

The finding of bacilli in sweat glands and ducts, sebaceous glands and hair follicles is most interesting. The secretion from these glands will doubtless carry the bacilli to the surface of the skin. The significance of these findings in the dissemination of bacilli will be discussed.

IV 138

Secondary bacterial infections in chronic trophic ulcers in leprosy

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Chronic trophic ulcers are a common complication and a leading cause for long-term hospitalization in patients with Hansen's disease. Secondary bacterial infection of these ulcers is often a reason for their delayed healing. Smears of pus and discharges taken from the chronic ulcers of patients admitted to the National Leprosy Control Center, Sungei Buloh, between 1 January 1976 and 31 December 1977, were cultured for growth and sensitivity on 500 occasions. Results indicated an alarming proportion of organisms resistant to the antibiotics commonly used to treat surrounding soft tissue infection in these ulcers. The problems facing the use of systemic antibiotics in the treatment of these ulcers is discussed in this paper.

SESSION V
IMMUNOLOGY

Wednesday, 15 November 1978
9:00-13:00
Auditorium 1
Chairman: **B. R. Bloom (USA)**
Rapporteur: **F. Cottenot (France)**

Invited Papers

Abstracts

V/139 Immunology of leprosy and the WHO special program.
T. Godal (Norway)

V/140 A revival of interest in antibody studies in leprosy?
M. Harboe, O. Closs (Norway)

V/141 Cell-mediated immunity to *M. leprae* in mice.
M. J. Lefford (USA)

V/142 Studies on *M. leprae*-induced suppression of *in vitro* responses in leprosy patients.
V. Mehra, B. R. Bloom, L. Mason, J. Fields (USA)

V/143 Significado de la activación polimorfonuclear en la lepra lepromatosa reactiva. Efectos *in vivo* e *in vitro* de la talidomida.
M. Goihman-Yahr, G. Rodriguez-Ochoa, N. Aranzazu, J. Convit, M. E. de Gomez, A. Ocanto (Venezuela)

Free Communications

Abstracts
V/144-V/154

Free Communications

15:00-18:00
Abstracts
V/155-V/164

Poster Communications

Exhibition Area
Abstracts
V/165-V/206

IMMUNOLOGY

V 139

Immunology of leprosy and the WHO Special Programme

T. GODAL

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The major areas of immunological research activities over the past five years will be reviewed. Special attention will be given to the following problem areas:

1. Mechanisms involved in nerve damage in leprosy.
2. Pathogenesis of *erythema nodosum leprosum.*
3. Types of nature of immunological deficiencies in leprosy.
4. Immunoepidemiological features in leprosy.

A scientific working group on the Immunology of leprosy (IMMLEP) was started in December, 1974, as a pilot project of the Special Programme for Research and Training in Tropical Diseases of the World Health Organization. The objectives, organization and achievements of this programme will be discussed. How can its contribution to the overall effort in the area of research on leprosy immunology be perfected?

V 140

A revival of interest in antibody studies in leprosy?

M. HARBOE O. CLOSS

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Since cell-mediated immune reactions are considered to be responsible for protective immunity in leprosy, antibody studies have attracted less interest in the last decade. This tendency needs to be reversed in various areas of leprosy research.

1. Our initial studies of armadillo-grown *M. leprae* by crossed immunoelectrophoresis, using rabbit antisera, led to the identification of 7 distinct antigenic components of *M. leprae* which cross-react extensively with other mycobacteria. Leprosy is associated with antibody formation against all of these components, but the specificity of the response varies in individual patients.

2. A radioimmunoassay (RIA) has been developed for demonstration of antibodies against the widely cross-reacting *M. leprae* antigen 7. Anti-*M. leprae* ag. 7 occurs in higher titre in lepromatous than in tuberculoid leprosy. More striking is the marked variation in antibody content in individuals with similar clinical features, e.g. in tuberculoid leprosy. During treatment with dapsone, the antibody content decreases, and relapse appears often to be associated with a marked increase in antibody formation.

3. Another RIA has been developed for demonstration of antibodies reacting with antigenic determinants that are highly specific for *M. leprae.* Its potential in serological diagnosis of infection with *M. leprae* and in other areas of leprosy research will be illustrated and discussed.

V 141

Cell-mediated immunity to *Mycobacterium leprae* in mice

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Cell-mediated immunity (CMI) has been induced in mice following the subcutaneous injection of 100 μg armadillo-derived, irradiated *M. leprae* (I-ML). The criteria of CMI were: production of hypersensitivity granuloma at the immunization site with local but not systemic macrophage activation; induction of delayed-type hypersensitivity (DTH) to human tuberculin PPD, I-ML soluble antigen and human lepromin; protective immunity against systemic challenge with *M. bovis* BCG and *M. tuberculosis*; and the dependence of these phenomena on T-lymphocytes. It has been further shown that the resistance to *M. tuberculosis* that is

generated by I-ML vaccination is not non-specific, but is mediated by *M. leprae*-sensitized T-lymphocytes that recognize antigens shared with *M. tuberculosis.*

These observations encourage the view that I-ML should be regarded as a potentially effective anti-leprosy prophylactic vaccine in man.

V 142

Studies on *Mycobacterium leprae*-induced suppression of *in vitro* responses in leprosy patients

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Immunity to *M. leprae* is believed to be dependent on cell-mediated immune responsiveness. Both *in vivo* and *in vitro* studies have indicated that there is an immunological defect in lepromatous leprosy specific for the lepra bacillus. In addition, a varying degree of non-specific depression of cell-mediated immunity may be superimposed on this basic deficit.

The mechanisms underlying the immunodepression of cell-mediated reponses in lepromatous leprosy remain obscure. The present studies were designed to investigate the involvement of suppressor cells in the impairment of *in vitro* lymphocyte responses in leprosy patients. A model for measuring *M. leprae*-induced suppression was developed based on the suppression of the Con A mitogenic response by Dharmendra lepromin. When lepromin was added together with Con A to the peripheral blood lymphocytes to 19 normal donors, significant suppression (greater than 20%) of ^{3}H-TDR incorporation was seen in none. Similarly, only one of six TT patients showed any lepromin-induced suppression of the Con A response. In contrast, 20 of 24 LL patients had greater than 20% suppression of ^{3}H-TDR incorporation induced by Con A. In addition, all of 18 patients characterized clinically as borderline (BL, BB and BT) showed significant *M. leprae*-induced suppression. The suppressive activity seems to be mediated primarily by cells having the properties of glass adherence and forming rosettes with IgG-coated RBC, possibly under control of T-cells. The potential usefulness and limitations of this approach will be discussed.

V 143

Significance of polymorphonuclear activation in reactional lepromatous leprosy. Effects of thalidomide *in vivo* and *in vitro*

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A proportion of circulating neutrophils is able to reduce nitroblue tetrazolium (NBT) *in vitro*. Such cells show blue formazan precipitates in their cytoplasm (FP cells). The proportion of FP cells is raised in many bacterial infections because of increased oxido-reductive activity (activation).

This may also be induced *in vitro* by incubation with endotoxin. We reported previously that while in lepromatous leprosy (LL) there was no activation, a significant elevation in proportion of FP cells took place in reactional lepromatous leprosy (RLL). RLL is reported to be a form of immune complex disease, therefore neutrophils would be involved in tissue damage.

Signs and symptoms of RLL are dramatically improved by thalidomide. We have now studied neutrophil activation in patients with RLL just before and during treatment with thalidomide. Clinical improvement produced by this drug took place before lowering of proportion of FP cells. Concomitant infectious processes induced activation even if patients were under thalidomide treatment. Thalidomide, tested *in vitro*, did not affect spontaneous reduction of NBT by neutrophils, nor did it block endotoxin-induced activation. The therapeutic effect of thalidomide is not related to its inhibiting properties on neutrophil activation. These findings do not support the hypothesis that tissue damage in RLL is due to neutrophil action by a mechanism similar to that of immune complex disease. Neutrophil activation may be a specific epiphenomenon in RLL.

V 144

Antigenic analysis of *Mycobacterium leprae*

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Better knowledge of the antigenic composition of *M. leprae* probably represents an important step towards understanding the role played by individual antigens in the immune response to this mycobacterium. Previous attempts to produce experimental antisera against *M. leprae* have not been completely successful and the number of antigenic components detected has been much lower than in cultivable mycobacteria or *M. lepraemurium*. Based on model experiments with BCG, we have now applied a new immunization schedule. Using concentrated *M. leprae* sonicate as antigen, and concentrated rabbit anti-*M. leprae* immunoglobulins, more than 20 antigenic components could be detected in crossed immunoelectrophoresis. This has provided an improved reference system for *M. leprae* antigens. The crossed immunoelectrophoresis system was used to characterize purified *M. leprae* prepared by different methods. By using other anti-mycobacterial antisera, additional components could be detected in some *M. leprae* preparations, indicating that *M. leprae* contains more antigenic components than the present system detects. Incorporation of other mycobacterial antisera in the intermediate gel of the reference system indicated that most of the 20 components are cross-reacting with antigens in other mycobacteria. Preliminary results indicate that antibodies in sera from leprosy patients react with a restricted number of the components in the reference system.

V 145

Lymphocyte transformation test in healthy leprosy contacts. Influence of household exposure

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The study was carried out in the Gurage Area of Ethiopia where 53 household contacts of lepromatous patients, 37 household contacts of tuberculoid patients, and 91 control persons were examined with the lymphocyte transformation test (LTT) for their responses to whole and sonicated antigen preparations from *M. leprae*, to BCG, *M. avium*, *M. gordonae*, and phytohemagglutinin (PHA).

Household contacts of lepromatous patients showed significantly greater LTT responses to antigens from *M. leprae* than the controls, whereas household contacts of tuberculoid patients did not respond differently from the controls. Household contacts of lepromatous patients had significantly greater responses to *M. leprae* antigens when the index patients were "active", i.e. highly bacilliferous, than when they were "inactive", i.e. having a low bacillary load. The degree of sensitization, as indicated by the LTT response, in different exposure groups paralleled therefore the degree of probable infectivity of the index patients. The LTT responses to PHA were significantly lower in the household contacts of "active" lepromatous patients than in the controls.

A preparation of antigen from whole *M. leprae* proved to be more sensitive and more specific in the LTT than did a sonicated preparation. A significant degree of cross-reactivity was found between the various mycobacteria in the LTT.

V 146

In vitro lymphoproliferative response to *Mycobacterium leprae* in normal siblings of lepromatous leprosy patients

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We have studied the responses to *M. leprae* in the lymphocyte transformation test (LTT) of 23 lepromatous and borderline lepromatous patients and 27 of their normal siblings. In order to detect HLA-linked genetic control of the lymphoproliferative response to *M. leprae*, we identified the normal siblings who were HLA-identical to the patient by the absence of a mixed lymphocyte reaction between them. Of the 23 patients, 22 were negative in the LTT (Stimulation Index less than 3). In contrast,

26 of the 27 normals were positive. Seven of the normals were HLA-identical to their lepromatous sibling. All of them responded positively, and as a group their responses did not differ significantly from the responses of the 20 HLA-non-identical normals. The presence of 7 HLA-identical normals among the 27 tested indicates no selection against shared HLA-haplotypes in siblings discordant for lepromatous leprosy.

We conclude that the specific unresponsiveness of lepromatous leprosy patients is an acquired, rather than an inherited, defect. However, though our results indicate that lepromatous patients are not genetically-determined "non-responders" to *M. leprae*, they do not exclude some type of HLA-linked genetic control of the cell-mediated immune response to *M. leprae*. If HLA-linked high responders and low responders to *M. leprae* do exist, it seems possible that some lepromatous patients may be in the high responder group.

V 147

Double blind trial to determine the late reactivity of leprosy patients and unaffected persons to different concentrations of armadillo lepromin in comparison to human lepromin

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The object of the study is to compare the late (30 days) reactivity of leprosy patients and unaffected persons to armadillo lepromin (160, 40 and 20 million bacilli/ml, designated as A 160, A 40 and A 20 respectively) and human lepromin (40 million bacilli/ml, H 40). The test was performed in 105 leprosy patients and 35 unaffected young males 14 to 17 years old. Each patient or healthy boy received simultaneously the four preparations on the interscapular region, in a randomized order of 24 possible permutations. The study was carried out as a double blind trial and only one of the authors was aware of the identity of all the factors involved in the investigation. The reading of the lepromin reaction was performed by only one of the investigators.

In unaffected persons and leprosy patients (no matter what their classification), mean sizes of Mitsuda reactions with different concentrations of armadillo lepromin, even with A 20, were higher than those with human lepromin. In L cases the number of positive macroscopic reactions was higher with A 160 (5 cases) and A 40 (3 cases) than with A 20 (1 case) and H 40 (1 case). The size of the reaction and of the scars left by armadillo lepromin (mainly 160 and 40 million bacilli/ml) represent an inconvenience for its current use and a nuisance for many patients and non-affected persons.

V 148

Delayed hypersensitivity responses to *Mycobacterium leprae* and *M. vaccae* cytoplasmic protein antigens

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The antigenic relations which may exist between *M. leprae* and *M. vaccae* have been the subject of a number of investigations in recent years. *M. vaccae* is a rapid grower isolated from soil and cattle. Several recent isolates of this organism have been inoculated intravenously or subcutaneously into specific pathogen-free ICR mice or strain 2 inbred guinea pigs. Quantitative viable counts of the mycobacterial populations in the footpad, popliteal lymph node, lung, liver and spleen indicate that *M. vaccae* is unable to establish persisting systemic infections in these aniamls. The decline in viability of *M. vaccae* in the mouse footpad was similar in its rate and extent to that observed earlier for the non-immunogenic streptomycin-resistant mutant of BCG Montreal. Neither group of animals was able to express significant levels of cellular hypersensitivity to the appropriate tuberculins. In order to determine whether *M. vaccae* possesses antigens capable of sensitizing the host, mice and guinea pigs were immunized with killed *M. vaccae* or *M. leprae* suspended in Tween saline or in Freund's incomplete adjuvant. The animals received a second dose of antigen 14 days later and were

skin tested weekly with graded doses of PPD, or with cytoplasmic proteins prepared from *M. vaccae* or from human or armadillo-derived *M. leprae*. Quantitative skin or footpad measurements were made at 3, 6, 24 and 48 hours and any nonspecific swelling responses were subtracted before the reaction was assessed for its specific and cross-reactive activity. The significance of the findings is discussed in relation to possible cross-reactive antigens present in the two mycobacterial species.

V 149

Various methods of stimulating cell-mediated immunity in cases of lepromatous leprosy: a clinical, bacteriological and histopathological study with immunological control

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The authors have shown the clinical, bacteriological and histopathological efficacity of the following substances: BCG, levamisol, *Neisseria perflava*, glyco-proteic bacterial extracts — either alone or associated with chemotherapy in polar lepromatous leprosy. Tolerance was good, with the exception of some local necroses and moderate episodes of erythema nodosum leprosum, which was precipitated by BCG; these episodes were less frequent when the vaccinating dose was one-tenth of the normal dose. The polynephritis was sometimes improved and sometimes unchanged. There was a positivization of the Mitsuda test in 30% of cases after BCG vaccination. This appeared on average about a year after the vaccination; it was histologically confirmed, and appeared after eruptions that were clinically and histologically borderline.

The cell mediated immunity is therefore partly preserved in polar lepromatous leprosy. The combination of two stimulating products does not improve this capacity for cell-mediated immunity, and seems sometimes even to impair it. Chemotherapy alone, even after many years, does not lead to an improvement in the cell-mediated immunity, which, however, improves when a stimulating factor is introduced.

The authors controlled these *in vitro* findings with macrophage migration inhibition tests (rapid action with PHA and slowly progressive action with lepromin). Variations of this test are compared with changes in the clinical appearances and in the bacteriology.

The combination of rifampicin 900 mg weekly for two months with sulphones or clofazimine together with immunological stimulation is recommended. For mass campaigns levamisol is the most convenient.

IV 150

Immunological studies in patients with indeterminate and dimorphous leprosy

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Previous studies have shown that there is an important specific cellular immunological deficiency in lepromatous leprosy whereas the response is practically normal in tuberculoid leprosy. In intermediate groups (indeterminate and dimorphous) there is no accurate knowledge on immune response to *M. leprae*. It was decided therefore to study these patients and to compare them with the polar groups.

The subjects were 25 patients: 10 indeterminate, 5 dimorphous, 5 tuberculoid and 5 with lepromatous leprosy. They were studied by means of the following investigations: skin tests (trichophytin, PPD; candidin and varidase), lepromin reaction, lepromin biopsy, immunoglobulins C_3, C_3, CH_{50}, MIF to lepromin and PPD, total lymphocytes, Y-lymphocytes (E rosettes) and B-lymphocytes (EAC rosettes).

RESULTS

There was an important response to PPD and varidase, without significant differences between the four groups. All the patients had a significant increase in the immunoglobulins. The lepromin biopsy was positive (with bacilli) in lepromatous cases and in two patients with dimorphic leprosy and Mitsuda-negative. The MIF (lepromin and PPD) test was greater in tuberculoid and dimorphous cases, whereas it was minimal in lepromatous and indeterminate cases. There was a significant fall in total and T-lymphocytes as

compared with normal subjects; the lowest figure was in dimorphous subjects. B-lymphocytes were normal with the exception of the dimorphous patients, who had a significant fall.

It is probable that T-cell deficiency favours the development of a lepromatous picture. An increase in these cells in indeterminate leprosy and the lack of response to lepromin appear to indicate that this group constitutes the initial stage of leprosy.

V 151

Characterization in mouse and man of two distinct forms of delayed skin-test response, relevant to mycobacterial infections

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The principal problem facing the mycobacterial immunologist is the relation between positive skin-tests, tissue damaging hypersensitivity, and protective immunity. Thus Koch described a tissue damaging phenomenon taking 4-6 weeks to develop in guinea pigs, and Mackaness, working in the mouse, described the appearance within 3 days of T-lymphocytes able to activate macrophages in the presence of antigen. Both phenomena can be regarded as skin-test positive, yet neither is a reliable indication of protection from mycobacteria. The relation between the two phenomena has not been explored because such comparisons cannot be made until both types can be demonstrated in the same species.

We can now induce both types of response to mycobacteria in mice. They differ in time of appearance, time course, antigen dose/response and drug susceptibility *in vivo*. Moreover they are accompanied by different "regulator" or "suppressor" cell responses demonstrable both *in vivo* and *in vitro*.

Epidemiological studies indicate that the type of response induced in mice by a mycobacterial species correlates with the effect which contact with that species has on the protective efficacy of BCG in man.

The criteria used for the recognition of the two types of response are readily applicable to man, and encouraging preliminary results will be presented.

V 152

Attempts to induce delayed type hypersensitivity (DTH) to *Mycobacterium leprae* in healthy individuals and in "burnt-out" lepromatous patients

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Four mycobacterial preparations were tested for their ability to induce DTH to *M. leprae*. The preparations were constituted from: *M. leprae*, purified by Drapers' method and derived from experimentally infected armadillos, and killed by ^{60}Co gamma irradiation: BCG (Japanese BCG Laboratory, Tokyo). The purified *M. leprae* were given unmodified or chemically modified by acetoacetylation (AC) with acetoacetic anhydride (Diketene, Sigma), at a dose of 2.0×10^8 AFB and BCG at a dose of $1.5 - 2.0 \times 10^6$ viable units. DTH was measured at 72 hr. as the diameter of induration (MM) to PPD (ITU, RT23) or to 1 μg soluble protein obtained from ultrasonicated purified *M. leprae* (A8), given intradermally.

The 4 mycobacterial preparations were:
A. *M. leprae* (AC)
B. A plus BCG
C. BCG
D. *M. leprae* (unmodified) plus BCG.

Healthy volunteers, skin-test negative to PPD *and* A8, were given one of the 4 mycobacterial preparations and 6 weeks later retested with PPD and A8. Only *M. leprae* (AC) plus BCG induced significant DTH to A8 (in 9/10 volunteers) — BCG alone or with unmodified *M. leprae* and *M. leprae* (AC) alone failed to induce DTH to *M. leprae*. However, in burnt-out lepromatous patients, *M. leprae* (AC) plus BCG failed to induce DTH to *M. leprae*, although they became positive to PPD. The significance of these, and further results to come, will be discussed, particularly as they relate to the development of a "vaccine" for leprosy.

V 153

Immunological findings in lepromatous leprosy

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Cell-mediated immune reactions and antibody-mediated immunity in lepromatous leprosy have been the subject of a large number of studies over the last 20 years. Many workers have concluded that a deficiency in the cell-mediated immune reaction and an exaggerated autoantibody formation is peculiar to patients with lepromatous leprosy. However, some questions remain unsettled: for example, there is no unanimity of opinion concerning the etiopathogenesis of these processes, and we do not know whether the defect in the immune system is primary or secondary.

We have studied in 71 lepromatous patients the lymphocyte counts, percentages of T and B lymphocytes and those of surface immunoglobulin bearing cells (polyvalent, IgA, IgG, IgM), the amounts of serum immunoglobulins and C_3, C_4, non-organ specific antibodies (SMA, ANA, ARA, AMA, GPC) in order to establish the cell-mediated immune reactions and AMI. Intradermal reactions to soluble antigens (PHA, PPD, DNCB, SK-SD) and lymphocytic reactions to *in vitro* mitogen (PHA) have also been studied in some patients. Reactions to PPD and PHA were satisfactory (72%, 86%) in some patients, whereas in other patients the *in vitro* reaction to mitogen was significantly low.

The percentages of T-lymphocytes in LL patients were also significantly low, whereas those of B cells were significantly higher than those of the controls. The increase in the B cells was especially significant in those cells whose surface contains IgA. The serum IgA also increased (the mean value of the controls was 187^{+} 38 mg/100 ml and that of the patients was 348 141 mg/100 ml).

The increase (25%) of the SMA and (20%) ARA antibodies was noted in LL patients. HLA antibodies have been examined further in 19 LL patients.

V 154

On the assessment of immunological status of lepromatous patients

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The immunological state and delayed hypersensitivity (DTH) was studied by the lymphocyte transformation test (LTT) in 55 outpatients (33 with stable or regressing leprosy and good tolerance to antileprosy drugs, and 22 with unstable leprosy and receiving less intensive therapy because of some contra-indications), 26 inpatients (including some with proven sulphone resistance) and 15 healthy controls. Mitogens for LTT were PHA-P (Difco), lipopolysaccharide *E. coli* 0.55, PPD (human and bovine type), standard Mitsuda lepromin and lepromin from *M. lepraemurium* (1.6×10^8 mycobacteria/ml), and solusulphone.

The study of the immunological status of the patients with lepromatous leprosy showed significant depression of T-cell function against a background of marked DTH to mycobacterial antigens compared to control group; B-cell activity did not undergo significant changes.

Outpatients with unstable or regressing leprosy showed significant decrease of T-cell function compared to those with stable leprosy.

The lepromatous patients with sulphone resistance showed more marked sensitization to solusulphone than those without resistance or the control group ($p < 0.01$).

The importance of the data obtained for assessment of immunological reactivity and early identification of the patients with tendency to relapse is discussed.

V 155

Foetal immunity in leprosy: lymphocyte responses to *Mycobacterium leprae* and phytohaemagglutinin in mother and baby at the time of birth

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In a study of patients with leprosy, and healthy controls, it was found that where the mother had positive lymphocyte transformation responses to whole *M. leprae*, the cord lymphocytes of the neonates of these mothers had high responses also: indeed, the responses in the neonate were higher than those of the mother. The sensitization seemed to be specific, since the same effect was not seen with BCG or PPD in the neonates. It seems likely that foetal lymphocyte sensitization results from transplacental passage of a soluble lymphocyte factor.

Lymphocyte responses to PHA were also studied in patients with BT leprosy, BL and LL leprosy, and healthy controls, in both pooled serum and autologous serum. It was found that plasma from each mother markedly suppressed the lymphocyte responses of both mother and neonate: also, the plasma from the leprosy mothers had a greater inhibitory effect on their babies' lymphocytes than plasma from healthy mothers. It is probable that plasma from leprosy patients contains suppressive factors other than those associated with pregnancy. Babies of LL mothers, who might have been exposed to mycobacterial antigens *in utero* had higher responses than the other babies, possibly due to a compensatory reaction to early stresses of the immune system.

V 156

Fluorescent leprosy antibody absorption (FLA-ABS) test for detecting subclinical infection with *Mycobacterium leprae*

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Humoral immune response to *M. leprae* as a sign of subclinical infection in healthy contacts may be detected if a highly sensitive and specific serological test is used. For that purpose, the FLA-ABS test was improved by absorbing the serum with the suspensions of BCG and *M. vaccae*, in addition to the absorption with cardiolipinlecithin. The antibody-titre to *M. leprae* of the serum from leprosy patients was not significantly lowered by such absorption, while it rendered the serum non-reactive with 19 strains of cultivable mycobacteria which were cross-reactive with unabsorbed serum. On the other hand, the absorbed serum from tuberculosis patients did not react with *M. leprae* or with *M. tuberculosis*, but still cross-reacted with some of the other strains.

This test gave positive results in 38 sera (88.4%) out of 43 healthy household contacts, whose ages ranged from 2 to 68. Among 173 school children in leprosy endemic areas who had palpable auricular nerves or doubtful skin eruptions, 109 (63%) showed a positive reaction. The immunological and epidemiological implications of these results will be discussed.

V 157

Conversion of Mitsuda negative normals into Mitsuda positive through repeated testing with diverse antigens

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Diverse antigens are tested in statistically comparable groups of normal people living in areas of low endemicity for leprosy in Venezuela, to assess their potential to convert those who initially give negative Mitsuda reactions, into Mitsuda-positives. The persons studied were divided into five groups. Four of these groups were tested with armadillo lepromin at 160×10^6 acid-fast bacteria per ml. The other group was tested with lepromin prepared with bacilli purified by the Draper method, at the same concentration. All these persons were also tested with two soluble antigens prepared from armadillo *M. leprae* and with PPD. The reactions were read at 48 hours and at 30 days. All those who were Mitsuda negative at the first injection were re-injected one month later with lepromin, lepromin and BCG, lepromin plus BCG, saline and lepromin from purified bacilli. The tests with soluble *M. leprae* antigens were also repeated. The 48-hour and 30 day reactions were recorded. One month later, all those still giving negative Mitsuda responses were injected with the same antigen as for the second injection, and with the soluble antigens. The 48-hour and 30 day responses were recorded. One month later, all those persons who gave negative Mitsuda reactions after the initial testing were injected with human standard lepromin. The results of the conversion to Mitsuda positive in the various groups are being analysed statistically.

V 158

A specific leprosy antigen isolated by affinity chromatography using gel immobilized lepromatous IgG as the stationary phase

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It is generally accepted that non-protective humoral antibodies to leprosy antigens occur in the sera of lepromatous leprosy patients. This paper describes a procedure to utilize these antibodies as the immobilized substrate to select their counterpart antigens from a suspension of lepromatous leprosy tissue.

IgG from pooled lepromatous patient sera was bound to a sephadex gel and the gel-bound IgG was placed in a separatory column. Membrane filtered (0.2 μ) lepromin was allowed to pass through the column and the column was brought to a stable baseline using pH 7.0 phosphate buffer. The subsequent gel-bound antigen-antibody complex was eluted with acetic acid and passed through a membrane molecular sieve to obtain a fraction with a molecular weight lower than 100,000. This fraction formed a white precipitate on concentration and neutralization.

The white precipitate was washed with and resuspended in 0.5% phenolized saline. This preparation gave a positive reaction in the light scatter test against lepromatous sera, but not against normal sera. Intracutaneous skin tests using 0.1 ml of a 0.4 OD suspension of the precipitate, were positive in lepromatous, tuberculoid and normals from the endemic area. Mice showed no visible effect to IP inoculations of the material.

V 159

Immunological studies in guinea pigs and in man on bacteria and cell-free extracts of purified armadillo-derived (PAD) *Mycobacterium leprae*

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For the first time substantial amounts of *M. leprae* are available in the laboratory from experimentally infected nine-banded armadillos, and this source has been exploited by the World Health Organization IMMLEP Programme aimed at developing a vaccine for leprosy. Our contributions to this Programme have been concerned with the purity and standardization of the bacteria and their cell-free extracts, based on their immunological properties. Because several methods have been developed for extracting *M. leprae* from armadillo-infected tissues, our studies have also included comparative assessments of the immunological properties of the bacteria purified by different methods. These studies have demonstrated the value of the guineapig for standardizing and indicating the reproducibility of the sensitising capacity of PAD *M. leprae* from batch to batch and the eliciting capacity of their homologous cell-free extracts.

The immunological properties of PAD *M. leprae* compared with standard human-derived *M. leprae* for the preparation of Mitsuda-lepromin have also been compared in guineapigs and in man. The histological features of these two lepromins have also been assessed in guineapigs.

The results of all these comparative methods will be discussed.

V 160

MIF response to lepromin, PPD and SK-SD in patients with lepromatous leprosy and healthy individuals*

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Immune responsiveness was explored by the MIF test in the following groups: a) 54 nodular lepromatous leprosy patients, b) 49 diffuse lepromatous leprosy patients, c) 75 healthy individuals living in close contact with patients, d) 55 healthy individuals unrelated to leprosy patients, living in an area of substandard economic and sanitary conditions, and e) 102 healthy individuals unrelated to leprosy patients,

but living in better, middle class economic and sanitary conditions.

The results, expressed as % of positivity, show a significant specific unresponsiveness to lepromin in both diffuse and nodular lepromatous leprosy, as compared with healthy individuals. On the contrary, responsiveness to PPD in the patients was at least as good as in the control groups. There was no difference in the response to SK-SD between the studied groups.

*Supported in part by Grants from CONACYT and WHO.

V 161

Comparative study on skin reactions to *Mycobacterium leprae*-lepromin and to ICRCin — an antigen from cultivable acid-fast bacilli from *Mycobacterium leprae* isolated from lepromatous nodules

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The failure of skin responses to lepromin — termed negative late reaction in lepromatous leprosy — is a specific phenomenon and characteristic of *M. leprae*. In the present study, skin test antigens, both Dharmendra and Mitsuda type, were prepared from *M. leprae* (lepromin) and from a culture of ICRC bacilli (ICRCin) Strain C-44 (1969). They were standardized to contain 2×10^8 organisms per ml.

Simultaneous skin tests were conducted in 76 leprosy patients at Acworth Leprosy Hospital, Bombay. Both early and late reactions were recorded. In 29 lepromatous (LL) cases, 25 exhibited a totally negative response to both antigens at the third week. Out of 31 tuberculoid cases, 22 were positive (>4.5mm) to lepromin and 23 to ICRCin at the third week. The BB group (16 cases) showed comparable reactions in individual patients. The cellular reactions in TT cases consisted of lymphocytic infiltration, epithelioid cells and Langhans' type cells and were indistinguishable from each other.

The skin tests with these antigens were also conducted at JALMA — Agra — (15 cases) and at Chandigarh — (30 cases). The reactions in these groups, although differing in degree, were comparable in individual patients suffering from LL and TT forms, and supported the above data.

The high degree of correlation in reactions to lepromin and ICRCin, provide strong evidence that ICRC bacilli strain C-44 are antigenically closely related to or identical with *M. leprae*.

These data will be presented and the future implications of the search for an anti-leprosy vaccine will be discussed in the light of studies on bacilli from the armadillo.

V 162

The effect of thalidomide on *de novo* antibody synthesis

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Thalidomide is well documented as an effective treatment for erythema nodosum leprosum (ENL) occurring in lepromatous leprosy. In order to be beneficial, thalidomide must interfere with one or more of the several essential steps which culminate in this syndrome, which is presumed to be a clinical manifestation of an Arthus type hypersensitivity.

Since complexes of antigen and antibody would initiate these events, thalidomide could exert its most direct influence or reactants in this essential step. In order to determine if thalidomide affected *de novo* antibody synthesis, the antibody response of mice fed with concentrations equivalent to human therapeutic doses of thalidomide was investigated.

Thalidomide in concentrations of 0.003%, 0.01% and 0.03% w/w in powdered diets significantly inhibited IgM antibody formation if fed to mice for 5 to 7 days prior to immunization with sheep erythrocytes. Similarly, in leprosy patients being treated with thalidomide for ENL at Carville, we found a selective decrease in serum IgM concentrations as measured by radial immunodiffusion when compared to active leprosy patients not receiving the drug.

One of the clinically relevant sites of action of thalidomide in ENL appears to be on IgM antibody synthesis. The target site of the drug among the macrophage, antibody forming, helper or suppressor lymphocytes remains to be elucidated.

V 163

The effect of colchicine on serum amyloid A elevation during erythema nodosum leprosum reactions

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Colchicine prevents secondary amyloidosis both in patients and Familial Mediterranean Fever and in experimental animals. Our studies examined the effect of colchicine on the serum amyloid protein SAA, a putatively immunosuppressive apoprotein, which we have shown to be acutely raised during erythema nodosum leprosum (ENL) reactions. Fifty lepromatous patients were bled before, during and after ENL reactions. A significant correlation was observed between change in neutrophil leucocyte count (a measure of severity of ENL reaction) and change in SAA titre (measured by radial immunodiffusion using antibodies to denatured amyloid fibrils). SAA concentrations were determined daily in 24 lepromatous patients treated with colchicine 0.5 mg t.i.d. for 3 weeks. Colchicine did not prevent increases in SAA concentration, which continued to occur during acute ENL reactions. Clinically severe ENL reactors had high mean SAA concentrations, while mild and non-reactors had low mean SAA levels ($p < .001$). Thus SAA concentrations were related to the severity of inflammation. These studies suggest that colchicine works by preventing amyloid fibril formation from the serum precursor protein, rather than by preventing synthesis or release of SAA into the serum. The role of neutrophils and their tryptic lysosomal enzymes in causing amyloid fibril formation from SAA remains hypothetical.

V 164

Neutrophil activation in adjuvant disease. Its implications for reactional lepromatous leprosy

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Adjuvant disease (ADJ) is induced in rats by killed mycobacteria suspended in an oily vehicle. Inflammatory lesions, due to delayed hypersensitivity, appear in joints, skin and eyes. Thalidomide alleviates signs of ADJ. Reactional lepromatous leprosy (RLL) resembles ADJ, and its signs and symptoms are suppressed by thalidomide. In RLL there is a specific increase in the proportion of nitrobluetetrazolium-reducing neutrophils (activation). Reducing neutrophils are called formazan-positive (FP).

We studied neutrophil activation in rats of two strains — one susceptible, and the other refractory to ADJ. Neutrophils from rats of both strains were activated *in vitro* by endotoxin, latex particles and *Staphylococcus aureus* suspensions. After injection of mycobacteria, rats from the refractory strain showed little or no ADJ or neutrophil activation. Susceptible rats had intense ADJ. There was a significant increase in proportion of FP cells, but this took place shortly after injection of mycobacteria and before signs of ADJ or the maximum degree of local inflammation occurred. Activation disappeared by the time that ADJ became apparent. There was no significant activation when susceptible rats received the vehicle alone.

Activation may be in ADJ, as in RLL, a specific epiphenomenon induced by a lymphokine.

V 165

Humoral and cellular immunity in lepromatous leprosy

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The presence of autoantibodies (AAbs) and of deficiency of cell-mediated immunity (CMI) has been investigated in 54 patients with lepromatous leprosy (LL).

A high incidence of AAbs together with a depression of CMI has been observed in the majority of the patients, mostly with the active form of the disease.

Not only cutaneous delayed allergic responses to common microbial agents, but also inflam-

matory reactions to chemical irritants have been found to be depressed in a large number of lepromatous leprosy patients.

The close correlation found between autoimmunity and CMI deficiency is discussed in the light of the recent advances in immune regulation mechanisms. LL is postulated as an elegant *in vivo* model of a disease with immunological (humoral and cellular) aberrations and a known etiological agent.

V 166

Immunochemical study of mycobacterial antigens*

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One of the important problems of modern leprology is the practical use of *M. leprae* strains derived from experimentally infected animals (mice, rats, armadillos) in the diagnosis and prophylaxis of leprosy. For this it is necessary to know the antigenic structure of *M. leprae*. The antigenic structure of 6 strains of *M. leprae* derived from rats, 7 strains of atypic and saprophytic mycobacteria (*M. avium*, *M. kansasii*, *M. scrofulaceum*, *M. marinum*, *M. xenopi*, *M. smegmatis*, *M. phlei*) and 3 cultivable "leprosy" strains (M. No. 7, M. No. 25, *M. kedrowsky* (all sonicated)) was studied in double gel diffusion and immunoelectrophoresis. Antisera from immunized rabbits were used. The following results were obtained:

1. The antigenic spectrum of *M. leprae* derived from rats and mice included up to 12 components.

2. The greatest antigenic similarity was found between *M. leprae*, cultivable "leprosy" strains and *M. avium*.

3. Three or four components common to genus of mycobacteria and 3 components belonging only to *M. leprae* were revealed in the structure of mycobacterial antigens.

*Investigation received financial support from WHO.

V 167

Demonstration of intracytoplasmic *Mycobacterium leprae* antigen in the inflammatory exudate of reactional lepromatous leprosy

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Vascular lesions in reactional lepromatous leprosy (Lucio phenomenon or erythema nodosum leprosum) have been attributed to immune complexes fixed to vascular endothelia. However, the absence of demonstrable *M. leprae* within inflammatory cells in some cases with severe vascular lesions is surprising.

With this in mind, we prepared a pool of sera from patients with lepromatous leprosy; the IgG fraction was precipitated and concentrated, and then labelled with fluorescein. This antiserum showed fluorescent positive reaction against *M. lepraemurium*, in both bacillary suspensions and frozen sections of infected mouse tissue.

Frozen tissue sections from lesions of patients with either Lucio phenomenon or erythema nodosum leprosum, were stained with this anti-*mycobacterium* serum, and microscopically examined under ultra-violet light. In all cases, a positive granular pattern type fluorescent reaction was observed in the cytoplasm of macrophages, this indicating the presence of a *mycobacterium*-soluble antigen fraction. This finding was independent of the identification of acid-fast bacilli by the Fite-Faraco staining method. This hitherto undescribed antigen-fraction may play an important role in the pathogenesis of the vascular damage in reactional lepromatous leprosy.

V 168

Determination of T and B lymphocytes in patients suffering from different types of leprosy*

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It is well known that patients suffering from leprosy, particularly of the lepromatous type, show a specific defect in their cell-mediated immunity to *M. leprae* and in advanced cases a more generalized impairment in their cellular immunity. In these patients, however, the humoral immunity does not seem to be depressed, and most of them have the ability to respond with antibodies to a variety of antigenic stimuli. For these reasons, it seemed to us interesting to look for the relations between the immunological state in a group of patients suffering from distinct types of leprosy and the numbers of circulating T and B lymphocytes, as determined by the rosette-forming cells technique.

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V 169

Anti-connective tissue antibodies in leprosy

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Immunological changes have been described in patients with leprosy, who have been found to have antibodies to various antigens. Using the technique of haemagglutination, antibodies against human collagen have recently (1978) been described in patients with leprosy. Antibodies against connective tissue have been described in Crohn's disease, coeliac disease, dermatitis herpetiformis and IgA deficiency, and they have been demonstrated by indirect immunofluorescence.

Serum was taken from 25 patients with lepromatous leprosy in the active phase without reaction, and from 20 control subjects. The specimens were tested for antibodies against connective tissue, smooth muscle, and against glomerular basal membrane and gastric mucosa of rat, using the Saint-Marie (1962) indirect immunofluorescence technique and human anti-globulin serum labelled with fluorescein. Positive sera were titrated with progressive dilutions, from 1 in 10 to 1 in 1280.

Antibodies against smooth muscle were demonstrated in 64% of patients, the highest titre being 1 in 640. There was the same percentage of positive findings with regard to antibodies against glomerular basal membrane, the highest titre being 1 in 1280. In 56% of the patients both antibodies were present and showed the classical pattern.

V 170

Antibodies reacting with fibroblasts, Schwann cells and connective tissue microfibrils in leprosy

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Immunologically mediated lesions seem to be at least partly responsible for the wide spectrum of disease manifestations seen in leprosy patients. Apart from immune responses to the leprosy bacillus, a variety of autoantibodies has been described. The present study focusses on the involvement of connective tissue and nerves in leprosy patients, and describes circulating autoantibodies directed against fibroblasts, connective tissue microfibrils and Schwann cells.

Sera were obtained through a research association with the Armauer Hansen Research Institute (AHRI), Addis Ababa, Ethiopia. 97 sera were tested by indirect immunofluorescence for antibodies against cultured embryonal fibroblasts (HEF), Schwannoma cells (SC) and human foetal connective tissue. 67 sera (69%) showed staining of both HEF and connective tissue microfibrils (MF). SC staining was seen with sera exhibiting a strong reaction with HEF and MF. Antibodies were shown to react with cyto-skeletal intermediate filaments. The possibility that autoantibodies may be involved in the pathogenesis of connective tissue and nerve lesions is suggested.

V 171

Cross-reactions between serum proteins and liver tissue antigens of the nine-banded armadillo (*Dasypus novemcinctus* Linn.) and man. The implications for leprosy research

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At present, tissues from experimentally infected armadillos are the main source of *M. leprae* to be used for skin testing and vaccination trials. Cross-reaction between armadillo and human serum proteins was initially demonstrated in double diffusion tests in gel in the clear supernatant obtained from homogenates of infected armadillo liver. Various *M. leprae* preparations, made from infected armadillos, were found to contain from 2 to 9 contaminating antigens when tested, using anti-armadillo liver serum in crossed immunoelectrophoresis (CIE). Since injection of cross-reacting antigens in adjuvant is the classical way of breaking tolerance, an attempt was made to obtain detailed information on the extent of the cross-reaction between serum proteins and liver tissue antigens of the nine-banded armadillo and man. Armadillo serum, tested with rabbit antiserum against human serum proteins, gave 12 components in CIE. An ultrasonicate of normal armadillo liver gave 20 anodic and 7 cathodic liver tissue antigens, out of which 12 of the former and 6 of the latter cross-reacted with those of man. The finding is important from the point of induction of autoimmune diseases. It is, therefore, concluded that *M. leprae* preparations of armadillo origin should meet strict criteria for purity before they are injected into healthy people.

V 172

Lymphocyte function in progressive *Mycobacterium lepraemurium* infection

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Varying susceptibility of different strains of mice to *M. lepraemurium* infection presents histopathologically as a spectrum of disease somewhat similar to that of human leprosy. The susceptible C_3H strain of mice shows a progressive disease with granuloma formation in the deeper tissues, while the relatively resistant $C_{57}BL$ strain shows a cellular reaction which has the appearance of a delayed type hypersensitivity reaction. In our study we have investigated the functional activity of the splenic lymphocyte populations from these two strains of mice at different periods following infection. Lymphocytes from spleens of infected animals were cultured in the presence of non-specific mitogens, phytohaemagglutinin and concanavalin A, group specific PPD antigen and *M. avium* ultrasonicate and the specific *M. lepraemurium* antigen (ultrasonicate) and the uptake of 3H-thymidine was determined by a standard technique. Results show that the lymphocytes from relatively resistant $C_{57}BL$ mice demonstrate a gradual increase in transformability to both non-specific mitogens as well as to group specific avium antigen until about 4 weeks after infection. Following this there was a gradual reduction in mitogen-induced transformation to almost normal levels during the course of the next ten weeks. Transformation to avium antigen, however, showed a continuous upward trend until the termination of the experiment. Results of these studies and that with C_3H strain mice will be presented in detail.

V 173

An investigation of mechanisms regulating skin test responsiveness in leprosy patients using soluble *Mycobacterium leprae* and *M. tuberculosis* antigens and a mixture of the two

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Many leprosy patients are positive to Tuberculin and negative to *M. leprae* reagents. The negative response to *M. leprae* might be

attributable to a regulatory mechanism such as suppressor T-cells. Cells of this type have been demonstrated in the blood of leprosy patients *in vitro* by several other laboratories. Such cells may be triggered by *M. leprae* antigen to exert a non-specific suppressive effect. This leads to the hypothesis that a mixture of *M. leprae* and *M. tuberculosis* antigens would give a negative response in a patient who was positive to Tuberculin and negative to the *M. leprae* reagents given separately. Our investigations indicate that the situation is more complex than was thought.

V 174

Skin-reactive antigens of *Mycobacterium leprae*

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Preliminary studies have been made to characterize and purify the soluble antigens of *M. leprae* in armadillo lepromin which produce cutaneous reaction in sensitized persons at 48 hours. These studies have been carried out on crude supernate separated by centrifugation of autoclaved integral lepromin at 48,000 g for one hour. All fractions have been tested for activity and specificity in groups of Mitsuda-positive and Mitsuda-negative patients and controls. Precipitation with increasing concentrations of ammonium sulphate and liquid chromatography on Sephadex G-100 and Ultrogel 22 reveal the presence of multiple skin-reactive components. Separation by ultrafiltration demonstrates marked activity in two soluble fractions, one with a molecular weight between 20,000 and 30,000, and the other with a molecular weight greater than 100,000. Specificity of these two fractions has been tested in human beings with other mycobacterial infections and in sensitized guinea-pigs. Liberation of skin-reactive material from integral lepromin by other procedures to be described shows marked activity in preparations containing less than one mcg of protein per injection. The importance of the use of relatively pure and highly specific soluble antigen preparations in epidemiological studies of leprosy will be discussed.

V 175

Study of the immunity, after an interval of 3 years, of leprosy patients having undergone BCG immunotherapy

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Several studies have shown the role played by BCG immunostimulation in leprosy, but the development after some time has not been specified. Is stimulation followed by a transitory improvement or by a process of regression?

Twenty patients, mainly with lepromatous forms, received intradermal lyophilised BCG every fortnight for a period of 6 to 14 months in 1974, in conjunction with treatment with Disulone.

In 1977, a complete assessment was made, including in particular: research into precipitating antibodies and lymphocyte transformation test, using antigens derived from *M. lepraemurium*.

Bacteriological and anatomopathological results

In the majority of cases: bacteriological negativation, and transition towards an indeterminate form.

Immunological results

— *in vivo:* positivation of the Mitsuda test in more than half the cases;
— *in vitro:* in comparing the results (serology and LTT) of these patients with groups L, T or I of patients who have not been subjected to immunotherapy, we notice a close analogy with the I form.

BCG immunotherapy seems to be followed in time by regression; it is more marked after 3 years than immediately after cessation of stimulation.

The development of the biological improvement gives grounds for the assumption that it will lead to the attainment of delayed hypersensitivity, and we can envisage the cessation of treatment for certain patients, originally lepromatous, who have become indeterminate.

V 176

BCG immunotherapy trial in lepromatous leprosy

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Thirteen patients with polar lepromatous leprosy and two patients with borderline-lepromatous leprosy were studied. This group has been under medical control at the Korean Leprosy Institute and most of them were on combined chemotherapy with rifampicin, thiambutosine and dapsone. In all of them the disease was still active.

Fifteen patients were given progressively increasing doses of BCG, intradermally, beginning with 0.1 ml of 1 in 100 dilution. This dose was increased fortnightly, until a maximum of 0.1 ml of a 1 in 10 dilution was attained. Thereafter, this same dose of BCG (1:10) was injected fortnightly. The injections were well tolerated, except that necrotic nodules developed at some injection sites in some cases.

Rapid clinical improvement was observed in all patients.

All fifteen patients were Mitsuda negative with standard lepromin antigen before the BCG trial; however, five months after the BCG trial the following results of Mitsuda reaction were observed.

moderately positive (+ +)	1 case
weakly positive (+)	7 cases
doubtful (±)	3 cases
negative (—)	2 cases
not tested	2 cases

Bacteriological improvement was observed in all cases. Before the BCG trial, BI was 3.3 + on average; however, five months after BCG trial it had fallen to 2.6+ on average, and the MI fell from 18% to 0.8% during the same period.

Six months after the BCG trial, histopathological findings showed borderline-lepromatous changes in two cases and indeterminate change in one case, and a small localized foamy cell mass in all cases.

Of fifteen patients, eight cases showed positive conversion of Mitsuda reaction five months after BCG repeated injections in this trial. These results showed that CMI stimulation by BCG is possible and therefore BCG immunotherapy can increase the digestion of *M. leprae* and thereby prevent drug-resistance.

V 177

Double blind trial on the effect of certain soluble cytoplasmic mycobacterial antigens on the reactivity to lepromin

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Kwapinski *et al* (1975) and Bechelli *et al* (1977) observed that the incidence and intensity of late response to lepromin were significantly reduced in children preinjected with soluble cytoplasmic antigens (X: *M. avium* and *M. gallinarum*; Y: *M. simiae, M. gallinarum* and *M. avium*; Z: *M. leprae, M. simiae* and *M. borstelense*).

In the present double blind trial other antigens have been studied: F: *M. tuberculosis, M. aquae* and *M. lepraemurium*; G: *M. simiae, M. piscium* and *M. balnei*; H: *M. leprae*, in comparison with BCG and placebo.

The tests have been performed in 254 children between 6 and 59 months; the five randomized groups were comparable regarding the total number and distribution by age and sex.

The percentage of positive reactions on the late lepromin reading observed in the groups inoculated with antigens G, F and H was similar to that observed in the placebo group.

In the BCG vaccinated children there was a higher percentage of lepromin reactors (89%). The difference was statistically significant.

Comparing the findings of the first and the present trials, it is apparent that the antigens of *M. borstelense* and either of *M. avium* or *M. gallinarum*, would have been instrumental in the lepromin impairment observed in the first trial.

V 178

Protein derivative prepared from *Mycobacterium leprae* suspensions maintained in a semi-synthetic medium

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The purpose of this trial is to obtain a skin test allergen with the following characteristics, to be used in leprosy research: a) good potency and specificity in the Fernández and Mitsuda reactions, b) it should be composed of proteins and be free from bacilli and host tissue, and, c) its composition should not vary from batch to batch. The last characteristic would allow easy chemical and biological standardization, like that of PPD in tuberculosis.

Purified suspensions of whole bacilli from leproma were inoculated into Murohashi medium without agar. These suspensions were incubated at 37°C for two years, after which they were treated with phenol and filtered through 0.45 and 0.22 μm filter sheets. The proteins in the filtered solution were separated by the addition of trichloroacetic acid. A protein-buffer sterile solution was prepared from the washed sediment and diluted to 1.5 mg/ml.

The solution was employed as a skin test sensitin (Fernández and Mitsuda tests) in patients with tuberculoid and lepromatous leprosy, in healthy people and in tuberculosis patients. A good correlation between reactions to the assayed allergen and lepromin was observed. Rare cross reactions with *M. tuberculosis* PPD were observed.

V 179

Mitsuda antigen of animal origin. Absence of Hanseniasis in armadillos living in the natural state; human hypersensitivity to the animal antigen.

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The author studied Mitsuda antigen of animal origin and of human origin in Hanseniasis patients, contacts and medical students. Skin tests were carried out and after 48 hours and 21 days a biopsy was performed with close resemblance in the majority of cases. However the reaction was stronger with animal antigen, mainly after 48 hours.

Three armadillos were collected in the state of Minas Gerais and in the necropsy material there was no evidence of Hanseniasis.

From the skin of those armadillos an antigen was prepared by the same technique used to prepare Mitsuda antigen. This bacilli-free animal antigen was injected into healthy people and only 5% were positive after 48 hours.

In this way a cellular human hypersensitivity to armadillo antigen which is able to interfere in the result of Mitsuda reaction became manifest.

V 180

Prognostic considerations based on a study of 38 Hanseniasis patients submitted to Mitsuda tests 23 to 35 years previously

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Out of 2775 Hanseniasis patients Mitsuda tested by one of the authors (R) from 1933 to 1947, 38 were reexamined in 1970—1971. Twenty-eight had been treated regularly, four irregularly, six had not received sulphones. Improvement or disappearance of skin lesions occured in 31 (81%) independently of reactivity. All 11 bacteriologically positive out of 19 Mitsuda negative patients became bacteriologically negative, which is partly attributed to sulphones. One treated bacillary negative patient became positive. *Twenty-eight (76%) were neurologically aggravated, independently of reactivity, but more evidently among the stronger reactors.*

As regards classification, all initially tuberculoid, Virchowian and dimorphous patients continued so, but only 7 out of the 17 initially indeterminate remained in the group. Four, of which two Mitsuda + +, two +, changed to reactional tuberculoid. Six (of which three Mitsuda negative, two + and one + +) changed to Virchowian. Mitsuda reactivity remained usually unchanged, rarely increasing or decreasing. These developments according to reactivity confirm the pathogenetic theory postulated in 1937 by one of the authors (R).

The good prognostic value of a strong Mitsuda test is generally confirmed, but only as regards bacillation, dermatological lesions and classification, *not from the neurological and social viewpoints.*

V 181

Results of the lepromin test using human lepromin (H) and armadillo lepromin (A)

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The authors report on the largely concordant results obtained in administering lepromin H and lepromin A to leprosy patients and healthy family members living with them, to subjects suffering from TB of the lungs and healthy subjects living in a presumably healthy environment. Studies are being conducted to establish the causes of non-concordance of the results in a very limited number of cases.

In no case has the repeated inoculation of lepromin A given rise to abnormal phenomena.

The authors are of the opinion that lepromin A could replace lepromin H in current practice: this would facilitate the widespread application of the Mitsuda test, which should be administered to all individuals living in endemic areas, in order to detect the subjects showing a negative lepromin reaction.

Until such time as it becomes possible to cultivate *M. leprae* and produce a specific vaccine, it is considered that lepromin A could be used in immunological research in lieu of vaccines such as BCG, which are not derived from *M. leprae*.

V 182

Dinitrochlorobenzene responsitivity throughout the granulomatous spectrum of leprosy

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To try to understand the absence of anergy, i.e. a generalized impairment of cell-mediated immune (CMI) responses in our polar lepromatous leprosy (pLL) patients, but its presence in those of many others, we have extended our study of dinitrochlorobenzene (DNCB) responsitivity to include the entire granulomatous spectrum of leprosy.

DNCB sensitization was attempted in 37 untreated patients (classified by the Ridley system), and in 40 controls.

Allergic sensitization to DNCB was found in 34 of 40 controls, 5 of 5 BT-TT patients ($p > 0.9$ compared with controls), 4 of 6 BB ($p > .7$), 3 of 6 BL ($p > 0.1$), 1 of 6 LI ($p < .005$) and 9 of 14 pLL ($p > 0.2$). The following groupings showed DNCB responsitivity to be statistically significantly less than in controls; multibacillary or BB-LL ($p < .01$), unstable bacillary or BB-LI ($p < .005$) and lepromatous or pLL-LI ($p < .01$). Thus anergy can be found in our leprosy patients but remains undemonstrable in the pLL class.

Our results suggest that several conditions are necessary, none of which is by itself sufficient, as causes of anergy. Such conditions are: antigen load, infiltration of lymphoid organs and CMI responsitivity to antigens of the etiological agent. Perhaps our pLL patients are tolerant toward *M. leprae* and therefore fail to develop anergy. Spectral impurity could explain the insignificant degree of DNCB unresponsiveness in the pLL group.

V 183

Lymphocyte transformation test (LTT) in leprosy patients, in the presence of phytohemagglutinin, lepromin and *Mycobacterium leprae*, in culture medium with normal homologous serum

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In order to verify the correlation between lymphocyte transformation test (LTT) and forms of leprosy and also lepromin reactions, the authors studied it in 42 leprosy patients in the presence of phytohemagglutinin (PHA), lepromin and *M. leprae*. The lymphocytes were separated by ficoll-hypaque and cultured in Eagle's medium with 20% of homologous serum of unaffected persons, in a concentration of 0.75×10^6 cells per ml. The blastogenic response was assessed by cellular incorporation of 3H-thymidine.

In all patients, the blastoid response to lepromin and *M. leprae* was lower than that to PHA. The cultures from polar tuberculoid and polar lepromatous, and from borderline patients, exposed to PHA, lepromin and *M. leprae*, apparently have similarly incorporated 3H-thymidine.

The blastoid response to lepromin seemed slightly higher in patients with Mitsuda reaction 2+ and 3+ than in those negative or weakly (1+) positive, which was not observed with PHA and *M. leprae*.

So far, the above findings on LTT with homologous serum, in the presence of PHA, lepromin and *M. leprae*, do not suggest that it may replace the lepromin test in the current evaluation of the immune responsiveness of leprosy patients to *M. leprae*.

V 184

Effect of specific vaccine on cell-mediated immunity of armadillos against *Mycobacterium leprae*

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Five armadillos vaccinated by intramuscular injection of heat-killed *M. leprae* A in Freund's incomplete adjuvant were infected together with nine untreated armadillos by intracutaneous inoculation of 10^6 *M. leprae* A. Vaccination engendered in the five animals capability to respond with strong Koch reactions to lepromin, delayed type hypersensitivity to *M. leprae*-protein and (with one exception) significantly increased lymphocyte blast transformation in the presence of *M. leprae*.

One of the vaccinated armadillos had signs of disseminated leprosy after 1005 days. Another was autopsied after 690 days and had no leprosy. The remaining three vaccinated armadillos are without signs of leprosy after 1184 days. Eight of the unvaccinated armadillos had signs of disseminated leprosy between 349 to 1184 days after infection. The remaining unvaccinated armadillo has no sign of dissemination after 1184 days.

The findings show that some armadillos are immunizable, and development of a susceptibility test based on CMI responses to vaccination seems feasible. Challenge with 10^6 *M. leprae* A is too overwhelming for validating the predictions of a susceptibility test. Dose-response experiments to determine the proper test dose are in progress. The increase in resistance is probably significant. ($X^2 = 4$ for 1 degree of freedom with Yates' correction.)

V 185

Antigenic evaluation of *Mycobacterium vaccae*—a mycobacterium possibly related taxonomically to *Mycobacterium leprae*

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Inability of *M. leprae* to grow *in vitro*, has of necessity directed efforts toward studying the antigenic analysis of other mycobacteria that share some of their antigens with the leprosy bacillus. These efforts stem from the fact that such antigens if obtained individually in large quantities would best permit a number of immunological studies, which could afford a better understanding of the host-parasite interaction in leprosy infections either of humans or of laboratory animals.

A recent report from Dr. Stanford's laboratory in England, indicated a possible immunological relation between *M. leprae* and *M. vaccae*. This report prompted our laboratory to investigate the possible taxonomic relation between these two organisms. Preliminary studies, employing the immuno-diffusion and immuno-electrophoretic analysis, showed that *M. vaccae* possesses at least six detectable antigens, some of which it shares with other mycobacteria, when the *M. vaccae*-anti-*M. vaccae* system was compared with the several mycobacterial reference systems routinely used in this laboratory. Although it appears that *M. vaccae* shares a majority of its antigens with *M. leprae* derived from infected armadillos, it shares only a few with *M. leprae* derived from human sources and with other mycobacteria capable of growing *in vitro*; this suggests that there might not be a very definite taxonomic relation between *M. leprae* and *M. vaccae*. These studies have been extended to confirming the initial

observations and also to employing other immunological parameters that would support or otherwise the preliminary observation.

This investigation was supported by a grant from the National Institute of Allergy and Infectious Diseases (Grant R22-AI-08647).

V 186

FLA-ABS test as a screening test for the detection of cases at an early stage of leprosy

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The FLA-ABS test (Abe *et al*) was performed on 21 family members and contacts of patients treated for lepromatous leprosy at the clinical Center for leprosy in Athens.

In four cases (almost 20%) the test was positive, while the BI in the skin smears of all 21 persons tested was negative. Two of the four persons who were found to be positive in the serodiagnostic test developed six months later definite clinical and bacteriological signs of indeterminate and tuberculoid leprosy.

V 187

Morphological changes in mast cells and levels of serotonin and histamine in leprosy patients

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The skin biopsies obtained from 40 leprosy patients were studied for changes in the morphology of the mast cells. The blood levels of serotonin and histamine from the same patients were also estimated. An appreciable alteration in the morphology of the mast cells and a significant rise of serotonin and histamine were observed in leprosy patients as compared to controls. It appears that the level of the biogenic amines increases with the increased degranulation of mast cells in leprosy. However, the changes are variable and depend upon the stage and severity of the disease.

V 188

Suppressor cells in human leprosy

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The presence of a subpopulation of lymphocytes exerting suppressor effects *in vivo* and *in vitro* has been recently demonstrated in animals. It was thought pertinent to delineate the role of such cells in human leprosy where cell-mediated immune responses are known to be depressed. This paper discusses the results obtained in 3 different approaches, using peripheral blood lymphocytes.

(i) *Con A generated suppressors* : *In vitro* activation of suppressor cells was achieved by Con A and their effects noted on blastogenic responses of autologous lymphocytes. Normals as well as patients along the leprosy spectrum showed suppressive activity. Tuberculoid patients showed higher than normal suppressive activity, whereas bacillary positive lepromatous patients showed lower suppression. The lack of suppression in the latter group was reversed by prolonged treatment and during ENL reactions.

(ii) *Antigen derived suppression* : The effect of *M. leprae* on PPD, Con A and PHA responses of leprosy patients was studied by lymphocyte transformation. Both tuberculoid and lepromatous patients showed suppression effects.

(iii) *Enumeration of T cells bearing Fc receptors* : Ox erythrocytes coated with IgG fraction of anti-Ox antibody were used for rosettes against a subpopulation of purified T cells. Normal numbers of Fc-bearing T cells were obtained in patients with leprosy.

V 189

Fluorescent leprosy antibody absorption (FLA-ABS) test for early serodiagnosis of leprosy

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Clinical signs, aided by smear and histological examinations, are the conventional means used

for the diagnosis of leprosy. However, the above criteria have inherent limitations, and it is sometimes difficult to diagnose the very early stages of leprosy.

Recently, antibody-combining specificity of *M. leprae* has been established by an indirect immunofluorescence test, using anti-human globulin fluorescent antibody and leprosy patients' serum which has previously been absorbed with cardiolipin, lecithin and the polysaccharide of tubercle bacilli. The test is very sensitive and has given reliable results.

The FLA-ABS test has been standardized in this laboratory and found to be sensitive and specific. Sera of 106 cases of different types of leprosy, including very early cases, and also the sera of 29 healthy contacts of leprosy cases and 14 healthy controls not exposed to leprosy, have been examined. The results are promising with regard to its wide application, which will be discussed.

V 190

Micro-technique enzyme-linked immuno-sorbent assay of Clq-reactive circulating immune complexes in leprosy

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Circulating immune complexes have been detected by Clq gel precipitation and radio-immune assay. This study reports on a micro-technique enzyme-linked immuno-sorbent assay of Clq-reactive circulating immune complexes, a highly sensitive and relatively simple procedure when compared to the previously mentioned techniques.

Micro-titre polystyrene plates were coated with Clq which captured circulating immune complexes from the test sera subsequently added. Alkaline phosphatase labelled anti-human immunoglobulin conjugates were then reacted with substrate, yielding a color change read at wavelength 405 for absorbance. Thus the test sera were qualitatively and quantitatively analysed for circulating immune complexes.

The sera of 17 patients with leprosy (2 tuberculoid, 5 borderline with tuberculoid features, 7 borderline with lepromatous features, and 3 lepromatous) were examined and compared with 10 normal controls. Circulating immune complexes were found in 2 of the lepromatous patients, 3 of the borderline with lepromatous features, and 1 of the borderline with tuberculous features, but in none of the tuberculoid patients. One control was positive for immune complexes. This patient was also rheumatoid-factor positive. The greatest concentration of circulating immune complexes was detected in the borderline with lepromatous features and the lepromatous patients.

V 191

Direct and indirect immuno-fluorescent studies of the lesions, normal skin and sera of leprosy patients

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In recent years it has been understood that immunological reactions play an important role in the pathogenesis of leprosy. According to these suggestions the detection of the antibodies in tissues and sera of leprosy patients can indicate the immunological aspects of the disease.

Direct immunofluorescent methods have been applied to the lesions and the normal skin of a large group of leprosy patients, including lepromatous and borderline cases. The localization of the IgG, IgA, IgM and C_3 was investigated in the epidermis and dermis and the results obtained from this study are given in detail.

In addition, the sera of the same patients have been examined by indirect immunofluorescent method, using normal human skin. The sera of a large percentage of the patients have shown intercellular IgG antibodies — an interesting finding.

The results obtained from direct and indirect immunofluorescent studies of leprosy patients are compared with those in other publications, some of them rather conflicting.

V 192

Immune complexes in erythema nodosum leprosum

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Skin and nerve biopsies were obtained from confirmed cases of lepromatous leprosy. Twenty-five of them had erythema nodosum leprosum (ENL) reaction. The tissues were processed for light and electronmicroscopic observations. In addition, the skin specimens were studied for immune complex deposits by immunofluorescence.

On the basis of localization of the fluorescent deposits, the ENL lesions were classified under three groups, correlating with the onset of the reaction. The complexes seen in the lumen of the wall of the blood vessels or in the surrounding inflammatory cells are strongly suggestive of a definite shift in the complexes, and they may have a role to play in hypersensitivity reactions.

V 193

Cellular responses in leprosy and related diseases with particular reference to cells of the mononuclear-phagocyte series

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Cells trapped in the lesion, as constituent cells of the granuloma, are more closely related to their immunological function than those in peripheral blood.

Rosette tests for E, EA and EAC binding sites as well as immunofluorescent methods were applied to cryostat sections of leprosy, sarcoidosis, *M. ulcerans* infections and related diseases. Lymphocytes were identified as T cells in TT/BT and B cells in BL leprosy. Two patterns emerged in cells of the mononuclear-phagocyte series; BT/BB showed a strong depression of the C_3 receptor site in epithelioid cell granulomas and around epithelioid cells in particular. On the other hand, active LL leprosy showed an increase of the Fc receptor. This was related to bacterial load. No binding was seen in foam cells of regressing or extreme polar LL.

In vitro studies have shown a fall in C_3 binding sites after BCG similar to BL leprosy. No change was seen after latex ingestion. This may be concerned with complement activity.

V 194

Autoantibodies in leprosy

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Many investigators have studied the incidence of various iso-and auto-antibodies in leprosy patients and most of them reported that leprosy, especially the lepromatous type, is associated with some serological features suggestive of an autoimmune aberration. With the generalized deficiencies in cell-mediated immune responses, the excessive auto-antibody production is a characteristic of populations with lepromatous leprosy. But these conclusions are not generally accepted.

This report concerns the prevalence of auto-antibodies directed against a variety of tissue constituents, including smooth muscle, nuclei, mitochondria, parietal cells, thyroid microsomial, thyroglobulin, in a random population of 111 patients with lepromatous leprosy and 75 patients with tuberculoid leprosy. The results are summarized.

There are no significant differences between the two groups of leprosy patients, apart from the incidence of auto-antibodies against smooth muscle which is higher in the lepromatous forms.

V 195

Ancestral immunity in the evolution of endemic leprosy in the tropical zones

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In Mitsuda-negative contacts of index cases of leprosy, early cases of indeterminate leprosy

develop into tuberculoid forms in 80% of cases in Asia and Africa, and into lepromatous forms in America and the Pacific islands.

The author attempts to show, in this paper, the influence of the immune status of the parent on the clinically diverse types of leprosy in the secondary cases, and relates the beginnings of cellular immunity in the latter to the observed proportions of tuberculoid and lepromatous patients in areas where leprosy is endemic.

V 196

Immunoglobulin concentration in mothers and in healthy controls and their babies at the time of birth

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Immunoglobulins were quantitated in the sera from matched cord bloods and maternal bloods of 52 mothers at the time of delivery. Thirty-eight of these suffered from leprosy; of these, 13 had active lepromatous leprosy, 9 inactive lepromatous leprosy and 16 borderline tuberculoid leprosy, while 14 were matched controls. The immunoglobulin quantitation was done with a modified Manchini technique (to enable measurement of the low IgA concentration found in the cord sera).

The median concentrations of IgG and IgM in cord blood were equal in all the four groups. The median IgG concentration in the sera of patients suffering from active lepromatous leprosy was slightly higher than in the three other groups, but this was not significant.

The median IgA concentration in cord blood from babies of mothers with active lepromatous leprosy was significantly higher than the IgA concentrations in the three other groups.

Active lepromatous leprosy patients have large quantities of *M. leprae* antigens in their tissues and blood. The rise in IgA concentration in the cord blood of babies belonging to this group indicates a possible intrauterine exposure of the foetus to *M. leprae* which causes a selective production of IgA without concomitant IgM production.

V 197

A comparative serum profile in leprosy-related and non-leprosy-related families

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Escuela Nacional de Ciencias Biológicas, Mexico

The study was carried out in seven families in which a leprosy patient per family was included (32 members, patients included) and in five similar families which had no relations with leprosy (21 individuals). Although all the patients were adults between 30 and 50 years old, the family relatives showed a major variability in regard to age compared with the respective spouse and children.

In a general way, the patients' relatives were not different from the control families in relation to the studied parameters, while the patients themselves showed significant differences when compared with their own family members and their healthy counterparts. The most obvious differences shown by the patients were: (a) an increase in the gamma-globulin serum fraction with a concomitant decrease in the albumin, (b) an increase in the levels of IgG, IgA and IgM immunoglobulins and (c) the presence of anti-mycobacterial antibodies in 6 of the 7 patients. Immune complexes reactives with Clq were not detected, nor alterations in the levels of C_3 and C_4 components of complement.

V 198

The immunological profile of patients with different types of leprosy resident in a hospital for the treatment of leprosy

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C. RODRIGUEZ E. PEDROZA
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Although it is not now recommended that patients with leprosy be admitted and kept in hospital, the leprosy hospital at Zoquiapan has

been active since it was opened in 1939. This provides an opportunity to study patients who have long had the disease and patients who have had prolonged treatment. Moreover, there are patients with almost all the types of leprosy in the different stages of evolution.

The patients and some members of their families had a thorough clinical examination and the following laboratory investigations: C50%, C_3 and C_4, total proteins, electrophoresis of plasma proteins, determination of IgG, IgA and IgM, immunoelectrophoresis with the antigens of *M. lepraemurium* and BCG, determination of immune complexes, intradermal tests with PPD, varidase and candidin, MIF with lepromin, PPD and varidase. Many of the patients had marked changes in the gamma globulins, immunoglobulins, in the T and B cells and in the MIF with lepromin. These features were especially pronounced in patients with lepromatous leprosy. The majority of patients gave positive results for antimycobacterial antibodies by contraimmunoelectrophoresis and a high percentage of patients with lepromatous leprosy had circulating immune complexes.

V 199

Importance of the effect of Levamisole on lymphocytes in household contacts of bacilliferous lepromatous patients

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The changes in cellular immunity of lepromatous patients correspond to a depression in the thymus-dependent lymphoid tissue. It also corresponds to a decrease in the number of cells which demonstrate spontaneous rosette formation with sheep red blood cells; these identify the T or thymus-dependent subpopulation.

The peripheral blood of Bursa- or bone marrow-dependent lymphoid population does not show quantifiable changes in respect of the number of cells which have surface immunoglobulins (Ig) and receptor for C_3 complement (receptors on B-lymphocytes); up until now we have not known whether changes exist, either in number or function, within the B subpopulations, and whether these could be temporarily modified by immunomodulators (Levamisole, BCG etc.) in the household contacts of lepromatous patients.

Experiments using different markers were carried out with the object of identifying subtypes within the B subpopulation, for example: spontaneous rosette formation, both complement dependent with sheep erythrocytes, spontaneous rosette formation with rat red blood cells, *Staphylococcus aureus*, with *Saccharomyces cereviceae*, etc.

The specific aim of this study is the identification of lymphocyte subpopulations and the effect of immunomodulating drugs (Levamisole and/or BCG) on the distribution of the different lymphoid subpopulations in the peripheral blood of household contacts of lepromatous patients, with gram-positive bacilli.

V 200

Studies on the anti-inflammatory mechanism of action of thalidomide in leprosy

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Thalidomide is effective in suppressing the clinical manifestations of erythema nodosum leprosum (ENL). Earlier studies in the carrageenan rat paw œdema model have indicated that thalidomide has, as one of its modes of action in ENL, a purely anti-inflammatory effect. The property of thalidomide to inhibit carrageenan-induced œdema was abolished in animals depleted of neutrophils by methotrexate pre-treatment. Thus, the anti-inflammatory action of thalidomide appears to involve neutrophils. Thalidomide does not induce a neutropenia, and thus its action on neutrophils presumably involves functional changes. Thalidomide inhibits the chemotaxis of human neutrophils *in vitro* in response to complement-derived chemotactic factors from zymosan-treated autologous serum. Thalidomide does not affect the number of neutrophils which phagocytize opsonized zymosan particles *in*

vitro, but it does significantly reduce the total amount of opsonized oil red O emulsion phagocytized. Thalidomide does not influence the release of lysosomal enzymes from human neutrophils during phagocytosis *in vitro* or from isolated granules of guineapig peritoneal exudate neutrophils. The neutrophil appears to be one site of action of thalidomide in ENL and its relevant action at that site appears to be inhibition of chemotaxis.

V 201

Immunological studies in leprosy patients in leprosy reaction treated with thalidomide

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Thalidomide is at present widely used to treat leprosy reactions. Previous papers agree that this drug is a cellular immunodepressant. The present investigation sought to determine whether such an effect exists in our patients.

Thirty patients (22 men and 8 women) with leprosy reactions were investigated by intradermal tests, haematology, bacilloscopy, MIF, T and B cell studies, immunoglobulins and complement. Twenty-five patients were treated with thalidomide and five were not treated with that drug. Twenty-one patients had nodular and 9 diffuse leprosy. Bacilloscopy was positive in 23. The majority were positive reactors, principally to varidase and to PPD. All the patients had erythema nodosum leprosum and 20% had also a polymorphous erythema; the latter were treated with thalidomide.

The patients treated had marked changes in the following manner: MIF to lepromin reduced ($p < 0.001$), T cells reduced (p 0.01), C_3 reduced ($p << 0.001$), C_4 increased (p 0.02) complement 50% increased (p 0.01), IgG and IgM increased ($p < 0.001$) and IgA increased (p 0.05) in comparison with healthy controls. However, there was no important difference between patients treated with thalidomide and those not so treated.

V 202

In vitro lymphocyte responses in borderline leprosy reactions

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Reversal reactions are the major cause of nerve damage in leprosy. We have studied 81 patients with borderline leprosy (BT, BB, BL) for a period of between one and two years from commencement of therapy, correlating the clinical, the histological and the immunological findings.

Seventeen patients developed reversal reactions, all during the first year of treatment. In fifteen of these, there was a marked rise in lymphocyte transformation responses to preparations of *M. leprae* during the reaction. On treatment with steroids, the responses fell to baseline levels. There was no concomitant rise in humoral antibodies to *M. leprae*. These findings confirm that reversal reactions are an example of delayed hypersensitivity reactions.

When the patient's lymphocytes were tested with two different preparations of *M. leprae* antigens (whole washed bacilli, and sonicated bacilli), the patients who had skin reactions without neuritis had high responses to whole *M. leprae* but not to sonicated *M. leprae*, and those with neuritis but without inflamed skin lesions had high responses to sonicated *M. leprae* but not to whole *M. leprae*. Those with both skin and nerve involved in the reaction had high responses to both antigen preparations.

When the patients who did not develop reaction were studied, it was found that BT patients had higher lymphocyte transformation responses than those with BL leprosy. However, there was great variation in the responses of both groups: those with inflamed skin lesions had significantly higher responses to *M. leprae* than those with non-inflamed lesions both in the BT and BL patients. Indeed, those with BL leprosy and inflamed lesions had significantly higher responses than those with BT leprosy and non-inflamed lesions. This implies that the lymphocyte transformation responses reflect the degree of delayed hypersensitivity rather than that of protective immunity.

V 203

Antigenic substances of *Mycobacterium lepraemurium*

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α and β antigens were detected by Yoneda and Fukui (as major extracellular products of *Mycobacterium tuberculosis*). They separated and purified these antigens from extracellular protein of unheated culture filtrate of mycobacteria. α and β antigens have been important in the identification and classification of mycobacteria by a serological method. Mycobacteria have been classified into several groups by the distribution pattern of these antigens detected in culture filtrates. This classification has good correlation with other classification methods which have been commonly used.

Ogawa *et al* succeeded in culturing *M. leprae* on Ogawa's 1% egg yolk media. It is, therefore, now possible to obtain large quantities of *M. leprae* uncontaminated by tissue components. In this report we present evidence of the isolation of antigenic substances from cultured *M. leprae*, which included a substance with antigenicity to rabbit. We could purify this α antigenic substance to make single band in 0.1% SDS polyacrylamide gel by disc electrophoresis. Some characterizations of this substance have been attempted.

V 204

Dissociation in mice between delayed type hypersensitivity to a sonic extract of *Mycobacterium lepraemurium* (MLM) and resistance of MLM infection

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Ullevaal Hospital, Olso, Norway

When C57BL mice are infected with *M. lepraemurium* (MLM) the bacilli will multiply for about 4 weeks until an immune reaction terminates the infection and renders the animals immune against reinfection. In contrast, C3H mice are highly susceptible to infection with MLM, and do not develop measurable delayed type hypersensitivity (DTH) to bacillary antigens during infection. Both strains were immunized by injecting 25 μl of MLM sonicate with Freund's incomplete adjuvant sc on the thorax. By footpad testing with diluted MLM sonicate, strong DTH was found in the C57BL strain, but only a very weak reaction was seen in the C3H strain. Adminstration of cyclophosphamide, 3 days before immunization with MLM sonicate, resulted in a much increased DTH in C3H mice. Various groups of mice of both strains were challenged with live MLM in the footpad to test the protective effect of immunization with MLM sonicate. In C3H mice, the induction of DTH to MLM sonicate had no effect on the multiplication of the bacilli, not even in mice given repeated injections of MLM sonicate into the infected footpad, which elicited a marked but transient local reaction. In C57BL mice the sonicate immunization did not, in itself, confer protective immunity but seemed to accelerate the development of such immunity.

V 205

The role of thymectomy and whole body irradiation on the development of immunity to mycobacterial infections

E. FREERKSEN M. ROSENFELD
H. GRAEF

Borstel Institute, Hamburg, Germany

Experiments on theymectomized and whole-body-irradiated animals (mice) showed that these animals did not lose their capacity to develop protective immunity because of these procedures.

V 206

Rubino's reaction by microtechnique with sheep and horse erythrocytes

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M. J. DE O. ANGELO
R. P. DE S. CARVALHO
C. S. PANNUTI

Institute of Health, Mexico

Microtechniques for Rubino's reaction using either sheep or horse erythrocytes were devised and standardized.

Equal percentages of positive reactions were observed in 18 serum samples from Virchowian patients using the standard Rubino's reaction and the microtechnique with sheep erythrocytes.

The microtechniques using either sheep or horse erythrocytes were applied to the sera of 53 Virchowian patients. 50.9% of positive reactions using horse erythrocytes were observed in the Virchowian patients tested, against 41.5% when the reaction was made with sheep erythrocytes.

No positive Rubino's reactions were found in the sera of 30 non-Virchowian patients by either technique.

Sera from a control group (40 serum samples, from blood donors and from hepatitis, leptospirosis and syphilis patients) were tested by the microtechniques with negative Rubino's reactions.

SESSION VI
SOCIAL ASPECTS

Wednesday, 15 November 1978
9:00-13:00
Auditorium 2
Chairman: **A. D. Askew (Great Britain)**

Rapporteur: **T. E. Surty (India)**

Invited Papers

Abstracts

VI/207 Community factors influencing the leprosy patient and his treatment.
T. F. Frist (Brazil)

VI/208 The methodology of investigating social aspects of leprosy work.
C. M. Varkevisser (Netherlands)

VI/209 Non-medical objectives of a leprosy control program.
P. J. Neville (Great Britain)

VI/210 Employment and re-employment.
E. P. Fritschi (India)

Free Communications

Abstracts
VI/211-VI/220

Free Communications

15:00-18:00
Abstracts
VI/221-VI/224

SOCIAL ASPECTS

VI 207

Community factors influencing the leprosy patient and his treatment

T. F. FRIST

Society for Rehabilitation and Reintegration of the Handicapped, Sao Paulo, Brazil

The author discusses what he considers to be three of the principal factors affecting the leprosy patient and his treatment.

The first factor considered is *the nature of the resources and priorities of the country concerned.* The quality of life depends on the local availability of adequate solutions to his problems — be they leprosy-related or not. Developing countries often lack the infrastructures necessary to provide such solutions.

The second factor discussed is *the extent to which leprosy services are isolated from mainstream health and social services.* It is the author's contention that geographically and/or administratively segregated delivery systems of services unnecessarily disrupt the patient's life, are unnecessarily expensive and, perhaps more than anything else, maintain the image of leprosy as a disease apart.

The third factor considered is *the extent to which authorities are willing to overcome this segregation.* Integration efforts are hampered not only by a lack of resources, but also because of the loyalties of some leprosy authorities and workers to traditional segregated institutions and programmes, and their disagreement on the problem of contagion.

In conclusion, the author emphasizes the importance of institutions in shaping opinion and calls for a renewed effort to bring about their rapid de-segregation.

VI 208

The methodology of investigating social aspects of leprosy work

C. M. VARKEVISSER

Royal Tropical Institute, Amsterdam, Netherlands

Despite the evident value of studying how social and cultural factors influence a leprosy patient's choice of what treatment to pursue, when to pursue it and how, there is a danger in placing too much weight on such factors exclusively and not also evaluating the role of the dependability and quality of treatment available. Given the goal of optimal dapsone intake, social scientific research needs take into consideration *both* the socio-cultural and socio-medical settings in which dapsone is available.

Various techniques can help reveal what factors determine prompt self-reporting and regular clinic attendance, and what factors retard them. In our project (Western Province, Kenya and Mwanza Region, Tanzania 1974—76) we combined a factor analysis of data on patient registration cards (limited in value because of the low quality of the data) with in-depth interviewing (patients, relatives, neighbours, false-alarmists, community leaders, traditional doctors). With a set of "test" statements, we measured prevailing community attitudes towards leprosy patients and then compared the results with our observations. At the same time we interviewed health personnel intensively, and observed patient-staff interactions.

In-depth research is able to generate valuable suggestions for strengthening the leprosy services available, for training and retraining health personnel, and for educating patients and communities about leprosy control essentials.

VI 209

Non-medical objectives of a leprosy control programme

P. J. NEVILLE

Leprosy Mission, London, England

The aim of a leprosy control programme is to treat all existing cases of leprosy in a defined area with regular treatment and for as long as is necessary. This implies widespread acceptance of treatment by patients, and the co-operation of the general public.

There are many difficulties in putting this ideal into practice. Two major areas of neglect may be key factors when a leprosy control programme does not achieve expected results. These are the failure to recognize the importance of human relations, and the attitude of society towards the patient.

The author discusses these and other factors, and from them develops non-medical objectives which could be included in the planning of leprosy control programmes, and in the training of personnel.

VI 210

Employment and re-employment

E. P. FRITSCHI

Schieffelin Leprosy Research and Training Centre, Karigiri, South India

Creative and remunerative employment is the undisputed birthright of all human beings.

These two requirements, namely creativity and income, are difficult to achieve in the appropriate combination, whether we live in the privileged or the underprivileged section of the world.

For leprosy patients there is an additional factor that operates — the factor of unwantedness, of unreasonable fear. The presence of deformity produces awkwardness on the part of the 'normal' as well as 'disabled' co-workers.

Employment of the disabled requires an effort of will on both sides. The community must be taught to extend help naturally when it is needed without patronising or pity. The disabled person must accept the help that he might need, without self-consciousness, resentment or self-pity.

Obviously this situation demands training both of society and of the individual. This process is rehabilitation.

The rehabilitator must accept his role without any feeling of special virtue and without expecting gratitude from his client. The client has to accept his employment with grace, conscious that, though it is his fundamental human right, the enjoyment of this right is itself a privilege.

Rehabilitation is a cooperative enterprise involving the medical team, the employer, the patient and society at large, and requiring faith in one another and hope for the future.

VI 211

World Leprosy Day

A. RECIPON

Fondation Follereau, Paris, France

World Leprosy Day, founded in 1954 by Raoul Follereau, was celebrated for the 25th time in 1978.

Raoul Follereau spent his life fighting to eradicate from the hearts of men the prejudices associated for centuries with this terrible disease. In this connection, the most spectacular of his initiatives, and undoubtedly the most effective, was World Leprosy Day.

Raoul Follereau wanted to organize a universal manifestation which would at the same time help sufferers and mobilize the healthy into action.

For the first World Leprosy Day, he asked the question: there are millions of leprosy sufferers in the world. Why them and not me? In 1956 he called for personal and collective involvement, so that leprosy sufferers would no longer be for ever sufferers.

In 1960 the Cameroun made World Leprosy Day a national festival.

In 1961 the Indian Union made World Leprosy Day, which it fixed at 30 January, anniversary of the death of Gandhi, a national festival.

The 25th World Leprosy Day was celebrated in 1978 throughout the world; many heads of State participated in it.

Raoul Follereau has left us, but his work continues. He had announced that the 25th Appeal was the last that he would launch, and he has entrusted to the International Association of Raoul Follereau Foundations and to the International Federation of Anti-Leprosy Associations the task of compiling the annual message, aimed at healthy individuals, to solicit their generosity, at doctors, research workers and nurses, to encourage and help them, and at patients, so that they may live as others do.

VI 212

The several faces of leprosy

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Bethesda, Md., U.S.A.

Traditionally and historically, the clinical faces of leprosy have included everything from

disease of the soul to scurvy. From these multiple and often inaccurate sources, the modern social face of leprosy finds separation difficult. With effective treatment for leprosy now available, escape from the past is well under way, yet it is still hampered by political problems of eradication of practices of medieval origin. Noteworthy among these is the outdated leprosarium, which still persists. Leprosy rapidly ceases to be contagious, when treated with minimal adequacy. General dermatological, medical, and surgical clinics are now opening to the leprosy patient, and modern nursing homes can provide excellent long-term care. The serious and sometimes unsolved economic problems of leprosy are favoured by open-house treatment. Results of both medical and social treatment progress steadily. The stigma of leprosy promises to remain as long as the patient is shunted to the outdated specialized institution, which, while protecting and preserving the patient, alienates him from society.

VI 213

Stigma and leprosy

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The objective of this multidisciplinary paper is to study stigma in the leprosy patient and its psychological and social connotations.

It is mainly based on Goffman's "Stigma".

The method has consisted in going from general to particular, that is, from the study of stigma in general to the study of stigma in leprosy, with examples taken from our own experience.

Stigma in leprosy is made up of four components: physical, psychological, moral and social; and it is contagious.

The patient does not fulfil the identity norms imposed by society and is segregated from it.

The patients form a characteristic endogroup.

Leprosy interferes with communication with others.

Perceptibility is a fundamental characteristic of the leprosy patient.

The patient follows a "moral career" in which the fact of being an inmate in a specific hospital exerts great influence. He tries to conceal information about himself, employing techniques of information control.

The patient suffers ambivalence with respect to himself and his group and the normal with respect to the patient and the illness.

This investigation helps to face leprosy treatment in its totality because it takes into account its somatic, mental and social aspects.

VI 214

Leprosy stigma and its effects on patients' self-concept and attitudes towards society

L. Meisels S. Kav-Venaki
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A study has been made of 12 long-term inpatients and 22 outpatients of Jerusalem Hansen Hospital, 10 families of patients, 13 members of the staff, and 463 persons with no known contact with Hansen's disease.

The points studied were:-

(a) The knowledge and attitudes of the Israeli population towards Hansen's disease patients, according to origin, education, sex and age;

(b) The effects of leprosy stigma on the patients' self-concept and attitudes towards society, according to such criteria as hospitalization, kind of deformity, origin, sex and age;

(c) The daily confrontation with the stigma among: (1) the patients; (2) the patients' families; (3) the staff of the hospital.

Variable (a) was studied by a questionnaire especially designed for the research; variable (b) was examined by the Tennessee self-concept scale and variable (c) was studied by participant observation of one month in the Hansen Hospital in Jerusalem. This included interviews, personal talks, participation in the patients' activities in the hospital, and interviews with members of the staff, in addition to visiting the patients' families and presence at medical examinations of patients and their families all over the country.

A discussion of the results of the study attempts to classify the origins of leprosy stigma, its effects on the scope of self stigmatization and on the psychological state of the patients, and raises possibilities of solving these problems.

VI 215

The term *leprosy* carries prejudice

M. DE MANGIATERRA

Córdoba, Argentina

The methodology of social science was adopted in the approach to this study:

1. Statement of the problem: the non-clinical use of the word within culture, personality and society is illustrated from fact.

2. Hypothesis: the term leprosy carries prejudice.

3. Explanation of the theory and testing of the hypothesis: the hypothesis is tested using causal analysis on six levels of validation: object stimulus, phenomenological level, personality structure and dynamics, situational level, socio-cultural, historical.

The study focusses on each of these levels both separately and interdependently.

Once the hypothesis had been tested it became necessary as a corollary to this to include the concept of semantics in all antihansenian political teaching. This would mean an end to the word *leprosy*, which would increase the efficacy of health information and would benefit the integration of the sick person into society.

VI 216

Psychological rehabilitation of leprosy patients using group dynamics

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M. BALINA DE VALDEZ

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The conclusions of a 3 year study carried out by a group of leprosy doctors at Muniz Hospital are as follows:

a) interdisciplinary involvement of psychologists and sociologists is most effective.
b) rehabilitation should be started at the diagnostic stage.
c) the diagnosis should be discussed at several different meetings.
d) weekly meetings with groups of patients should be arranged in order to: internalize concepts, accept and face the illness, get to know peers, express fantasies and fears, involve the family so that it may play a helping role in the rehabilitation of the patient, provide psychotherapeutic support to prevent the abandonment of treatment and the emergence of drug-resistant bacteria.

VI 217

The mental state of the patient with leprosy

F. J. CAMPOS S. CASTANEDA
L. AGOITIA

Centro Dermatológico Pascua, Mexico

Fifty patients with leprosy were studied at the Centro Dermatológico Pascua in Mexico City. A structured questionnaire was used in order to obtain specific information on the mental state. This presents advantages over the traditional history, as it provides the physician with a rich group of psychiatric symptoms which are otherwise overlooked in the standard psychiatric history.

Using the chi square test, the results of the examination of the mental state in patients with leprosy were compared statistically with those in a group of 50 patients with another chronic dermatosis, vitiligo. The results will be described by illustrative tables.

In the field of leprosy, mental health is very important and requires a psychosomatic approach in order to provide the best assistance for the patients.

VI 218

Leprosy, social change and social class

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A. E. KAUFMANN

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In order to understand the segregation to which leprosy sufferers have been subjected throughout the centuries, we have to consider the illness and its consequences by means of sociological variables, which may help to explain and understand this phenomenon.

These variables are: *social change* and *social class*. I shall briefly explain the meanings of these concepts and then show how they can be applied to analyse the ideas we are interested in.

Though many people may think that the idea of leprosy remains the same, I shall demonstrate by means of comparative analysis of different editions of the Bible how the terminology on the subject tends to be more scientific, as well as changes that have taken place in other areas. I shall specify in which way the Bible mentions the idea of social class and how this concept appears in reality, producing a rejection of those who suffer the illness and who happen to be from a lower social stratum.

VI 219

Psycho-social change in leprosy in the National Dermatological Centre of Nicaragua

G. SOTO GARCIA
M. JUAREZ MADRIGAL
F. GOMEZ URCUYO

National Dermatological Centre, Managua, Nicaragua

This study shows the conversion of the old "leper colony" called San Lazaro into a National Dermatological Centre. Taking into account its urban position, the report shows, on the basis of investigative study and group techniques, the acceptance by the community in that area and in the town of Managua and the change in the attitude of the hospitalized leprosy patient.

This study was based on the 200 people questioned whose replies reflect the following facts: there was no prejudice with regard to the illness — 92%; acceptance of the Centre by the community — 60%; knowledge of the illness — 10%.

This leads us to infer that cultural factors in different countries determine the control of Hansen's disease.

VI 220

The social aspects in 1063 cases of leprosy

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Centro Dermatológico Pascua, Mexico

During the nine years between 1968 and 1976, 1063 patients with leprosy were studied as out-patients, 64% of them male and 36% female. Seventy-two per cent of the patients had lepromatous leprosy; 42.7% were resident in Mexico City and its suburbs.

Socio-economic state. Peasants (39.21%) and workers (9.11%) predominated. Half the patients were illiterate and only 10% had had secondary and higher education. A large percentage (74%) of the patients lived in precarious circumstances, with poor nutrition (62%) and low incomes which were insufficient to meet the most basic needs.

Psychosocial state. Before coming to the centre, patients had been badly treated by doctors or faith-healers, with economic consequences, or had suffered from family or community problems which affected them psychologically.

Medicosocial treatment. The management was as for other skin conditions and was aimed at achieving full rehabilitation.

Objectives. To make the patient, his family and society aware of the problems of leprosy.

Method. Direct interviews with the patient and the family group, in the office and at home. Instruction of medical and paramedical staff, talks at schools, occasional use of television and press.

VI 221

Domiciliary visiting in cases of leprosy

S. CASTANEDA T. GARCILASO
R. ARENAS

Centro Dermatologico Pascua, Mexico

Domiciliary visiting is one of the most important functions of the social worker in the management of leprosy. Its objectives include the following:

1. To acquaint the family with present knowledge of leprosy and to enlist the full participation of the family in the rehabilitation of the patient.

2. The medical treatment of patients with lepra reactions and education in hygiene.

3. Follow-up of contacts.

4. The discovery of patients who have given up treatment and the ascertainment of the reasons for doing so from the family.

5. "Domestic" rehabilitation, indicating to the patient the methods of physical rehabilitation which can be used.

Some aspects of this kind of activity are presented objectively and their results discussed, as obtained by a group of persons working in a leprosy centre run by the State.

VI 222

Importance of methods of communication in the fight against leprosy. Experiment in the Dominican Republic (1966—1977)

M. HILARIO DE GONZALEZ
H. BOGAERT DIAZ

Instituto Dermatologico, Santo Domingo

The writers report on experience obtained in the Dominican Republic during the period 1966—1977, using different communication media (radio, the press, T.V., cinema, etc.) in the development of the programme of leprosy control that is being carried out by the Dominican Institute of Dermatology. The characteristics of its slow and progressive development with lesions (which are often clinically almost invisible and lacking in symptoms), make leprosy a special disease, for which we must find new mechanisms to help in its detection. The frequent supply of detailed information to the public, directed by experts in health education, offers a mechanism for compensation. The writers also point out the need for a new strategy in the fight against this disease, in which the community takes an active part, unlike the situation that exists in most countries where the problem is kept hidden and no information is provided about it.

VI 223

Social aspects of leprosy in Pará State, Amazon valley

G. E. APPEL

Belém Pará, Brazil

For centuries, the immense rain forest of the Amazon valley has been a challenge to progress in transportation, communication, education and above all, public health.

Fifty years ago the Amazon valley of Brazil was without roads. Transportation was entirely fluvial, utilizing the Amazon River and its numerous tributaries. The only medical facilities available were in the two State capitals, Belém and Manaus.

The Amazon valley has a high prevalence of leprosy. The leprosy patients in Pará State either hid their disease (and their deformities) in the jungle, or else made the long and tiring boat trip to the capital, Belém, to seek asylum in the leprosarium.

Today, after a slow but steady transformation of Pará State (roads, telephone and television, hospitals, clinics and doctors in the interior) there is a new outlook. There are still 1100 patients in two "colonies", but the emphasis now is placed on the 7000 outpatients and their treatment by specially trained doctors and para-medical workers in the capital and in the jungle; there is a control programme and stress is placed on rehabilitation and prevention of deformities.

This new medical approach has also improved the social aspects of the disease. Ignorance, prejudice and fear of leprosy are not completely eradicated but are truly "fading away."

VI 224

The Leprosy Board of Paraguay — present programme of leprosy control

D. A. MASI

Dermatology Clinic, Asunción, Paraguay

In the 48 years since the Leprosy Board of Paraguay was founded, it has taken part in the National Programme for Leprosy Control in accordance with the prevailing political thinking and available scientific advances. From 1972, the Board adopted a new approach which laid emphasis on the psycho-social aspect of the problem, especially on educating the patient, his family and the community as a whole.

The results are expressed as follows:

1. A significant increase in the number of consultations as much by the sick as by their contacts.

2. Achievement of a big step forward in the health education of the sick person and of his family group.

3. A marked increase in the percentage of contacts examined at the Clinic: from 36% to 60%, which means that more new cases are being discovered.

4. Education has succeeded in regaining the 15% of sick who had given up regular treatment.

5. The new way of thinking is bringing about a decrease in lepromatous leprosy (from 60% to 50%), and a marked increase in indeterminate leprosy (HI) (from 7.7% to 23.3%). Early diagnosis constitutes a real achievement resulting from education and the systematic examination of contacts.

6. An important factor in education at public and private school level has been achieved, together with the development of a programme of education aimed at informing and bringing up to date the knowledge about leprosy of the medical and nursing staff who work in general back-up services mainly in rural areas.

With the new focus of the programme of leprosy control, it is hoped that there will be a change of attitude by the general population towards leprosy and its victims, which will allow their social rehabilitation. The home of the patient with Hansen's disease is the best place to educate him about the illness. The family group can be made aware of it, and all the contacts can be examined to discover the incipient cases; also those who by their own decision have given up treatment can be 'won back'. This domiciliary work in Paraguay showed that there need not be family tension nor a breaking of matrimonial ties.

SESSION VII
EXPERIMENTAL CHEMOTHERAPY

Thursday, 16 November 1978
9:00-13:00
Auditorium 2
Chairman: **C. C. Shepard (USA)**
Rapporteur: **E. Freerksen (FRG)**

Invited Papers

Abstracts

VII/225 Pharmacological considerations of drug combinations for the treatment of lepromatous leprosy.
G. A. Ellard (Great Britain)

VII/226 Persistence and drug resistance of *Mycobacterium leprae* — major obstacles to successful chemotherapy of lepromatous leprosy.
L. Levy (Israel)

VII/227 Mechanism of action of clofazimine.
N. E. Morrison (USA)

VII/228 Tissue levels of dapsone during combined dapsone-rifampin therapy.
J. H. Peters (Great Britain)

Free Communications

Abstracts
VII/229-VII/236

Poster Communications

Exhibition Area

Abstracts
VII/237

EXPERIMENTAL CHEMOTHERAPY

VII 225

Pharmacological considerations of drug combinations for the treatment of lepromatous leprosy

G. A. ELLARD

Royal Postgraduate Medical School, London, England

The evidence derived from experimental studies in the mouse footpad system of the relative potencies of currently available anti-leprosy drugs will be reviewed. From estimates of the minimal inhibitory concentrations (MICs) of dapsone, rifampicin, several long-acting sulphonamides, thiambutosine, thiacetazone, ethionamide and prothionamide against *M. leprae* and pharmacological studies of these drugs in man, it is possible to calculate the period during which well tolerated doses of these drugs are likely to exceed their MICs against *M. leprae*. This information, taken together with estimates of their bactericidal activity, makes it possible to assess the probable relative potencies of these drugs in clinical therapy. Some of the ways in which combinations of the most potent drugs might be used for treating lepromatous patients will be discussed.

VII 226

Persistence and drug resistance of *Mycobacterium leprae* — major obstacles to successful chemotherapy of lepromatous leprosy

L. LEVY

Hebrew University-Hadassah Medical School, Jerusalem, Israel

Several drugs of proven effectiveness are now available for the chemotherapy of lepromatous leprosy. One of these is dapsone, which is extraordinarily potent; *M. leprae* are inhibited from multiplying by concentrations of 0.001 to 0.005 microgram per ml. Another is rifampicin, which is rapidly bactericidal; a single large dose kills no fewer than 99.9 per cent of the living *M. leprae* present. With drugs of such potential usefulness available, why isn't chemotherapy of lepromatous leprosy much more effective than it appears to be?

Two properties of *M. leprae* appear to account for many of the failures of chemotherapy of lepromatous leprosy. A proportion of these organisms appears to survive years of treatment with one or two drugs in full dosage, although fully susceptible to the drugs. This phenomenon is termed "microbial persistence". *M. leprae* also appears to throw off drug-resistant mutants capable of multiplying in the face of treatment with a single drug. These phenomena appear responsible for most relapses.

The tasks of the THELEP Programme are to promote the development of the new methods required for evaluating the effectiveness of combined treatment regimens in preventing multiplication of drug-resistant organisms and eradicating persisting *M. leprae*, and to sponsor clinical trials of new regimens based on the new methods.

VII 227

Mechanism of action of clofazimine

N. E. MORRISON

Johns Hopkins University, Baltimore, Maryland, U.S.A.

Clofazimine binds to double- or single-stranded DNA. The strength of interaction is dependent upon the G+C content of the strand. A possible mode of action indicates that clofazimine will inhibit either strand template or strand replication activity in a selective sense since mycobacterial G+C content is higher than human. DNA-dependent RNA polymerase is inhibited by clofazimine when using a high G+C template for assay.

VII 228

Tissue levels of dapsone during combined dapsone-rifampin therapy

J. H. PETERS

Life Sciences Division, SRI International, Menlo Park, Ca., U.S.A.

Combination chemotherapy for the treatment of lepromatous leprosy has become mandatory to combat the twin problems of bacterial persistence and resistance during chemotherapy

with single agents. We have found in Malaysian patients (collaboration with Dr. R. Gelber) receiving 100 mg dapsone (DDS) daily that addition of 600 mg rifampin (RFM) daily caused a dramatic reduction of DDS levels in plasma, skin, and nerve compared with levels found in patients receiving DDS alone. Also, reductions of DDS in plasma and skin were found in U.S. patients (collaboration with Dr. R. R. Jacobson) receiving 50 mg DDS daily with 600 mg RFM compared with levels found in the same patients receiving DDS alone. No relation between levels of DDS and the extent of bacterial infiltration in the skin samples was noted in this study. The implications of these results in the chemotherapy of leprosy will be discussed.

We have also examined the relation between plasma and saliva levels of DDS in normal volunteers receiving 50 mg DDS orally. Saliva and plasma levels were predictively related, suggesting that saliva measurements may be employed to monitor DDS intake by patients.

VII 229

Metabolic disposition of dapsone (DDS) and rifampin (RFM) in nine-banded armadillos (*Dasypus novemcinctus*)

J. F. MURRAY, JR. G. R. GORDON
J. H. PETERS J. GROVE
G. P. WALSH

SRI International, Menlo Park, Ca., U.S.A.

To define the metabolic disposition of DDS and RFM in armadillos, we determined the clearance of intravenously administered DDS (1 mg/kg) and RFM (10 mg/kg) in AFB-free armadillos. Plasma levels of DDS ranged from a mean of 589 ng/ml at 2 h to 28.0 ng/ml at 48 h in 5♂ and 3♀ animals. Clearance was biphasic with an early distribution T½ of 3.3 h and an elimination T½ of 20.2 h. Mean percentage acetylation of DDS to monoacetyl DDS was 8.9%. The sexes did not differ significantly in any measured parameter.

Plasma levels of RFM ranged from a mean of 5.9 μg/ml at 2.5 h to ⩽0.03 μg/ml at 48 h in 4♂ and 4♀ animals. Clearance was monophasic with the ♂ exhibiting a significantly longer T½ of 6.3 h than that of the ♀ of 4.5 h. No desacetyl RFM could be detected at any time.

In an *ad libitum* feeding trial of DDS (0.001%) to 3♂ and 4♀, we found that doses of DDS varied from 150 to 600 μg/kg/day, which produced levels of DDS in plasma ranging from 20 to 90 ng/ml. Plasma levels of DDS were directly related to dietary DDS ($N = 28$; $r = 0.580$; $P < 0.005$). Again, no significant difference between the sexes was noted in any measurement. Feeding trials employing 0.0001% DDS are underway.

Supported in part by NIH Grant AI-08214.

VII 230

The activity of dihydrofolate reductase inhibitors against *Mycobacterium leprae* infection of the mouse footpad

R. GELBER L. LEVY

USPHSH, San Francisco, U.S.A.

Because of the dual problems of drug resistance and persistence in lepromatous leprosy, new antimicrobial agents are worthy of pursuit. Dapsone acts like the sulphonamides at the level of the paraminobenzoic acid condensation reaction in folate biosynthesis. Sequential blockade of folate biosynthesis by sulphonamides and a dihydrofolate reductase inhibitor (DHFRI), trimethoprim, result in synergism against a wide variety of aerobic bacteria which has proved efficacious clinically. Trimethoprim is inactive against *M. leprae* and does not potentiate the effect of dapsone. We have screened 16 other dihydrofolate reductase inhibitors, including eight 2,4-diaminoquinazolines, by continuous feeding for 150 days following mouse footpad infection. Fourteen of these compounds were active, including 6 of 8 of the 2,4-diaminoquinazolines. A structure activity relation was established for the quinazolines. Further studies with certain of these agents alone and in combination with dapsone by the kinetic technique of Shepard resulted in synergism and bactericidal type activity. Two of the quinazolines fed to mice, alone and together with 0.0001% dapsone from the time of infection, were studied by the proportional bactericide technique in order to quantify their actual killing potential. Synergism could not be demonstrated, as dapsone and the combinations were 89—95% and 89—98% bactericidal respectively. Quantification of the killing potential of the same quinazolines alone

and in combination with dapsone against an established *M. leprae* infection and their activity against a dapsone-resistant strain of *M. leprae* will be presented.

VII 231

An *in vitro* test for drug response and drug resistance of *Mycobacterium leprae* using labelled metabolites

E. J. AMBROSE S. R. KHANOLKAR
N. H. ANTIA R. CHULAWALA
K. K. KOTICHA

Foundation for Medical Research, Bombay, India

Highly purified suspensions of *M. leprae* obtained from untreated or relapsed lepromatous leprosy patients have been set up for culture on agar films for subsequent autoradiography or in suspension for subsequent scintillation counting. 3H thymidine has been used for pulse labelling at times 0, 6 and 9 days. Absence of contaminants has been confirmed using nutrient agar, Sabouraud's agar and Jensen-Lowenstein slants. 3H DOPA has been found to be specifically taken up, mainly by solid bacilli of *M. leprae* in autoradiograph, not by *M. smegmatis, M. phlei* or *M. tuberculosis*. Autooxidation by traces of connective tissue can be avoided by addition of the reducing agent, ascorbic acid. Parallel tests with both metabolites have revealed inhibition down to 0.08 μgm/ml of DDS with untreated cases. Variable response in relapsed cases was observed. Some cases which showed resistance in the mouse footpad also showed resistance in the *in vitro* test. Response to rifampicin was still observed. Repeat biopsies taken from new patients receiving chemotherapy have also shown progressive decrease in growth rate as estimated by our *in vitro* test.

VII 232

Mutagenesis-carcinogenesis of antileprosy drugs in animal systems: pertinence to man

J. H. PETERS G. R. GORDON
V. F. SIMMON W. TANAKA

SRI International, Menlo Park, Ca., U.S.A.

Dapsone (DDS) and acedapsone (DADDS) were reported to be non-carcinogenic in earlier tests in rodents. Recently, others found DDS and ethionamide (ETH) to be weak carcinogens (DDS and ETH in mice; DDS in rats). But studies of leprosy patients receiving sulphones since 1950 did not indicate a higher incidence of cancer compared to patients not receiving DDS before 1950 or to control populations.

We examined the mutagenic potential of dapsone and its metabolites and derivatives using *Salmonella typhimurium* strains TA-1535, -1537, -1538, -98, and -100 and post-mitochondrial supernatants (S9) from livers of Aroclor 1254 pretreated mice, rats, or hamsters. At levels up to 5000 μg/plate, we found that DDS, monoacetyl DDS, DADDS, and 4,4'-bis (N, O-diacetylhydroxyamino) diphenyl sulphone were not mutagenic. The sulphide and sulphoxide analogues of DDS were mutagenic — weakly without and strongly with S9 activation for TA-98 and TA-100. Neither of these analogues is a metabolite of DDS in rodents or man. Studies of the mutagenesis of other DDS derivatives, ETH, and other anti-leprosy drugs are underway.

Supported in part by NIH Grant AI-08214.

VII 233

Carcinogenic activity of dapsone

M. BERGEL

Rosario, Argentina

Carcinogenic activity of 4-4 diaminodiphenyl sulphone (dapsone) is found in white male Wistar rats fed for two years with this compound at a concentration of 0.3 per cent in the diet. The incidence reaches practically 100 per cent of the rats in contrast with no tumours in control animals. Tumours produced are of a high degree of malignity, and are found in the retroperitoneal tissues, mesentery, intestines, spleen, thyroid and liver, being histopathologically fibrosarcomas, reticulosarcomas, adenocarcinomas, fibroangiomas and angiomas. Similar results were found in work done at the National Cancer Institute of the United States Department of Health in male Fischer 344 rats.

The carcinogenic activity of sulphones is apparently related to their biological activity and also to their radiosensitizing activity.

VII 234

The effect of intermittent ethionamide and combinations of ethionamide and dapsone in experimental leprosy in mice

M. J. COLSTON G. R. F. HILSON

St. George's Hospital Medical School, London, England

Ethionamide has been shown to be bactericidal against *M. leprae* in the mouse footpad at a dietary concentration of 0.1%. It has also been shown that the serum concentrations required to produce this bactericidal effect are easily achievable in man by the administration of well-tolerated dosages of ethionamide. In this study, we have investigated the ability of intermittently administered ethionamide to inhibit and kill *M. leprae*.

The suppressive effect of ethionamide when given (a) continuously at 0.1%, (b) 3 times weekly at 500 mg/kg, (c) once weekly at 500 mg/kg and (d) once every two weeks at 500 mg/kg has been investigated using the kinetic approach. The bactericidal activity of ethionamide given in the same dose regimens, and also given in combination with dapsone, has been investigated using the proportional bactericidal test. The results of these investigations suggest that the efficacy of ethionamide is significantly decreased by increasing the period between doses, and this will be contrasted to the results obtained with rifampicin in a series of similar experiments.

VII 235

Effect of Sulphetrone treatment on pathological changes of the deep organs of mice infected by passage strain of *Mycobacterium leprae**

Z. G. UMEROV G. M. TSVETKOVA

Central Research Institute of Skin and Venereal Diseases, Moscow, USSR

Changes in the lymphnodes, spleen, kidneys, lungs and heart were studied histologically and histochemically 12—14 weeks after the mice were inoculated with *M. leprae*.

One group of animals was subjected to Sulphetrone treatment from the day of the inoculation with *M. leprae*. The second group (control) did not receive any treatment. 12—14 weeks later hyperplasia, plasmatization and macrophage reaction of the lymphnodes and spleen and folliculi were seen in the mice of the second group. Lymphocytic infiltrates were seen in the liver, kidneys and lungs. Similar changes were found in the lymphnodes of the mice in the first group. However, the inflammatory infiltration in the deep organs was less pronounced. There was a correlation between the number of mycobacteria and the degree of the pathological changes in the organs in the first group of animals.

*Investigation received financial support from WHO.

VII 236

"Mandukaparni" — a common Indian herb effective against leprosy

S. CHAUDHURY S. GHOSH T. CHAKRABORTY

School of Tropical Medicine, Calcutta, India

Charaka, the great Indian physician of A.D.600 successfully treated all types of leprosy with "Mandukaparni". It has been further reported that (1) The active principle (a glycoside) isolated from this herb is capable of dissolving the waxy covering of *M. leprae*; the bacilli become fragile and may be destroyed by the body tissue or by drugs. (2) It has an inhibitory effect on the biosynthesis of acid mucopolysaccharide (hyaluronic acid), which is now thought to be one of the important nutrients for the growth of *M. leprae*. Attempts have recently been made to kill or eliminate *M. leprae* from the tissues, either by chemotherapy or by enhancing immunity. The line of approach with this product is to attack the bacilli in their metabolic path.

A therapeutic trial with this product has now been in progress on 20 active lepromatous cases for the last two years and they have been periodically examined clinically, bacteriologically immunologically (lepromin test), and biochemically (by estimating the acid mucopolysaccharide-mucoproteins and *in vitro* demonstration of its effect on staining character and morphology of *M. leprae*).

One case became bacteriologically negative within one year, and six cases within two years of

treatment, and all the cases showed remarkable clinical and bacteriological improvement. Mucoprotein estimation at intervals revealed interesting results. Mild leprosy reaction was observed in two cases only.

VII 237

A. The activity of combined drugs on *Mycobacterium leprae* in mice

S. R. PATTYN

Institute of Tropical Medicine Prince Léopold, Antwerp, Belgium

Results obtained in the proportional bactericidal test after administration of drugs in single dosage and in different combinations will be presented, especially combinations of dapsone + streptomycin, dapsone + prothionamide, dapsone + streptomycin + prothionamide, dapsone + thiacetazone.

B. Evaluation of the antileprosy activity of streptomycin in the laboratory mouse

Results of streptomycin treatment of mice inoculated with *M. leprae* will be presented: determination of minimal effective dose, results of the proportional bactericidal test and the total minimal effective test.

SESSION VIIIA CLINICO-PATHOLOGICAL ASPECTS

Thursday, 16 November 1978
9:00-13:00
Auditorium 1
Chairman: **O. Rodriguez (Mexico)**
Rapporteur: **A. Laterza (Mexico)**

Invited Papers

Abstracts

VIIIA/238 Enfermedad de Hansen, aporte histológico a su diagnóstico temprano.
O. Bianchi, H. Cabrera (Argentina)

VIIIA/239 Lepra de lucio.
E. Castro, J. Novales (Mexico)

VIIIA/240 Aspectos clinicopatológicos de la lepra.
J. C. Convit, N. Aranzazu, M. E. Pinardi (Venezuela)

VIIIA/241 A study of proven dapsone-resistant leprosy in Cebu, Philippines.
T. T. Fajardo, R. M. Avalos (Philippines)

VIIIA/242 Classification of leprosy: three instructive cases.
W. H. Jopling, D. S. Ridley (Great Britain)

VIIIA/243 The clinical spectrum of leprosy.
D. V. Opromolla, R. N. Fleury (Brazil)

Free Communications

Abstracts
VIIIA/244-VIIIA/246

Free Communications

15:00-18:00
Abstracts
VIIIA/247-VIIIA/253

Poster Communications

Exhibition Area
Abstracts
VIIIA/254-VIIIA/263

CLINICO-PATHOLOGICAL ASPECTS

VIII A 238

The contribution of histology in the early diagnosis of leprosy

O. BIANCHI H. CABRERA

University of Salvador, Buenos Aires, Argentina

In its early stages, leprosy produces few clinical and histological abnormalities, and this is the cause of great diagnostic difficulties.

In this paper the authors show the importance of the following histological finding: the presence of *M. leprae* in cutaneous nerves which have not been invaded by inflammatory infiltrate.

Material and method

The subjects were two patients with early leprosy, men aged 20 years who came from areas where the disease is endemic and who had areas of hypaesthesia in the limbs, with macular lesions. In both patients bacilloscopy was negative in mucus and in skin, and the lepromin reaction also was negative. Neurological examination was negative. Histology in both cases revealed very scanty perivascular inflammatory lymphocytic infiltrations and no acid-fast bacilli. There was no neuritis. Thus there was no support histologically for a diagnosis of leprosy. However, bacteriological investigation of those dermal nerves demonstrated the presence of groups of acid-fast bacilli within them (punch biopsies in hypaesthetic areas). Staining with haematoxylin-eosin; Sudan IV for lipids negative, Kinyoun for acid-fast bacilli.

The aim of this study was to demonstrate the diagnostic importance of investigating *M. leprae* in *normal* cutaneous nerves, at least in hypaesthetic skin, when there are no other data of diagnostic value, as is the case in the early stages of the disease.

There is only scanty previously published information on the presence of acid-fast bacilli within cutaneous nerves: Souza Campos and Souza Lima, Khanolkar, Binford. However, even those authors failed to point out that this may be the only way of establishing the diagnosis of leprosy in cases which are doubtful initially.

The present findings lend support to the view that *M. leprae* is carried along peripheral nerves ("All leprosy is neural leprosy").

VIII A 239

Lucio leprosy

E. CASTRO J. NOVALES

Centro Dermatologico Pascua, Mexico

Woman aged 37 years with a dermatosis of the face and lower limbs, consisting of discrete diffuse infiltrations and irregular reddish purple macules. In addition, she had rhinitis, alopecia, loss of eyelashes and loss of body hair.

The disease first manifested 10 years earlier with dark areas in the legs.

Biopsy of red macule (Lucio's phenomenon): the dermis and hypodermis show vasculitis affecting the small and medium-sized vessels with infiltrations by Virchow cells and lymphocytes and numerous leprosy bacilli.

Diagnosis: Diffuse lepromatous leprosy with reaction of the Lucio type.

Man aged 60 years with a generalized dermatosis affecting predominantly the face and the upper and lower limbs. This consists of diffuse infiltration, with numerous scars of varying sizes and shapes. Alopecia. Chronic course. The disease began 28 years ago with disorders of sensation and plaques of erythema and infiltration. In 1970 the lower limbs showed painful red macules (Lucio's phenomenon) and this recurred periodically, in association with systemic symptoms.

Biopsy: Lucio's phenomenon: loss of substance in dermis and epidermis, superficially and in deep layers; vasculitis of small and medium-sized vessels, Virchow cells, lymphocytes, numerous acid-fast bacilli.

Diagnosis: diffuse lepromatous leprosy with Lucio's phenomenon.

VIII A 240

Clinico-pathological aspects of leprosy

J. CONVIT N. ARANZAZU
M. E. PINARDI

Instituto Nacional de Dermatologia,
Caracas, Venezula

The authors present a simplified spectrum of the various forms of leprosy, on the basis of its clinical, bacteriological and immunological aspects. The indeterminate form is presented as one of the early forms of the disease.

The indeterminate form is described, and an effort is made to clarify the present views on this form of leprosy. The spectrum of leprosy and that of other diseases produced by intracellular parasites, such as leishmaniasis and the mycoses, are studied comparatively. Special emphasis is placed on the comparison between the various forms of leprosy and those of American cutaneous leishmaniasis. The lepromatous form of leprosy is compared with diffuse cutaneous leishmaniasis in its clinical, parasitological and immunological characteristics. In the same way, the localized forms of cutaneous leishmaniasis are compared with tuberculoid leprosy, and the borderline forms of each disease are compared with each other.

The results obtained with the Competency in Clearing Bacilli Test are presented, specifically in relation to the clearance of heat-killed *M. leprae* in lepromatous leprosy patients. Depending on the patient, the macrophages respond in the various forms of leprosy, in such a way as to support the proposition that there is a spectrum of responses within the lepromatous type of the disease. These different responses would condition the diverse responses to therapy of lepromatous patients.

VII A 241

A study of proven dapsone-resistant leprosy in Cebu, Philippines

T. T. FAJARDO R. M. ABALOS

Leonard Wood Memorial, Cebu, Philippines

Dapsone has been used continuously since 1952 in the treatment of bacilliferous leprosy in inpatients at the Eversley Childs Sanitarium (leprosarium) in Cebu. More than 960 dapsone-treated patients have been discharged (disease arrested/smear negative) from the institution during the last 10 years (1968—77). On the other hand, 250 relapsed patients, all formerly treated with dapsone, were readmitted to ECS during the same period. The surveillance and treatment of discharged patients in Cebu have been extremely irregular, so that a high proportion of secondary resistance to dapsone was suspected in the patients who had relapsed.

In an effort to determine the prevalence of dapsone-resistant leprosy in Cebu, animal experiments were started in 1975 at the LWM-ECS laboratory, in which *M. leprae* from relapsed patients with *prima facie* evidence of drug resistance were inoculated into the footpads of mice fed with various concentrations of dapsone in the diet. *M. leprae* obtained from 11 out of the first 12 such patients were found fully viable in mice fed with high concentrations of 0.01% dapsone or 0.001% dapsone in the diet, indicating that secondary resistance to dapsone is definitely a serious problem in Cebu. The above mouse footpad inoculations are continuing, and this paper will present a detailed study of the clinico-pathological, epidemiological and other particular features of proven dapsone-resistant leprosy in Cebu.

VIII A 242

Classification of leprosy: three instructive cases

W. H. JOPLING D. S. RIDLEY

Hospital for Tropical Diseases,
London, England

1. *An apparent discrepancy of classification hiding a wrong diagnosis of leprosy.*

A Nigerian presented with numerous papules distributed bilaterally and symmetrically, with some on the lips. Clinical diagnosis: leprosy of LL type. Skin smears were negative and biopsy showed a tuberculoid granuloma. The differential diagnosis will be discussed.

2. *Clinical examination alone may lead to a wrong classification.*

A Nigerian presented with two insensitive plaques suggestive of TT leprosy. However, the finding of several thickened nerves in the arms and legs suggested a possibility of BT, and this was proved by biopsy and lepromin test. The

importance of distinguishing TT and BT will be discussed.

3. *Relapse associated with upgrading of classification.*

A Pakistani with LL leprosy began treatment in 1961, and became bacteriologically negative in 1969. He continued to take dapsone in small doses and remained clear of bacilli until 1976, when bacteriological evidence of relapse was obtained. There are two points:

(1) the first finding of AFB on relapse was in the fingers. All other sites were negative and there were no skin lesions.

(2) later evidence (clinical and histological) showed that relapse was associated with an altered immune response (BL). This event, though transient, is not uncommon in relapse.

VIII A 243

The clinical spectrum of leprosy

D. V. OPROMOLLA R. N. FLEURY

Hospital Lauro de Souza Lima, Sao Paulo, Brazil

The indeterminate group constitutes the matrix of the clinical forms of Hansen's disease. Starting with lesions of this group, the patient will evolve to one of the polar types in accordance with his immunological characteristics. In this evolution, the patient follows his own path, which when chronic, is sometimes interrupted by downgrading reactions related to bacillary multiplication. Bacilliferous cases also might suffer another type of acute phenomenon, erythema nodosum leprosum (ENL), related to the release of antigens and the formation of immune complexes which are deposited either in the walls of the skin vessels and other organs, or in the basement membrane of the renal glomerulus.

In spite of the clear evidence of the existence of two poles of resistance (the tuberculoid and the lepromatous), it is also necessary to recognize the spectrum of clinical types. These different types either remain in the two poles mentioned above, or are located at an intermediate position (borderline), without, however, shifting from one type to another, all being stable and mutually incompatible.

The follow-up of cases and of their cutaneous and visceral manifestations supports this concept. It is as if the histofunctional substratum of these types were macrophages with different speeds of lysis.

VIII A 244

Clinical and histological evaluation of 417 suspected cases of Hanseniasis

G. DE SOUZA DELPINO J. FERREIRA C. D. V. BERNARDI T. C. PONZIO H. A. S. PONZIO

Porto Alegre, Brazil

A total of 417 suspected cases of Hanseniasis reported in Rio Grande do Sul State, Brazil, between 1 November 1974 and 31 December 1977 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 demonstrated 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, or because they revealed a granulomatous histological structure.

These findings reduced the proportion of this clinical form.

VIII A 245

Evolution of nasal mucosal lesions in leprosy — histopathological study

L. MEHTA V. KASBEKAR N. K. APTE N. H. ANTIA

J. J. Hospital, Bombay, India

The hypothesis of droplet infection from the respiratory tract in leprosy has become favoured in recent years. The present study is of the histology of the nasal mucosa in tuberculoid and

lepromatous leprosy patients. Observations were made on the epithelial lining, connective tissue, mucous glands, blood vessels, lymphatics and nerves. The nasal mucosa from otherwise healthy individuals was studied as a control. The significant observations were those of lesions in tuberculoid leprosy. These patients had no nasal symptoms. Data on the histology of such lesions are not yet available, though the lepromatous lesions are well described. In the present study, details of pathogenesis are described, and the possible correlation with the immunological status is discussed.

An additional study was performed on 30 cases who presented themselves in the Ear, Nose and Throat Outpatient Department with signs and symptoms of atrophic rhinitis. They were investigated by nasal biopsy. The most significant observation was that 8 out of 30 cases were histologically diagnosed as leprosy which had been missed clinically. The importance of nasal biopsy in atrophic rhintis is stressed.

VIII A 246

Primary leprosy involvement of nasal mucosa in apparently healthy household contacts of leprosy patients

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Nasal mucosal biopsies were obtained from 99 apparently healthy household contacts of leprosy patients from the Gudiyatham Taluk Leprosy Control Programme; these contacts had no clinical evidence of the disease, and their skin smears were negative. 63 of these were from the households of lepromatous patients and 33 from contacts of tuberculoid patients. Twenty-five of the lepromatous contacts and 15 of the tuberculoid contacts showed inflammation of nerves in the nasal mucosa. Smooth muscle inflammation was seen in 14 lepromatous and 11 tuberculoid contacts. Acid-fast bacilli morphologically resembling *M. leprae* were seen in 3 of the lepromatous contacts and one of the tuberculoid contacts. At the follow-up of the tuberculoid contact with bacilli, after an interval of 4 months, hypopigmented partially anaesthetic patches were seen on the gluteal region, which on biopsy showed indeterminate leprosy with thickening and inflammation of nerves containing a few acid-fast bacilli. Biopsy of the enlarged radial cutaneous nerve, showed mild inflammation and bacilli. These findings suggest that early lesions of leprosy can be seen in the nasal mucosa before overt lesions have appeared in other parts of the body; the nasal mucosa could therefore be a primary site of involvement in leprosy.

VIII A 247

Clinical and biochemical aspects of leprosy

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The disorders of the oxidation-reduction processes, particularly of glycolysis processes, are the main biochemical changes in leprosy patients. Combined application of biochemical tests (determination of lactate dehydrogenase and its isoenzyme spectrum, isocitrate dehydrogenase, sorbitoldehydrogenase in blood serum; glutathione in blood; concentration of pyruvate and lactate in blood and urea; vacat-oxygen in blood and urea and underoxidation coefficient of urea, permitted the determination of tissue hypoxia (dysoxia) in leprosy patients. The degree of tissue hypoxia correlated with the severity of the leprosy process. The degree of dysoxia was characterized by permeability coefficient.

Dysoxia causes increased tissue-vascular permeability that results in development of auto-allergic reactions. Allergic reactivity in leprosy patients was proved by low titres of antihistamine factor in their blood. Dysoxia decreases due to antileprosy drugs, but does not disappear even when clinical cure is achieved.

On the grounds mainly of observation, it is suggested that changes occur in the oxidation-reduction processes, and in relation to both the leprosy process and to the action of antileprosy drugs.

Investigation received financial support from WHO.

VIII A 248

99m TcO_4 brain scan in *Mycobacterium leprae* infection

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The blood-brain barrier was investigated by intravenous injection of 99m TcO_4 isotope into patients with lepromatous leprosy and into immunologically deficient lepromatous mice, with adequate controls. The advantage of this isotope is that it needs no preparation, is excreted within a couple of hours and has no side-effects.

VIII A 249

Aetiology of bone changes in the foot in leprosy: a population-based study

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A population-based study of plantar ulceration among leprosy patients was undertaken in an endemic area. A total of 1786 leprosy patients, who formed 2.15% of the total population, was included in the study, 17.1% of the patients had plantar ulceration. The findings in 247 patients with 412 ulcerated feet are reported here. The ulcerated feet were studied together with comparable controls from among the patient population matched for sex, age, type of leprosy, duration of disease and presence or absence of sensory loss. In addition, 60 sites of active ulceration and 458 sites of scarring due to previous ulceration were individually investigated.

The pattern of radiologically demonstrable bone changes closely followed the pattern of plantar ulceration. In comparable, non-ulcerated feet, no such radiological change was demonstrable. Primary leprous granulomatous lesions of bone were limited to the terminal phalanges and were seen very rarely either in the ulcerated or non-ulcerated feet. Loss of sensation, anhidrosis and localized high pressure recorded by Kinetograph were the high-risk factors for plantar ulceration.

The mechanism of evolution of the bizarre pattern of bone changes and deformities of the feet, which hitherto have been attributed to unexplained "neuropathic" factors, are explained with reference to exact anatomical, clinico-pathological processes. These are found to be primarily related to plantar ulceration, leading to bone destruction and followed by soft tissue contraction. The possibility of lowered threshold to trauma in denervated limbs merits further investigation.

VIII A 250

Renal dysfunction in leprosy

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Leprosy being recognized as a systemic disease, attention has long been focussed on different internal organs. Involvement of the kidney in leprosy was reported as early as 1937. Most authors have reported renal failure as the commonest cause of death in leprosy.

Studies on renal changes in leprosy by percutaneous renal biopsy are few. Observations of renal function in leprosy indicate that functional disturbances occurring during the course of leprosy are most marked during reactional phases. The types of pathology in the kidney reported by various authors from their autopsy studies are: acute and chronic glomerulonephritis, nephrosclerosis and arteriosclerosis, chronic pyelonephritis, interstitial nephritis, amyloidosis, leproma and other non-specific changes.

Work in this field is meagre in India and in Orissa, which is a hyperendemic zone of leprosy. The present study is designed to investigate the renal functions as well as the histopathological changes in the kidney of different types of leprosy, and to analyse and discuss the various findings.

VIII A 251

Lucio's phenomenon in tuberculoid leprosy

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The author has three times observed ulcerated skin lesions in patients suffering from tuberculoid leprosy undergoing reaction.

A recent similar case was studied, in order to demonstrate the presence of vasculitis in connection with the ulcerated skin lesions.

The result of the histopathological examinations showed a true vasculitis, similar to that found in Lucio's lepromatous leprosy.

The author could, at the same time, demonstrate the presence of blood immune-complexes, in other cases of acute tuberculoid leprosy, which may be responsible for the pathology of blood vessels in tuberculoid leprosy as well as for what occurs in lepromatous leprosy.

VIII A 252

Relapse in lepromatous leprosy

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Today in Japan, lepromatous relapse occurs in patients who have long been smear-negative and who were thought to be controlled for years by dapsone or other medicines.

To prevent this occurrence, the treatment-history, the serological (RA, ASLO, FLA-ABS, HI, C3 CH50....), immunological (Ig-G, -M, -A, including skin tests,...) and histopathological (Harada's stain, HE stain) examinations have been done regularly in both groups of patients — the relapsed and those not relapsed.

Leprologists should therefore undertake these examinations in patients who have long been smear-negative in order to detect early signs of relapse.

VIII A 253

Coronary heart disease in leprosy patients

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Coronary heart disease, its possible risk factors and epidemiological data of interest were studied in 491 leprosy sufferers by means of a questionnaire, physical and dermatological examination, electrocardiogram at rest and after exercise, biochemical, hæmatological and histological investigations. These investigations gave the following results:

The prevalence of coronary heart disease was 11.9%, which is higher than that found in epidemiological studies of non-leprous populations.

It is suggested that factors enhancing the development of coronary heart disease in this group may include, besides hypertension and obesity, psychological factors which are particularly common in them.

No statistically significant difference was found between coronary and non-coronary leprosy patients as far as the following are concerned: age and sex; the mean duration of leprosy; the mean age at entry into the Institution; the types of leprosy; whether the leprosy was active or inactive; antileprosy drugs taken; patients living in the Institution and those living at home.

No statistically significant difference existed in the prevalence of coronary heart disease between leprosy patients confined in the Institution and those living at home.

VIII A 254

Remnants of leprosy bacilli in deep organs of patients having had lepromatous leprosy, now quiescent — use of improved acid-fast staining method

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The discovery of remnants of leprosy bacilli in patients who have had lepromatous leprosy, now considered to be in the quiescent stage, is important, in view of the possibility of the occurrence of relapse.

However, when Fite staining is used, it is not easy to determine the existence and viability of bacilli in the deep organs of quiescent cases. We have obtained a better detection of bacillary remnants by using a modified allochrome procedure for differentiation of acid-fast stain, and periodic acid methenamine silver stain (Harada).

We have observed histopathologically the skin and various deep organs in autopsy material

(302 cases) obtained during 1955 and 1976 at a national leprosarium. In accordance with the improved staining method, we have found that even if the skin smears had been negative, remnants of solid rods and granular bacilli and dormant bacilli such as Leiker described were detectable in the deep organs in many tissues such as peripheral nerves, lymph-nodes, testis, nasal mucosa, etc. The presence and morphology of bacillary remnants in the deep organs compared with the skin in quiescent cases will be discussed.

VIII A 255

The importance of lipid staining in the classification of leprosy

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The authors routinely used Sudan III in 9315 cases and conclude that this technique is indispensable in the correct histopathological classification of the clinical forms of leprosy. Many cases regarded clinically as undifferentiated leprosy were histologically lepromatous, with lipids present. In cases of tuberculoid reactions the oedema which disorganizes the epithelioid cells and which forms vacuoles in the cytoplasm, takes up the dye diffusely. In lepromatous leprosy, the lipid degeneration of the cells of Virchow is nodular or granular in appearance. In the dimorphous cases, both pictures may be found and the diagnosis is rendered much easier.

VIII A 256

The phospholipid composition of leucocytes in lepromatous leprosy

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The phospholipid composition of leucocytes was determined in 22 patients with lepromatous leprosy. Isolation of total lipids of the leucocytes has been realized by the method proposed by Folch and colleagues. The separation of total lipids into neutral lipids, glucolipids and phosphorolipids has been realized by column chromatography of pyridic acid (especially for lipid chromatography).

The further separation of phospholipid fractions has been effected by the use of preprepared slides and by thin-layer chromatography.

The results of this study show significant changes consisting of an increase in phosphotidylcholine ($p < 0.01$), a decrease in phosphotidylinositol ($p < 0.01$) and an increase in diphosphotidylglycerol ($p < 0.01$).

These findings are compared in the results found in 20 healthy individuals, as controls. The possible significance of these findings is discussed in relation to disturbances in the immune response that have been observed in this disease.

VIII A 257

Blood sialic acid (N-acetyl neuraminic acid — NANA) levels in cases of leprosy — a diagnostic and therapeutic tool

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Serum sialic acid was estimated in normal subjects and in subjects suffering from leprosy, of both sexes and all age groups, by the method of Seibert, Pfaff and Seibert. These cases were followed up to about 20 weeks, with treatment, and sialic acid was estimated every week.

Significantly high values were observed in patients with tuberculoid leprosy compared with those with lepromatous leprosy. The levels fall to normal values earlier in lepromatous patients than in those with tuberculoid leprosy, with a graded response after specific treatment. The initial raised levels of sialic acid in the tuberculoid cases may be due to tissue response or increased synthesis and release from liver or extra-hepatic sources in response to tissue injury and inflammation. It may also be due to selective consumption and destruction of non-carbohydrate proteins like albumin. Non-specific stress plays a role too.

VIII A 258

Immune complex deposit in Hanseniasis: a percutaneous renal biopsy study

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Brazil

30 patients with lepromatous Hanseniasis were investigated for evidence of kidney disease. Tests for kidney function, urine and blood, and X-ray examinations were performed as well as detailed clinical examinations. Biopsies were studied by light and fluorescent microscopy.

All 30 patients have been treated for more than 5 years and were suffering from erythema nodosum leprosum.

Amyloidosis, chronic pyelonephritis and interstitial nephritis were found in a few cases.

No leproma were found in the 30 patients.

Focal glomerulonephritis was the most common histological feature, with IgG deposit, increased cellularity of the tuft and adherence to Bowman's capsule.

VIII A 259

Renal changes in leprosy — a clinical, bacteriological, histological and functional appraisal

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Twenty-five cases of lepromatous and borderline leprosy were studied for clinical, biochemical and histological evidence of renal involvement: 14 of them showed histological evidence of renal disease.

The clinical presentations were acute nephritic (4), nephrotic (3) and haematuric (4), and 3 were asymptomatic. The chief clinical manifestation of renal involvement was oedema and/or haematuria. Six cases had oedema without obvious renal involvement. The major urinary abnormalities were: proteinuria 56%, haematuria 48% and pyuria 40%.

Glomerular functional impairment was noted in 17 cases; and impaired tubular functions (defective concentrating ability — 11), acidification defects (4). The tubular defects appeared to be secondary to glomerular disease.

Pyelonephritis was seen in only one patient. Urinary tract infection was investigated both during reactive phases and non-reactive periods of leprosy, with suprapubic technique of urine sample collection for culture. Urinary tract infection was seen in only one patient.

The renal lesions were: amyloidosis (3); diffuse proliferative (2); focal proliferative (1) and mesangial proliferative (8) glomerulonephritis. All 3 patients with amyloidosis presented with the features of nephrotic syndrome with renal failure. A close relation was seen between severe recurring or chronic ENL reactions and amyloidosis.

VIII A 260

Esterase spectrum in epidermal cells and infiltrates in lepromatous skin lesions

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Activity of nonspecific esterase was studied in the epidermis and dermis in 20 healthy persons and in the epidermis and infiltrate cells of skin lesions in 44 patients with lepromatous leprosy. Frozen sections 10-12 mm thick were treated by Nachlas and Seligmann method in Gomori's modification with naphthylacetate as substrate. Inhibitors of aliesterase (phosphacol 10^{-5}M, sodium fluoride 10^{-1}M), cholinesterase (eserine 10^{-5}M), arylesterase (EDTA 10^{-4}M, n-sodium chloromercuribenzoate 10^{-4}M), aryl- and acetylesterase (cupric sulfate 10^{-3}M, silver nitrate 10^{-2}M) were used for the separation of esterases. The intensity of reaction and inhibitory action were assessed by means of cytophotometric methods. The study of cells of the epidermis in leprosy patients showed significant statistical decrease in total esterase activity: for healthy persons the extinction was 0.47-0.90, and in leprosy — 0.10-0.34. Application of specific inhibitors demonstrated that aliesterase promoted a decrease in esterase activity in the epidermis of

leprosy patients. Aliesterase was in macrophages which formed large infiltrates and contained a great number of *M. leprae* and aryl- and acetylesterases were in disrupted macrophages with few mycobacteria. In fibroblasts of infiltrates and dermal esterase activity was due to presence of aryl- and acetylesterase. Cholinesterase activity was found only in skin nerves and some endothelial cells.

VIII A 261

Phagocytosis in leprosy. Endocytic ability of peripheral blood leucocytes as measured by its capacity to ingest *Mycobacterium lepraemurium in vitro**

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Twenty-eight lepromatous patients and 19 healthy subjects were included in this study. Ten million peripheral leucocytes were added to Leighton tubes, each containing a coverslip and 1.0 ml of 199 TC-medium without supplements. The cultures were incubated for 3 hours (37°C, 7% CO_2), then the non-adherent cells were washed out and 1.0 ml of fresh medium and 12×10^6 rat-leprosy bacilli in 20μl of normal or lepromatous serum were added. Then non-phagocytized bacilli (in a 3 hour-period) were washed out and 1.0 ml of medium containing 10% normal human serum plus antibiotics was added to each culture. After 12 hours of incubation the coverslips were removed, fixed with methanol, stained, and observed under the microscope for endocytosis.

The following results were obtained: (a) the patients' phagocytic cells (PMN and MN) ingest bacilli less frequently than those from healthy controls under similar circumstances, e.g., whether they are incubated in the presence of normal or lepromatous serum while under phagocytosis, (b) the patients' sera contain a factor or factors that interferes with the endocytic ability of normal cells, lowering their efficiency, (c) normal serum does not correct the low rate of endocytosis shown by the patients' phagocytes and (d) there are no subpopulations within the MN and PMN cells of either group regarding their endocytic ability.

*Financed in part with the aid of CONACYT.

VIII A 262

PHA skin test in leprosy patients, compared with other delayed type hypersensitivity skin tests

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PHA (phytohemagglutinin) skin test is handled easily, does not require pre-sensitization, and can be used without side-effects in repeating tests for delayed type hypersensitivity.

This skin test has been done in leprosy patients and healthy subjects, comparing with tuberculin test (PPD-antigen), lepromin test (Dharmendra antigen), DNCB-sensitization test and *in vitro* lymphocyte transformation test (LTT).

Purified PHA (Wellcome) 2.5 μg/0.1 ml was injected intradermally in the forearm, and the local erythema and induration of diameter at 24 hours later was measured.

The results of tests show that there is good correlation with PHA and DNCB skin test, but not significant correlation between PHA, PPD and lepromin skin test.

Patients with progressive lepromatous leprosy revealed markedly decreased skin response to PHA, while those with retrogressive L-type and tuberculoid leprosy showed normal skin response.

PHA skin test provides useful information in the evaluation of nonspecific cellular immune deficiency in leprosy.

VIII A 263

Acro-osteolysis in Hansen's disease

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Acro-osteolysis in Hansen's disease is regarded as a non-specific change, due to sensory denervation, repeated microtraumata and secondary infection.

Materials and Methods: The radiological changes that took place in a series of 516 leprosy patients and the pathological changes that developed in the distal osteo-articular structures of 100 cases of acro-osteolysis, were studied.

Results: Acro-osteolysis was observed in 230 patients, corresponding to 46% of the total group and to 82% of those who experienced some kind of bone change, in accordance with one of the following five criteria of bone resorption:
1. distal; 2. concentric; 3. articular; 4. trabecular; 5. osteo-articular; 6. mixed.

The pathological study showed the existence of specific osteomyelitis with erosion due to granulation tissue and mono- and polynuclear osteoclasts, and fronts of remodelling due to osteoblasts.

Acro-osteolysis appears suddenly after long periods of infection and after devitalization of the osteo-articular structures by bacilli.

SESSION VIIIB CLINICO-PATHOLOGICAL ASPECTS: NERVE DAMAGE

Thursday, 16 November 1978
15:00-18:00
Auditorium 2
Chairman: **W. F. Ross (USA)**
Rapporteur: **T. Ramasoota (Thailand)**

Invited Papers

Abstracts

VIIIB/264 Ultrastructure of beginning and progressive nerve involvement in leprosy patients.
J. Boddingius (Great Britain)

VIIIB/265 Bases pathologiques et hémodynamiques de la décompression nerveuse.
A. Carayon (Senegal)

VIIIB/266 Pathological and immunological basis of medical intervention in leprous neuritis.
C. K. Job (India)

VIIIB/267 Nerve damage in leprosy: prospects for study and applications for therapy.
J. M. H. Pearson (Ethiopia)

VIIIB/268 Neuritis en intradermorreacciones con B de Hansen en Hansenianos tuberculoides.
A. Serial (Argentina)

Free Communications

Abstracts

VIIIB/269-VIIIB/273

Poster Communications

Exhibition Area

Abstracts

VIIIB/274-VIIIB/278

CLINICO-PATHOLOGICAL ASPECTS: NERVE DAMAGE

VIII B 264

Ultrastructure of beginning and progressive nerve involvement in leprosy patients

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Peripheral cutaneous nerve biopsies of 53 leprosy patients and 9 non-leprosy individuals were examined by electron microscopy. Leprosy ranged from TT to LL, clinical histories varied (1 month to 45 years), sensory losses in areas supplied by the nerves differed from nil to severe. Some patients were in reversal reaction, a few had ENL, 50% had not yet received treatment.

To elucidate the sequence and nature of tissue involvement during the pathogenesis of leprosy neuropathy, studies were undertaken in each patient on ultrastructural changes in vasa nervorum, myelinated and unmyelinated nerve fibres, Schwann cells, endoneurial connective tissue and perineurium. The presence and location of *M. leprae* and of infiltrating or inflammatory cells, directly or indirectly related to tissue damage, were recorded for endo- and perineurium.

Findings include the very early involvement, i.e. leakage and basement membrane changes, of the endoneurial microvasculature; early pathology of myelinated fibres; relatively early intra-axonal, in contrast to intra-endothelial, presence of *M. leprae*; later, pronounced Schwann I, but rare perineurial, cell bacillation (LL patients); micro-angiopathic changes throughout the pathogenesis with pronounced endoneurial vessel changes in patients with reversal reaction and, in late stages of the neuropathy, lumen occlusion (LL patients).

Perineurial histopathology, aspects of endoneurial fibrosis and the ultimate fate of Schwann cells in very advanced stages of the neuropathy are discussed.

VIII B 265

Pathological and hæmodynamic bases of nerve decompression

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Paucibacillary forms are provoked by reversal reaction which may be *prolonged* (in BL, BB, BT) interstitial neuritis with increased infiltration of epithelioid cells and lymphocytes, micro-angiopathic neuritis after downgrading reaction followed by reversal reaction, the nerve being of small calibre and soft; or of *short* duration and intense BT, TT with caseification.

In *multibacillary forms* there is little or no macrophages infiltration. LL neuritis presents as an oedematous type, in the first stage, which is subsequently aggravated by tunnel stricture. The evolution towards BL produces a multilayer perineurium and a dedifferentiation of the peripheral Schwann cells. ENL vasculitis provokes a polymorphonuclear infiltration, a thickening of peritroncular fascia and an increase of vaso-permeability.

Pathophysiology After a vasoconstrictive phase of the limb (with arterial hypertony and opening of shunts), some changes in the troncular hæmodynamic factors occur:

Vaso-dilatation with opening of supply circulation, paralytic vaso-dilatation, increase of vaso-permeability; and intratruncular circulatory slackening with stagnation of arterial and venous blood, difficulty of lymphatic drainage, ischaemia and hypoxia. Irreconcilable opposing forces: the hypertrophied trunk and the inextensible osteo-ligamentous tunnels; resultant progressive increase of proximal hypertrophy produces an aggravation of L or ENL neuritis and of BT neuritis.

Therapeutic trends. Decompression by anti-inflammatory drugs is better in neuritis with infiltration (epithelioid and polymorphonuclear). The first goal of surgical decompression is the

restoration of the focal irrigation by anti-inflammatory drugs.

The second is decompression of nerve fasciculi, which will be more or less important according to the different form of neuritis.

VIII B 266

Pathological and immunological basis of medical intervention in leprous neuritis

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Leprosy manifests primarily as a disease of the peripheral nervous system. The mode of entry of *M. leprae* into the nerves is not yet fully understood.

The histopathological change that occurs in the infected nerve closely resembles that in the cutaneous lesions of leprosy. It varies from an anergic lepromatous inflammation to a hypersensitive tuberculoid granuloma, and the precise picture depends on the immunological status of the patient. Besides the immunological host response, the site and extent of nerve destruction appear to be influenced by regionally-acting factors like temperature, trauma and pressure. The primary lesions of the nerve may be further complicated and the local destruction enhanced by acute episodes of erythema nodosum leprosum in the lepromatous form of the disease and by a reversal reaction in the tuberculoid form of the disease.

In this paper, the histological and electron-microscopic appearances of normal peripheral nerves and the pathological changes brought about in them by the different forms of leprosy will be presented. The pathogenesis of such lesions will be described and correlated with the medical management of leprosy. The possible mode and site of action of such treatment in the reversal of nerve lesions will also be described.

VIII B 267

Nerve damage in leprosy: prospects for study and applications for therapy

J. M. H. PEARSON

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This paper will review the papers and poster presentations in the session and suggest ways in which clinical and pathological studies of neuritis in leprosy might profitably be developed. It will also highlight the practical applications to patient care of the presentations, at both field and hospital level.

VIII B 268

Neuritis after intradermal tests with *Mycobacterium leprae* in patients with tuberculoid leprosy

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For some thirty years studies of the histopathology following intradermal tests with *M. leprae* (either with the Mitsuda technique or with the Dharmendra bacillary antigen in patients with tuberculoid leprosy) have shown reactions affecting fine nerve fibres in the immediate vicinity of the tuberculoid structures. Such reactions are produced by the antigens.

In 1976 and 1977 the author was asked for his assistance in the study of 56 biopsies taken after lepromin tests with bacillary antigens (bacilli obtained by the method of Hans). The request came from a group of workers engaged in the quantitative standardisation of lepromin.

This group was led by Dr Lodner, Dr Cauzzi, Dr Morini and Dr Corona.

28 sections were cut for each biopsy and staining was with haematoxylin-eosin and the Masson trichrome technique. In 44 of the biopsies studied there were abnormalities of the fine nerve fibres in the vicinity of the tuberculoid follicular infiltrates. These changes were as follows:

1) Infiltration of the epineural connective tissue.
2) Infiltration of the epineurium (slight, moderate or severe).
3) Partial, and sometimes total, endoneuritis of some areas in the fine nerves.

These phenomena are undoubtedly caused by the endotoxins of *M. leprae*. These substances are very specific and have an affinity for the myelinated peripheral sensory nerves.

VIII B 269

Evolution of nerve lesions in leprosy

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The authors have previously demonstrated definite changes in the index branch of the radial cutaneous nerve (IRC) in an early case of leprosy where this nerve was normal by clinical and electrophysiological examination. This presentation deals with changes as observed on electron microscopy (EM) and fibre teasing of the IRC nerve in otherwise healthy contacts of leprosy patients and in the sciatic nerves of the mouse inoculated in the footpad with *M. leprae*.

In human studies the nerves were biopsied only after careful clinical and electrophysiological examination.

The earliest changes observed on EM were

1. Thickening and proliferation of Schwann cells and their processes in non-myelinated fibres.
2. Degeneration of non-myelinated fibres.
3. Degeneration of small myelinated fibres.
4. Thickening of basement membrane of perineural cells.
5. Proliferation of basement membrane of endothelial cells.

A very significant finding on fibre teasing was the marked presence of segmental demyelination.

In the mouse sciatic nerve biopsied at sequential time intervals from the first to the 24th month following footpad inoculation, the earliest changes were observed at the end of the fourth month. These changes in all the parameters of the nerves will be described as observed in the early preclinical stages of the disease.

VIII B 270

Assessment of nerve function in leprosy

B. NAAFS
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ALERT, Addis Ababa, Ethiopia

Although the mechanism of nerve damage in leprosy is not yet fully understood, it is clear that early detection and adequate treatment can prevent most of the damage.

Over the years many methods have been developed to assess the nerve function.

At ALERT we have developed an arbitrary system "nerve deficit" which enables us to assess the degree of nerve damage and nerve involvement at any time in the process of the disease. Serial readings will provide us with data concerning deterioration or improvement. These data can be used for adjustment and appreciation of treatment regimens.

The nerve deficit index is derived from 7 parameters, some objective, some subjective. The subjective ones are pain, size and tenderness of the nerve. In the final number representing the nerve deficit they are relatively unimportant. More important are the figures derived from voluntary muscle testing, sensory testing and motor nerve conduction velocity measurements. The relative importance of the different parameters wil be discussed. The use of the nerve deficit index in assessing treatment regimens will be shown in relation to the medical treatment of reversal reaction.

VIII B 271

Motor nerve conduction velocity in leprosy and its correlation with clinical and histological findings

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There is scanty information regarding correlation between clinical, electrophysiological and histopathological findings in leprous neuritis. The present study of motor conduction velocity (MCV) in various peripheral nerves in such patients was undertaken to demonstrate their correlation with clinical and histopathological features. 43 cases of lepromatous, dimorphous and tuberculoid varieties of leprosy were taken randomly. Following detailed clinical examination, MCV studies were performed on median, ulnar, lateral popiteal and posterior tibial nerves. Biopsied sural nerves were examined in 40 patients. 20 age-matched healthy people of either sex served as controls for comparison of motor nerve conduction with the patients. The majority of patients were between 21-40 years. The results

showed that MCV was diminished in all types of leprosy as compared with controls and was more diminished in lepromatous and dimorphous leprosy. MCV was lower in the superficial segments of the nerves. There was a direct relation between the clinical thickening of the peripheral nerves and the diminished MCV. A direct relation also exists between the degree of thickened nerves clinically and the abnormal histopathological changes in the biopsied sural nerves. This has shown an indirect evidence that the degree of conduction abnormality is directly related to the severity of the histopathological changes in the sural nerves.

VIII B 272

Involvement of cranial nerves in leprosy with reference to treatment

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Damage to the peripheral nerves has been extensively studied, for it is the cause of disabilities and deformities, but involvement of the central nervous system, especially of the cranial nerves, has not been well studied.

Among cranial nerves, the VII has been well studied because of the well-known facial deformities.

Damage to the X cranial nerve has been studied pathologically by Mitsuda, but the damage to its intracranial portion is little understood.

Damage may occur in the course of the Bulbar Syndrome, which, although rare, may be met in the reactional phase of patients with borderline leprosy: it is sometimes fatal.

Two cases were examined at autopsy: marked changes (such as glial cell proliferation and nerve cell atrophy) were observed in the nucleus ambiguus.

This syndrome is a medical emergency, and if the peripheral nerve changes are predominent, may well be suppressed by corticosteroids. Such treatment is ineffective when the central nervous system is involved. Since severe cranial nerve neuralgia (common as a prodromal symptom) appears during reversal reaction, all medication should be withdrawn except anti-inflammatory agents; antibiotics and other drugs may enhance the reaction.

VIII B 273

Symptomatic neuritic leprosy precipitated by rifampicin and isoniazid treatment of tuberculosis, and rifampicin-associated neuritis

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Royal Perth Hospital, Western Australia

In Western Australia during 1974-77, 72 new cases of leprosy were notified. Of these 12 were non-Aboriginal; 3 of the 12 and also one Aborigine developed neuritic leprosy during treatment for tuberculosis with rifampicin, isoniazid and ethambutol. The Aborigine was a male aged 44 and after two years' treatment for tuberculosis developed pain and tenderness in the left arm nerves, right median paralysis, and tenderness of both lateral popliteal nerves. A New Zealand man aged 38 from New Guinea developed acute leprosy neuritis in both arms after 6 months' treatment for tuberculosis. Two Anglo-Indian men, both born in India, aged 28 and 31, developed acute neuritic leprosy after 1 and 3 years' anti-tuberculosis treatment respectively. Both attributed their ulnar and median paralyses to accidents at work, but both had enlargement and tenderness of nerves in the neck, arm and leg, and leprosy bacilli were seen in a nerve biopsy of the former. Such a presentation of neuritic leprosy was not seen before rifampicin was used to treat tuberculosis.

Several other white and black leprosy patients have developed severe neuritis including drop-foot after being given rifampicin. Dapsone in large doses can precipitate neuritis but low doses have not produced such rapid paralysis. Rifampicin with steroids has aggravated leprosy neuritis. The anti-leprosy action of rifampicin still permitted the appearance of neuritic leprosy.

VIII B 274

Electrophysiological evidence for motor-unit impairment during the treatment of leprosy

A. SEBILLE

Study carried out at the Institut Marchoux of Bamako, Republic of Mali (OCCGE Member)

The course of popliteal and ulnar nerve damage was studied electrophysiologically at

intervals and over a period of 4 months in 15 treated leprosy patients: 8 of them received dapsone and 7 sulforthomidine; 9 of them had LL leprosy, and 6 BT; 4 patients (2 BT, 2 LL) developed reversal reaction or ENL during the study.

Two recording sessions were held, and the difference between the first and the last session was treated statistically. Three results were obtained. For BT patients and sulforthomidine-treated patients: the distal motor latencies of ulnar and popliteal nerves were significantly increased ($p < 0.05$); whereas the number of motor unit was significantly decreased ($p < 0.02$) in distal muscles. For the LL patients and the dapsone-treated patients, the motor conduction velocity of the popliteal nerve was significantly slowed ($p < 0.01$) at the knee.

During this study, a new nerve-growth-promoting drug — Isaxonine — was given simultaneously with leprosy treatment to 15 other patients, selected with paired controls. In this group, significant reinnervation of muscles was noticed in patients treated with sulforthomidine ($p < 0.05$) or dapsone ($p < 0.01$).

These results suggest that the course of the demyelination is not fully arrested by leprosy treatment. Furthermore, for BT patients, denervation of the distal muscles was recorded. Isaxonine could have a protective action against denervation in such cases.

VIII B 275

Peripheral vascular deficit in leprosy and its role in the pathogenesis of neuropathy

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There is considerable controversy regarding the significance of peripheral vascular lesions in leprosy and their role in the pathogensis of leprous neuropathy. Twenty patients with lepromatous and dimorphous leprosy below the age of 40 years (mean 29.9 years) were studied in detail by brachial percutaneous arteriography, motor conduction velocity (MCV) in ulnar, median, posterior tibial and lateral popliteal nerves, in addition to a detailed clinical examination. Sural nerve biopsies were taken in all the patients. The vascular involvement was severe in 6 patients, moderate in 5 and mild in 7 patients. The results showed that there was no relation between the nerve thickness clinically and degree of vascular insufficiency. There was no relation between the vascular insufficiency and the histopathological observations in the sural nerves. The MCV abnormalities were not affected by the severity of vascular insufficiency. This study does not support the view that the neurological syndromes in leprosy are due to reduced circulation to the peripheral nerves. The pathogenesis of histological features in the peripheral nerves in leprosy is unrelated to vascular involvement and is due to primary involvement of the Schwann cells by *M. leprae*. However, mutilation seen in leprous patients far more than in other types of severe neuropathies, may be due to many factors including peripheral vascular insufficiency and the peripheral neuropathy.

VIII B 276

Segmental demyelination in leprosy in the human and the mouse model as assessed by teased fibre technique with electrophysiological correlation

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The teased fibre technique was employed and correlated with nerve conduction velocity (NVC) to study the type and extent of nerve damage.

These parameters were studied in preclinical lesions of the index branch of the radial cutaneous nerve from 12 early cases of leprosy. Thirty-five family contacts with no clinical symptoms of leprosy who had been exposed to a patient with lepromatous (LL) leprosy, were subjected for NCV studies of the left and right index finger branch of the radial cutaneous nerve (IRCN). Of these, 10 contacts with reduced nerve conduction velocity and five contacts with normal conduction velocity were biopsied.

Segmental demyelination as evaluated by teased fibre technique ranged between 10 per

cent to 30 per cent in the 12 early cases of leprosy (6 BT to TT and 6 BL to LL), while 6 of the 10 contacts who showed reduced NCV and 2 of 5 contacts who had normal NCV, revealed an increased segmental demyelination as compared to normal (0 per cent to 4 per cent).

A longitudinal study was undertaken in a group of mice inoculated in the footpad. The sciatic nerve biopsies were collected at two-monthly intervals from the fourth to the 24th post-inoculation month. The sensory action potentials of these nerves were also recorded prior to each biopsy. A progressive reduction in nerve conduction velocity correlated with the increase in segmental demyelination in the nerves of these mice.

VIII B 277

Correlations of *in vitro* electrophysiological, light and electronmicroscopical studies in the neuropathy of leprosy

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After a detailed sensory examination, *in vitro* compound action potentials have been recorded from sural nerve biopsies from 6 leprosy patients (3 LL, 2 BB, 1 BT). The clinically suspected vulnerability of the small diameter fibres in this disease has been reflected in the alterations of the A delta and C potentials in the borderline cases. The records from the lepromatous patients are similarly, though less strikingly, altered. These findings have been compared to and correlated with histo-quantitative studies using light and electronmicroscopy, as has been reported by Dyck and Lambert.

This study was supported by a Grant-in-aid from the Bombay Hospital Trust.

VIII B 278

Ultrastructural changes in blood vessels of peripheral nerves and of skin in leprosy patients

J. BODDINGIUS R. J. W. REES
R. UNDERDOWN

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The blood vessels of peripheral cutaneous nerves were studied by electron microscopy in nerve biopsies from 25 patients with varying types (TT to LL) and differing histories of leprosy. Nerve biopsies from 9 healthy people served as controls. Changes in the nerve vessels were compared with those in the skin lesions of leprosy patients.

Endoneurial vasa nervorum in leprosy patients showed pronounced ultrastructural changes comprising in the endothelium: opening of junctions, formation of luminal and abluminal protrusions, attenuation, occasional fenestration, relatively late intra-endothelial occurrence of *M. leprae*, early thickening and later multi-layering of the basal lamina (BB to LL). The pericytal basal lamina was frequently multi-layered (TT to LL). Early signs of plasma leakage suggested "blood-nerve barrier" defects: basal laminal changes may therefore represent a "counter response". The marked involvement of endothelial and pericytal basal laminae in patients with reversal reaction is consistent with an immunological response.

In epi- and peri-neurium, comparable earlier but ultimately less pronounced, micro-angiopathic changes were found.

Micro-angiopathy was often seen only in nerves. However, in one patient in reversal reaction (BL) and one patient with dapsone-resistant leprosy (LL, with skin ulceration), distinct basal lamina multilayering was observed in skin vessels. The endothelium and lumen of skin vessels, in contrast to endoneurial vessels, frequently harboured *M. leprae*, indicating systemic spread of infection in the skin.

SESSION IX
THERAPY

Friday, 17 November 1978
9:00-13:00
Auditorium 1
Chairman: **M. F. R. Waters (Great Britain)**
Rapporteur: **J. Barba-Rubio (Mexico)**

Invited Papers

Abstracts

IX/279 The problem of microbial persistence in leprosy.
M. F. R. Waters, R. J. W. Rees, A. C. McDougall, A. B. G. Laing (Great Britain)

IX/280 Terapéutica de la lepra.
F. Noussitou (Argentina)

IX/281 Maintenance therapy in nonlepromatous leprosy.
C. Vellut, M. F. Lechat, C. G. Misson (India)

IX/282 The treatment of lepromatous lepra reaction, with special reference to thalidomide.
J. Sheskin (Israel)

IX/283 Resultados del tratamiento con sulfonas a largo término en la lepra lepromatosa con especial relación a las alteraciones renales y frecuencia de la sulfono-resistencia.
J. Terencio de las Aguas (Spain)

IX/284 The treatment of sulphone-resistant leprosy.
R. R. Jacobson (USA)

IX/285 The treatment of reversal reactions.
R. St. C. Barnetson (Great Britain)

Free Communications

Abstracts
IX/286-IX/292

Free Communications

15:00-18:00
Abstracts
IX/293-IX/300

Poster Communications

Exhibition Area
Abstracts
IX/301-IX/313

THERAPY

IX 279

The problem of microbial persistence in leprosy

M. F. R. WATERS R. J. W. REES
A. C. MCDOUGALL A. B. G. LAING

National Institute for Medical Research, London, England

It is generally agreed that a significant proportion of lepromatous patients will relapse if dapsone treatment is stopped after 10 years or even longer. However, the majority of such patients respond normally to a second course of dapsone therapy, their relapse being due to drug-sensitive *M. leprae*. At the Tenth International Leprosy Congress, we first presented direct proof that small numbers of viable, drug-sensitive leprosy bacilli — "persisters" — could be detected in selected tissues (skin, nerve, striated muscle and dartos) of lepromatous patients treated for 10 to 12.5 years with regular chemotherapy, principally or entirely with dapsone. In this paper, we shall review our subsequent, greatly expanded studies. These include the detection of "persisters", not only in dapsone-sensitive patients receiving long-term treatment with dapsone, but also in dapsone-resistant patients treated for 10 years with clofazimine, or five to 7.5 years with rifampicin with or without thiambutosine, or even in patients receiving combined therapy with rifampicin and clofazimine for five years. The significance of these findings will be discussed, especially in relation to possible treatment regimens in lepromatous leprosy.

IX 280

Therapy of leprosy

F. NOUSSITOU

Buenos Aires, Argentina

A. *Introduction.* Importance of an effective treatment of the disease from the point of view of the individual patient as well as a means to protect the healthy population (control of leprosy in a given community).

B. Tentative evaluation of the anti-leprosy drugs currently in use.

C. Regimens. Mono- and combined therapy in the different forms of leprosy and leprosy reactional conditions.

D. Need of controlled trials of mono- and multiple therapy regimens in different parts of the world on a long-term basis. Discussion of objectives and parameters. Definition of clinical, bacteriological and histopathological criteria to be used in the selection of cases and evaluation of results.

IX 281

Maintenance therapy in non-lepromatous leprosy

C. VELLUT M. F. LECHAT
C. B. MISSON

Polambakkam, South India

Over a 20 year period, 7500 cases of non-lepromatous leprosy were treated at the Leprosy Centre, Polambakkam, South India. Treatment included standard therapy with dapsone until all lesions subsided and the patient was declared inactive, followed by maintenance therapy until the patient was declared cured. Inactivation was defined according to standard criteria. Declaration of cure occurred at various intervals after inactivation. Patients were regularly followed up afterwards.

The probability of relapse was studied according to the number of years after being declared cured, and duration of maintenance treatment. For patients with single lesion at detection, it was also studied according to total duration of treatment. The risks of relapse decrease steadily with time after the patient has been declared cured. The results also show that the longer the maintenance therapy in inactive status, the lower the risk of relapse afterwards. Norms can be deduced for deciding on the optimal duration for

maintenance therapy as well as duration and periodicity of follow-up in cured patients.

IX 282

The treatment of lepromatous lepra reaction, with special reference to thalidomide

J. SHESKIN
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The author considers the history of palliative and preventive treatments of the lepra reaction: analgesics, antipyretics, tranquillizers, spasmolytics, vitamins, antimalarials, antimony, saline solution, calcium, antibiotics, blood transfusion, autologous haemotherapy, gamma-globulin and hyaluronidase.

The author discusses reduction of dosage of anti-leprosy medication as a way of preventing the lepra reaction.

He mentions the favourable action and the side-effects of steroids.

The author reviews in detail treatment with thalidomide and discusses its influence upon the various manifestations of the lepra reaction. He refers to some of the studies with thalidomide: double-blind technique; measurement of motor conduction velocity of peripheral nerves; interrelation between this drug and anti-leprosy drugs; side-effects; effectiveness of thalidomide in different climates and latitudes; tests with some of the derivatives of thalidomide, and finally, medicosocial aspects.

IX 283

Results of long-term sulphone therapy for lepromatous leprosy with special reference to renal abnormalities and to the frequency of drug resistance

J. TERENCIO DE LAS AGUAS
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The experience acquired in treating lepromatous leprosy with sulphones during 25 years is described and their effectiveness compared with that of other drugs.

With sulphones, negativization occurs within the first year of treatment in 4 per cent of cases; between 1 and 2 years in 14 per cent; between 2 and 5 years in 50 per cent and in the remaining 32 per cent of patients treatment had to be continued for more than 5 years in order to obtain bacteriological negativity.

The activity of the various sulphones was studied. The most effective was found to be Promin (daily injection of 5 cc), followed by dapsone in the initial dose of 50 mg per day in the first two months and then 100 mg daily.

In the group of patients with frequent lepra reactions in the first three years of treatment, it took longer for negativization to take place: in none during the first year, in 4 per cent between the first and the second year, in 47 per cent between the second and the fifth year and in 40% between the second and the fifth year.

The action of the sulphones is compared with that of clofazimine and rifampicin. With clofazimine in a trial lasting for 10 years, inactivation took slightly longer. With rifampicin over a period of five years, none of the cases became negative.

Renal lesions

These were found in 47% of the patients with lepromatous leprosy and in 25% of these there had been frequent reactions. These are attributable to antigen-antibody reactions and to the deposition of immune complexes, the cause of lesions progressing after a number of years to renal failure being amyloidosis in 61% of cases. These lesions led to death in 62% of the patients.

Drug resistance

Resistance can be primary or secondary. The former did not occur. The latter means the occurrence of positive smears after a minimum of one year of negative findings, in a patient with lepromatous leprosy. In the majority of cases, bacteriological recurrence was associated with clinical relapse; all patients had been inactive for many years, but had been treated irregularly or had stopped taking the drug, had taken inadequate doses, or had received depot preparations. Resistance occurred in 1.5% of cases.

IX 284

The treatment of sulphone-resistant leprosy

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USPHSH, Carville, La., U.S.A.

Over the last 20 years a steadily increasing number of patients treated for variable periods

with the sulphones has developed progressive disease no longer responsive to these drugs. All these patients have been shown, either clinically or on mouse footpad drug sensitivity studies, to be infected with bacilli that are sulphone-resistant. Most of these cases were initially treated with another drug such as clofazimine or rifampin given as monotherapy. Those on clofazimine have so far had a uniformly excellent response, but some of those receiving rifampin monotherapy have relapsed with rifampin-resistant strains of *M. leprae*. Because of this, we have begun trials with drug combinations, including in particular rifampin-ethionamide and clofazimine-ethionamide with overall good results, though toxicity may be a problem. We are also treating many of our new cases with combination regimens such as clofazimine-dapsone and rifampin-dapsone in the hope of preventing the appearance of, or at least reducing the incidence of, sulphone-resistant disease.

Complicating this picture has been our discovery, since 1971, of eleven new, previously untreated cases infected with bacilli that appear to be partially sulphone-resistant.

IX 285

The treatment of reversal reactions

R. StC. Barnetson

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It is now generally accepted that reversal reactions are delayed hypersensitivity phenomena which may occur throughout the borderline leprosy spectrum: the process may affect both skin and peripheral nerve, or either tissue separately. Patients may have these reactions whether or not they are receiving treatment.

The sheet anchor of treatment is steroid therapy. Reactions will normally improve with moderate doses of steroids (e.g. prednisolone 30 mg daily), and this treatment can be reduced over a period of 3 months to 1 year as the clinical picture improves. Provided steroid treatment is instituted promptly, even patients with marked nerve dysfunction resulting from the reaction will not usually suffer permanent damage. Treatment with immunosuppressives such as azathioprine in addition may be useful in the few cases where the response to steroids is unsatisfactory.

The role of dapsone (or other anti-leprosy drugs) in the causation of reversal reactions has long been a matter of contention. It has been suggested that dapsone plays an important part in precipitating reactions, but there is little scientific evidence to support this. In a recent study we have found that dapsone in a dosage of 50 mg daily, does not seem to predispose to these reactions, and, indeed, may prevent them. We therefore recommend that dapsone at such dosage should be the treatment of choice *ab initio* in all adult leprosy patients, and that it is continued at this dosage throughout any period of reaction.

IX 286

Relapse and dapsone resistance in Morocco

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A. Sekkat

Casablanca, Morocco

From 1 January 1950 to 1 January 1978, 6000 leprosy sufferers were examined. Of these, 2000 have been removed from the register for various reasons: 40% have died; 40%, considering themselves cured, have lost contact; 20% have defaulted. There remain therefore 4000 patients, followed up regularly, of whom 60% (i.e. 2400) have lepromatous forms of disease. In this group we have recorded between 3 and 10 relapses per year, totalling at present 180, of which 30 have tuberculoid and 150 have lepromatous forms. These latter, the majority, correspond to irregularity in treatment or to the failure, admitted or not, to take treatment. Clinically confirmed resistance to dapsone totals less than 10% of the number of relapses. Confirmation by mouse footpad (Prof Pattyn) inoculation has been used for only 3 patients.

IX 287

Practical experience with combined therapy in leprosy

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E. Bonnici G. Depasquale

Borstel Institute, Hamburg, Germany

Combined therapy proved to be superior to monotherapy. Dependent on dosage and duration of treatment, dapsone mono-therapy

leads to chemoresistance; besides, it is known to be unsuccessful in lepromatous cases.

Experimental and clinical investigations had shown a combination of rifampicin + (Isoniazid + PTH + dapsone) to be — until now — the most effective treatment. With this multi-drug regimen, patients suffering from lepromatous leprosy can be definitely cured in a relatively short time.

Therapy studies on humans will only be conclusive when they are followed by studies for the *occurrence of relapses after discontinuation of treatment*. The patients should be observed for a minimum of 5 years and be monitored by taking smears and biopsies. 47 cases which had been previously treated with dapsone, in part over a long period, were released from treatment and then kept under constant surveillance, including the taking of biopsies and smears. Relapses, if any, are extremely rare after the therapy applied by us.

IX 288

Status at ten years of the leprosy patients in the acedapsone (DADDS) trial in the Karimui, New Guinea

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Acedapsone, a repository sulphone injected every 75 days, has been used to treat all leprosy patients in the Karimui since 1967. All multibacillary patients (initial BI 2.0 or greater) have also received a 90-day course of rifampicin (600 mg daily) without interruption of the acedapsone. The total numbers of patients who have received DADDS therapy is 502. The injections have been well received. Regularity of injections and patient follow-up have been high. ENL has not been difficult to handle.

The number of patients starting in 1967 was 337. There were 108 indeterminate, 81 TT, 31 TT/BT, 60 BT, 15 LL and 19 BL/LL and 23 burnt-out tuberculoid and polyneuritic patients, and in each of these categories all had reached the healed or stationary stage by 1974. In 1977, 2 of 19 BB and BL patients were still graded as healing and improving because of remaining traces of clinical activity. All other patients now have no signs of clinical activity (erythema, infiltration, tender nerves, or reaction).

There were 28 previously untreated multibacillary patients who entered the study in 1967. After 3—5 years of acedapsone therapy, the initial improvement in BI ceased in 5 patients, and persister (viable and dapsone-sensitive) *M. leprae* were detected. The 90-day course of rifampin was then added to the regimen of all multibacillary patients. The BI of these 5 patients then fell promptly, and in 1977 their skin smears were negative. Only 1 acid-fast bacterium was found in the examination of all the skin smears of the other patients in this group. The graphed BI results provide strong evidence that the persister bacilli (which escaped the slow killing activity of dapsone, released from acedapsone) were nevertheless susceptible to rifampicin.

IX 289

Acedapsone in the treatment of 70 lepromatous patients

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Evaluations of acedapsone (DADDS) in mice and humans have shown that this compound is effective against *M. leprae* infections. The special merit of repository acedapsone is that known and continuous levels of dapsone are received by all patients. The paper will define the methods used, and the observations collected during 3 years of treatment of 70 carefully selected, untreated lepromatous patients.

Each patient received 225 mg DADDS in a deep intramuscular depot every 70 days. In 6 selected patients, the plasma levels of dapsone were determined after 35 and after 70 days. The patients had been classified according to age, sex, clinical criteria, duration and severity of disease and both bacteriological (BI) and morphological (MI) indices.

In 68%, the duration of disease (prior to treatment) had been 1—10 years. In 41% distinctive nodules were present. In 73% the BI ranged from 3—5 + (Ridley). The MI was below 5%.

Remarkably uniform plasma levels of dapsone were observed in the six patients followed in detail: at 35 days ± 54 ng/ml; at 70 days ± 13 ng/

ml. Clinical improvement occurred in the majority of the patients. In 61% of the patients the average BI decreased 1—2 values on the Ridley scale. In 7% the values increased. In 95% of the patients the MI fell to 0% within 200 days. These values increased in 3/70 (4%) persons. Lepra reaction occurred in 20% of the patients. It was concluded that the clinical and bacteriological improvements during treatment with acedapsone were comparable to those that had been recorded during oral administration of dapsone.

IX 290

Rifampicin in the treatment of lepromatous leprosy

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L. M. BALINA M. GABRIELLI
J. C. OCAMPO G. E. A. PIZZARIELLO
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O. BIANCHI E. SANTABAYA
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The results obtained in 208 lepromatous patients are communicated. Rifampicin was used alone or with other drugs during a period that varied between 2 and 57 months.

The patients were distributed in three groups according to the drug given and doses.

Group A: Rifampicin 300 mgrs/day.

Group B: Rifampicin 300 mgrs/day plus dapsone 25 mgs/day.

Group C: Rifampicin 600 mgrs/day plus Isoprodian 1 tablet per day.

The parameters used in the evaluation of the results, were: clinical, bacteriological and finally histological.

We specially emphasize factors relating to leprosy reaction (ENL) connected with doses, time of appearance, duration and therapy employed.

IX 291

Treatment with rifampicin of 5000 leprosy patients in Cuba

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The New Programme of Leprosy Control initiated in May 1977 planned controlled administration of rifampicin to all known leprosy sufferers, to the number of 5142, as well as to any new cases that might appear.

The dose given was 500 mg of rifampicin daily for 6 months to the patients with bacillary positive forms and for 3 months to the bacillary negative forms. This treatment was given to patients with any clinical form of the illness.

The medication was administered daily in the outpatients' departments of the general health services by nursing staff, or in the patients' homes if they had a physical handicap.

Clinical and bacteriological control was carried out monthly for bacillary positive forms and quarterly for bacillary negative forms.

99% of the patients received treatment during the early stages, according to the plan. In 70% of patients receiving treatment there was clinical and bacteriological improvement.

IX 292

Therapeutic effects of adding Rimactane^{R} (rifampicin) 450 mg daily or 1200 mg once monthly in a single dose to dapsone 50 mg daily in patients with lepromatous leprosy

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Thirty lepromatous leprosy patients from the Institute de Léprologie, Dakar, were randomly allocated to 6 months' oral treatment with one of the following two regimens:

A—450 mg Rimactane^{R} (Ciba-Geigy rifampicin) daily + 50 mg dapsone daily or

B—1200 mg Rimactane^{R} once monthly in a single dose + 50 mg dapsone daily.

Each treatment group comprised 15 patients. Marked clinical improvement was observed in 10 and 11 patients on regimens A and B respectively. The MI of the skin smears reached zero within 2 months' treatment in 53% and 60% of the patients on daily and once-monthly Rimactane combination treatment regimens respectively. The MI of nose-blow smears reached negativity within 2 months in 60% of the patients on regimen A and in 67% of those on regimen B. The average decreases in the BI of nose-blows and skin smears, and LIB were closely similar after 6 months' treatment with regimens A and B.

Due to severe ENL and haemolytic anaemia, treatment with daily rifampicin plus dapsone was discontinued in 2 patients. The once-monthly rifampicin schedule (regimen B) was better tolerated.

Contrary to expectations and despite the vast difference in total dosage, the therapeutic effects of adding Rimactane[R] 450 mg daily or 1200 mg once monthly, to a standard dapsone regime were clinically, bacteriologically and histologically practically identical in the six-month study period. Rimactane[R] 1200 mg once monthly in a single dose could therefore be therapeutically and economically an ideal component of combined drug regimens and merits further investigation for large-scale, initial and intensive treatment of LL, LI and BL leprosy.

IX 293

Short course rifampicin treatment of TT and BT leprosy

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In a pilot study on short course treatment of paucibacillary leprosy, 10 patients with newly diagnosed TT and BT leprosy were given under supervision 8 weekly doses of 900 mg rifampicin. Clinical examination and skin biopsy studies were performed at 2, 6 and 12 months.

At 6 months, there was clinically slight improvement or no change in all patients except in one who showed slight worsening.

The biopsies revealed granulomas of reduced size in 3 cases, and no changes in the others except for increased oedema indicating a reversal reaction. The results at one year follow-up will be presented.

IX 294

Four-weekly 'pulse' therapy with rifampicin in sulphone-resistant lepromatous leprosy — interim report

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The potent bactericidal effect of rifampicin together with the slow generation time of *M. leprae* suggested that intermittent treatment with rifampicin every four weeks might be a practical regimen in the treatment of sulphone-resistant lepromatous leprosy. A double-blind controlled trial was therefore planned in which in addition to rifampicin, patients would also receive a second-line drug, thiambutosine, to offset the emergence of rifampicin resistance that might be promoted by monotherapy. The trial includes two groups each of 10 patients, one receiving rifampicin 600 mg daily on two successive days every four weeks and the other 600 mg daily; both groups also receiving thiambutosine 1 g weekly by intramuscular injection.

Observations before and throughout the trial included clinical assessments, skin smears, and biopsies (skin, peripheral nerve and dartos) for footpad inoculation of T/R mice and for histopathology; in addition, patients were monitored by serological examinations at regular intervals for the development of anti-rifampicin antibodies.

The trial, which is open-ended, began in July 1973, the last patient entering the trial in January 1978. It is, therefore, possible to give only an interim report on results to date; these indicate that intermittent treatment with rifampicin and thiambutosine is as effective as daily rifampicin with thiambutosine and does not give rise to the formation of rifampicin-dependent antibodies. Details of the clinical, mouse footpad results and histopathology are reported.

IX 295

Results of the treatment of leprosy patients with prothionamide

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Leprosy Research Institute, Astrakhan, USSR

The results of prothionamide therapy in 30 patients with lepromatous leprosy are given. 26 of them received prothionamide for between 6 and 18 months, and in 4 patients the drug was discontinued because of side-effects. Among those treated for 6 and more months, 4 patients received only prothionamide, and 22 patients received prothionamide and either sulphones or thiambutosine.

After one to two months of treatment with prothionamide alone, clinical signs of the disease began to regress, and mycobacteria disappeared from the nasal smears. Six months later, regression of skin infiltrates and nodules was

marked, and bacteriological indices improved significantly. Skin biopsy also showed improvement.

Among 22 patients after six months of combined therapy, the disease regressed in most of the patients, including three cases who had previously relapsed after long-term sulphone treatment.

In 11 patients bacterioscopy of the smears became negative after 6 months of combined therapy.

Prothionamide together with other antileprosy drugs caused more rapid improvement of bacteriological indices than monotherapy with sulphones. After 6 months of combined therapy, BI declined by a factor of 5.8 times (0.9%) whereas under monotherapy with sulphone, BI declined by a factor of only 2 (5%).

Thus prothionamide has antileprosy activity, and it is recommended for treatment in leprosy.

IX 296

Diuciphon (Diuciphonum) — experimental and clinical data

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Diuciphon is an original Soviet antileprotic preparation, synthesized in 1968 at the Institute of Organic and Physical Chemistry, the USSR Academy of Sciences.

Its preparation and use in the treatment of leprosy has been patented in the USA, the UK and France.

The available results of clinical experimental studies lead to the following conclusions:

1. Experimental studies in mice infected with human leprosy showed the antileprotic effectiveness of Diuciphon to be double that of solapsone;
2. Diuciphon is nearly five times less toxic than diaminodiphenylsulphone (Diuciphone LD_{50} = 2,600 mg/kg; dapsone = 650 mg/kg);
3. Diuciphon produces no side-effects characteristic of sulphones, a fact which has been verified by determining its chronic toxicity in comparison with diaminodiphenylsulphone, and confirmed during clinical trials of these preparations;
4. Diuciphon causes an increase of the RNA content in the blood of humans. This gives grounds to presume its possible penetration through the cellular wall, which is of extreme importance, since the leprosy mycobacteria are frequently found intracellularly, in the lepra cells;
5. During the treatment of 105 patients with Diuciphon for periods from 6 months to 6 years, better results (clinical, bacterioscopic, histomorphological) were obtained than from treatment with other modern antileprotic remedies. This is confirmed firstly by discharging from hospital 58 of the 105 patients for outpatient treatment, and by the almost complete absence of relapses in those who continued Diuciphon treatment as outpatients;
6. Good results were obtained when treating patients resistant to antileprosy therapy, which indicates that the action mechanism of Diuciphon is different from that of the sulphone drugs (dapsone);
7. In contrast with other sulphones, Diuciphon stimulates the protective immunobiological reactions of the organism. This is confirmed by the transformation of lepromatous leprosy into the tuberculoid type in 10 out of 77 cases. This has not occurred in any of 87 patients, in a control group, receiving sulphone treatment for 20 years.

IX 297

The results of immunotherapy of patients with lepromatous leprosy

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There are several reports about positive results of immunotherapy in lepromatous leprosy patients after injection of intact leukocytes or transfer factor from healthy donors with positive tuberculin or lepromin reaction. Improvement in clinical state and in bacteriological indices has been noted; also, positive Fernandez reaction has been noted and, in some cases, there is a tendency to conversion of lepromatous (LL) into borderline-lepromatous leprosy (BL).

We observed 15 patients with lepromatous leprosy aged from 20 to 77 years; among them 3 patients were newly hospitalized, 3 had been treated for 15 years or more but had developed resistance to chemotherapy, and 9 patients had been treated for 1½ to 10 years after relapse.

Simultaneously with chemotherapy, leukocyte suspensions from healthy donors (of unknown

lepromin reactivity) were given to stimulate immune reactivity. The suspensions were injected subcutaneously at a dose of 10 ml 5 or 6 times at intervals of 1 to 1½ months.

Clinical improvement was noted in nine patients; two patients were discharged for out-patient treatment (one after relapse, and the other was newly hospitalized with borderline-lepromatous leprosy). Histological study in 9 patients showed a decrease in the size of the infiltrate, disruption or disappearance of leprosy bacilli, increase of lymphocyte reaction in a few cases, decrease of bacterial load, decrease or disappearance of granular or solid forms. The structure of the infiltrate in one patient became borderline-lepromatous. In 6 patients the morphological changes were insignificant.

The reversion of a negative Mitsuda reaction to positive, observed in 5 patients, deserves special mention. Such reversion occurred in 2 patients who were resistant to chemotherapy, in 2 with relapse and in 1 patient with borderline-lepromatous leprosy.

If previous lepromin testing of donors is not considered to be necessary, this method of immunotherapy becomes more widely available.

IX 298

Histopathologically documented reversal reaction in lepromatous leprosy following treatment with transfer factor

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Five patients with active leprosy, four with polar lepromatous (LL) and one with borderline-lepromatous (BL), were each treated with transfer factor (TF) from approximately 7.4×10^9 lymphocytes given in 36 divided doses over a 12 week period. The TF was prepared from blood donated by normal, healthy, lepromin skin-test-positive individuals. During treatment all four of the LL patients, but not the BL patient, developed "flare" type reactions, which on clinical grounds were thought to be reversal reactions. The present paper documents that these "flare" type skin lesions seen in at least 3 of the LL patients are, in fact, focal reversal reactions as manifested by focal infiltrations of lymphocytes and focal changes in macrophages from foamy histocytes laden with *M. leprae* to epithelioid cells and Langhans' giant cells essentially free of acid-fast bacilli. To the extent that reversal reactions are evidence of effective cell-mediated immunity to *M. leprae*, these results indicate that TF prepared from the blood of lepromin skin-test-positive healthy individuals is capable of at least partial correction of the immunological deficit of lepromatous leprosy.

IX 299

A placebo-controlled clinical trial of transfer factor in lepromatous leprosy

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The effects of repeated injections of transfer factor (TF) over a period of 20 weeks were investigated in bacteriologically positive lepromatous leprosy patients, who showed negative (0 mm) skin reactions to leprolin and lepromin. Seven patients received four weekly injections of TF with a total of 9 Units (1 Unit being defined as equivalent to 5×10^8 lymphocytes) and 7 patients received injections of a placebo. Maintenance treatment with clofazimine was continued.

TF was prepared from lymphocytes of donors showing a positive skin reaction to leprolin (average 15.5 mm) or lepromin (13.6 mm) and a positive lymphocyte transformation test *in vitro* to *M. leprae* (average transformation being higher than the average transformation of lymphocytes of tuberculoid patients).

No significant differences were found between the two groups as regards clinical course of the disease, histopathological and bacteriological evaluation of skin biopsies, changes in skin test reactivity to leprolin, lepromin, PPD, mumps, *C. albicans, Tr. rubrum, Varidase* and lymphocyte transformation test *in vitro* to *M. leprae*, leprolin, BCG, PPD, mumps, *C. albicans, Trichophyton, Varidase.*

No evidence was found that TF is a valuable adjuvant in the treatment of patients suffering from lepromatous leprosy and that it increases cell mediated immune reactivity towards *M. leprae.*

IX 300

Leprosy reaction and Levamisol (R 12564)

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L. M. BALINA J. C. OCAMPO
M. GABRIELLI J. J. AVILA M. LUPPI
L. FIOL M. A. TUCULET
M. FALCONE

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25 patients with ENL presented, most of them in a state of severe and constant reaction. Uninterrupted specific medication was given, and 22 of the 25 also received thalidomide.

All 25 received Levamisol (R 12564): 150 mg per day on two consecutive days of the week. This pattern was repeated every week. It was confirmed in the majority of patients and over a long period of time, that while using Levamisol we needed a smaller dosage of thalidomide than commonly used to control reaction. We consider the study to be highly significant.

IX 301

Pilot-trial of short treatment of leprosy by associated chemotherapy and immunotherapy

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Four cases of lepromatous leprosy and two of borderline-lepromatous were treated for a year or more in a pilot-type trial, with rifampicin plus the antigen POG (a polysaccharide of *M. tuberculosis* combined with specific IgG). It is thus a method of combined chemotherapy and immunotherapy. Evaluation of results was made with a bacteriological criterion determining the rate of fall of the bacteriological index and the morphological index, and with a clinical criterion determining the rapidity and extent of general improvement and of the cutaneous lesions. The BI of the nose scrapes fell from 3.1 to zero in three months. The BI of the skin fell from 4.1 to 0.8 in one year, and later to zero. The MI of the skin fell from 66.6 to 0.8 in three months and to zero in six. Clinical improvement was rapid and steady. Improvement was very good in four cases after one year's treatment, good in one case and moderate in the other. In two patients, reactions were recorded — ENL, fever and pains in joints and muscles. In most instances, reactions were mild to moderately severe. Treatment with CIA was continued during these reactions with no aggravating effect. The results show that associated chemotherapy and immunotherapy is an effective antileprosy treatment and merits further investigation.

IX 302

Study of the action of 2-mercapto-propionil glycine on leprosy

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2-mercaptopropionil glycine is the most recent discovery in the search for protective and regenerating substances in liver disease. It has a lipotrophic action (protecting against toxic substances) and a cytotrophic action (regenerating damaged parenchyma). Its pharmacological action is due to the reaction of enzymes, preventing oxidation of ascorbic acid and degradation. Furthermore, it has a mixed effect on the immune system in that it supresses allergic reactions, inhibits synthesis of ribonucleic acid in the lymphocytes and inactivates pathogenic immunoglobulins.

Therefore it was thought that this drug could be useful for leprosy where the direct action of the illness damages the liver and where sulphones used for treatment exert a hepatotoxic action in chronic cases.

The study demonstrates cytotrophic and lipotrophic activity confirmed by objective laboratory results showing improvement, and subjective results showing decreased asthenia and anorexia. At the same time there were no secondary effects, and the hepatic functioning became normal through accelerating the intermediate metabolism of liver function and metabolising endogenous and exogenous toxins such that the ultrastructure is restored through oxidation/reduction activity.

IX 303

Treatment of lepromatous leprosy with long-acting sulphonamides

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The action of sulfadoxine (Fanasil, Roche) and sulfamethopyrazine (Kelfizine, Farmitalia)

was tested in two groups of 23 patients each, while a third group of 23 patients receiving dapsone was used as a control. All patients showed clinical and bacteriological improvement. The average duration of treatment was 26 months in the patients receiving Fanasil, 30 months for the Kelfizine group and 30 months in the patients receiving dapsone. The number of patients who developed ENL in the groups was: Fanasil 14, Kelfizine 21, dapsone 15. The ENL started after an average of 9 months of treatment in the Fanasil group, 13 months in the Kelfizine group and 16 months in the dapsone group. The number of patients removed from the trial because of ENL was: 9 in the Fanasil group, 11 in the Kelfizine group and 9 in the dapsone group. The incidence of ENL was considerably higher in the Kelfizine group compared to the Fanasil and dapsone groups (91%, 60% and 65% respectively), but it was of a relatively mild degree not necessitating earlier removal of patients from the trial. No side-effects were noted from the long-acting sulphonamides.

IX 304

Comparative study of five groups of patients: dapsone with another drug

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Six groups of patients, chosen at random and each containing 33 persons, received daily dosages (as inpatients) of dapsone alone or dapsone associated with one of the following drugs:

II Decoction of 25 gram of *Smilax Ornata* root;

III Tablets of 0.25 gram of aqueous extract of *Smilax ornata* root;

IV clofazimine 400 mg and thiambutosine 1 gram;

V thiambutosine 1 gram and ethionamide 0.50 gram;

VI thiambutosine 1 gram, together with ethionamide 0.50 gram and sulphamethoxypyridazine 0.375 gram.

During the following three months, they all received dapsone as outpatients. All the initial examinations were repreated at intervals of one, two, three and six months.

The Bacterial Index (BI) varied little during the six months. In contrast, the initial Morphological Index fell in some groups, as did the activity as judged by the histopathological picture. Details will be given in the paper.

This enquiry demonstrated the activity of Sarsaparilla (especially in decoction) and of the combination of sulphamethoxypyridazine, thiambutosine and ethionamide. There were no reactional episodes in the group given clofazimine, but the bacteriostatic activity was less.

IX 305

Dimocifon in the treatment of leprosy patients

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Dimocifon is a new Soviet drug for the treatment of leprosy, which is three times less toxic than diaminodiphenylsulphone.

Thirty-seven patients with the lepromatous type of leprosy were treated with Dimocifon at a dose of 0.1 gm orally 2 to 3 times a day; 10 of these patients had developed resistance to anti-leprosy drugs. The drug was used alone and in combination with other anti-leprotic preparations.

Six months after the beginning of treatment, in 17 patients (4 of them resistant to sulphone) the erythematous spots had either disappeared or become pale, the infiltrates and the lepromas became smaller or almost completely resolved; in 20 patients there was a significant reduction in the numbers of *M. leprae* in the skin, especially of solid forms, and in 3 patients no bacilli were found in the dermis.

At the end of 7—8 months of treatment, the specific effect of the drug diminished and treatment was continued in only 14 patients, who under the effect of Dimocifon continued to show improvement.

The results show that Dimocifon has considerable anti-leprotic activity, which is marked in patients resistant to sulphone.

IX 306

Therapeutic trial with immunomodulators in Hanseniasis — Levamisol and Tetramisol

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Among well-known immunomodulators, like BCG, *Corynebacterium parvum*, methanol extraction residue, virulent fraction or attenuated fraction of BCG, Levamisol is much used.

Levamisol and Tetramisol have similar effects upon the immunosystem.

Levamisol increases the formation of antibody. The administration of Levamisol results in increased blood levels of total hemolytic complement in cancer patients and patients with hepatitis. Levamisol stimulates lymphocytes and increases the power of phagocytosis in macrophages.

Levamisol is used in Hanseniasis because of anergy in lepromatous (Virchowian) Hanseniasis.

We think that treatment with Levamisol is indicated for cases of leprosy reaction (type erythema nodosum).

We selected three cases of lepromatous leprosy with relapsing erythema nodosum leprosum, resistant to clofazimine.

Levamisol was administered at a dose of 150 mg daily on three successive days, and then followed by 12 days' rest.

After only three doses of 150 mg Levamisol the patients showed remarkable improvement, with normal temperature, no more nodules of erythema nodosum or arthralgia. No side effects were observed. Levamisol is a drug that requires further investigation in the treatment of leprosy.

We have now treated 25 cases with success.

IX 307

The immunomodulatory action of two drugs given together in bacilliferous lepromatous leprosy

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The object of the present study is to find a treatment which may be given to the contacts of patients suffering from lepromatous leprosy in order to increase their resistance to Hansen's disease. Previous work had shown a depression of cell-mediated immunity in these contacts. The group of contacts studied are those of patients suffering from lepromatous leprosy, multibacillary, from 2 to 20 years old and with a negative Mitsuda reaction.

The following immunological studies are made: 1) study of T lymphocytes: "E" rosettes culture of lymphocytes stimulated with PHA and with a suspension containing 100 million Hansen's bacilli per ml; 2) study of B lymphocytes: "EAC" rosettes.

In conjunction with the immunological study, we carry out the lepromin reaction tests, eliminating the positive contacts. The negative contacts are grouped as follows:
Group I: Control without drug.
Group II: Levamisol 2.5 mg/kg/day for 3 days and repeated 15 days later.
Group III: BCG with Mantoux previously negative.
Group IV: BCG plus Levamisol.

Four months later, the immunological study and the lepromin tests are repeated to determine the changes that occur after treatment.

IX 308

The combination rifampicin-Levamisol in a double-blind trial in the treatment of lepromatous leprosy

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The authors are impressed with the action of rifampicin in patients with lepromatous leprosy, and they have carried out a clinical trial of this drug in combination with Levamisol, which is known to increase cell-mediated immunity. The Levamisol was compared by the double-blind method with an inactive placebo, allocation to treatment group being random.

Specific treatment with rifampicin was maintained for 6 months in the 50 patients, at a dose of 150 mg per day.

The following parameters were studied: full blood count, liver function tests, ESR, blood sugar, urea and prothrombin, plasma proteins, blood lipids, biopsy, bacilloscopy, total protein lepromin. The total protein lepromin was used so as to avoid immune sensitisation occurring possibly with integral or bacillary lepromin, which may contain bacillary or tissue constituents which may complicate the interpretation of the findings.

The findings regarding occurrence and incidence of lepromatous reactions during the trial are considered under the following headings: type of reaction, dermatological features, pyrexia, spontaneous course and, in refractory cases, response to the administration of thalidomide.

The comparative results and conclusions are shown in posters.

IX 309

A medication monitor for studying compliance with anti-leprosy drug regimens

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A medication monitor has been developed utilizing radioactive material and photographic film to record the intervals at which patients take medication. In the author's opinion, this equipment represents the most efficient means for determining how regularly outpatients take medication. The monitor has been used in the treatment of patients with tuberculosis in Denver, Colorado and Malawi, Africa. Among 122 patients selected for their apparent reliability, 31% took less than 70% of their medication for one or more months. Race, sex and education level showed no statistically significant correlation with compliance. Physician and nurse predictions of patient compliance correlated with compliance $P > .005$, $P > .01$.

The device appears to be potentially useful in the field of leprosy for measuring the effect of irregular drug ingestion when any medication is being evaluated on an outpatient basis. It could be used to study the factors that lead to poor compliance in an effort to find ways to solve the problem. It could also be used to detect those patients who were poor compliers with self-administered medications in order to give them special attention to improve compliance or to change them to a directly administered medication programme.

IX 310

The treatment of leprosy neuritis

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Antileprosy therapy (sulphones, thiambutosine, Lamprene, rifampicin) does not prevent the development or progress of clinical and electromyographic signs of leprosy neuritis. Correlation of pathological and bacteriological data of autopsy studies on skin branches of tibial and radial nerves with the clinical findings proved that the replacement of the leprosy granuloma by fibrous connective tissue might explain the observed increase of nerve damage in leprosy patients, more often in those with lepromatous leprosy under treatment with antileprosy drugs. These investigations showed that under specific antileprosy therapy, *M. leprae* persisted in peripheral nerves longer than in the skin and the mucosa of the upper respiratory tract. Experimental studies on normal rats and rats infected with Stefansky's bacillus showed that intramuscular solapsone resulted in sufficiently high concentration in nerves. Clinical and immunological data suggested that the allergic mechanism was important in the pathogenesis of leprosy neuritis.

From our experience, combined antileprosy treatment is preferable for neuritis. Nonspecific treatment of leprosy neuritis including analgesics, anti-inflammatory and anti-allergic drugs, tranquillizers, neuroleptics, vitamins, biogenic stimulators, some aminoacids and physiotherapy is also recommended.

Schemes of specific and nonspecific treatment of leprosy neuritis should be related to the actual phase of the neuritis (acute or chronic). We suggested and effectively applied Tegretol as an analgesic, and hydrocortisone for the exacerbation of leprosy neuritis.

IX 311

Comparative assessment of various methods of treatment in leprosy

V. A. EVSTRATOVA V.S. BRAGINA

Leprosy Research Institute, Astrakhan, USSR

Comparative results of monotherapy with sulphones and combined therapy with several drugs, including non-sulphones, are given. During a period of 15 years, 142 hospitalized and 73 relapsed lepromatous patients were treated.

In the assessment of mono- and combined antileprosy therapy in newly hospitalized patients, combined therapy was seen to have a more rapid action. The duration of combined therapy for clinical cure was 45.1 ± 2.4 months,

while that of monotherapy was 65.8 ± 3.5 months.

Relapse due to drug resistance occurred more often in patients who had previously received monotherapy.

IX 312

Suphone-resistant leprosy: a case communication

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Today, sulphone-resistant leprosy is an undeniable phenomenon.

It is occurring with increasing frequency and raises a problem for the whole future of leprosy and for programmes of treatment and control. One of the most solid foundations for leprosy control today is the effectiveness of sulphone therapy. No comparable treatment is able to compete with sulphones because the high cost of alternatives makes them inappropriate for use on a large scale.

The case history of a girl with nodular leprosy is cited. In 1955 she was 9 years old and after 8 years of regular treatment she was found to be sulphone-resistant.

This was discovered when her mother's relatives were examined for the first time. Her mother has been diagnosed as having tuberculoid leprosy. Later on, indeterminate leprosy was diagnosed in 4 of her 7 brothers.

With 3 years of regular sulphone treatment she was cured clinically and bacteriologically; but in 1963 for no apparent reason, new nodules appeared and the bacilloscopy was positive. From then until 1977 the lesions persisted, and histopathological studies showed lepromatous leprosy with the presence of many leprosy bacilli, although treatment had been regular during the 22 years of observation.

From 1966 the patient presented with repeated serious and prolonged episodes of erythema nodosum, which could only be controlled in the last few months by thalidomide.

In 1978 the patient was given rifampicin for the first time and some improvement occurred.

IX 313

Clinical trial of rifampicin in lepromatous leprosy

N. V. BABU

Anandaban Leprosy Hospital, Kathmandu, Nepal

A total of 20 patients (17 lepromatous and 3 borderline-lepromatous) of whom five had previously had treatment with dapsone for many years, were given an introductory treatment with rifampicin at a dose of 750 mg daily for one week, 2 weeks of dapsone 50—100 mg daily, followed by another week of rifampicin in the same dose. Thereafter all the patients were treated with dapsone, except for 2 who were given clofazimine because of a strong suspicion of dapsone resistance.

Clinical and bacteriological assessments were done at the start, and after one week, one month, 3 months and 6 months of treatment. Seven of the patients were followed up for 1 year. Skin biopsies were done on most patients to confirm the diagnosis. Clinical photographs were taken.

The fall in MI was not very rapid, most cases taking 2—3 months to fall to zero; only 7 cases had an MI of under 1% at the end of one month. There was no significant change in the BI of lepromatous cases. All the cases registered very good clinical improvement initially during the first 3—6 months, after which it became rather slower, especially in those who had had previous treatment for long periods. Only 2 patients developed reactions. A few of them regained some sensation over the extremities. In 5 patients there was a fall in the platelet count. No other side-effects were reported.

The advantages of starting therapy with an introductory course of rifampicin are: rapid initial clinical improvement which continues; few reactions; a rapid fall in the morphological index. The drug was found to be very effective in borderline-lepromatous leprosy.

SESSION X
REHABILITATION

Friday, 17 November 1978
9:00-13:00

Auditorium 2

Chairman: **P. Brand (USA)**

Rapporteur: **J. A. Cap (Ethiopia)**

Invited Papers

Abstracts

X/314 Programación de la rehabilitación en lepra.
R. O. Manzi (Argentina)

X/315 Health education.
P. J. Neville (Great Britain)

X/316 The role of surgery in leprosy rehabilitation — a general overview.
N. H. Antia (India)

X/317 La prevención de la incapacidad en un enfermo de lepra.
J. J. Arvelo (Venezuela)

Free Communications

Abstracts

X/318-X/333

REHABILITATION

X 314

Planning the rehabilitation of patients with leprosy

R. O. MANZI

Sanatorio Baldomero Sommer, Argentina

The disabilities due to leprosy are physical, psychological, occupational and social.

The problems in rehabilitation of patients with leprosy are listed. The objectives and programme of rehabilitation are considered as public health measures, integrated or specific. Priorities must be established and the disease dealt with on the basis of technical knowledge and resources available, to be used rationally.

Regional variations are analysed from the points of view of decision making, execution and evaluation.

There are levels of assistance, ranging from the most complex (polyvalent or monovalent) to the simplest or elementary. The latter must form part of the primary care of the patient and are to be carried out by the general practitioner or the public health team. These simple measures include physical, psychological and social approaches and while the quantity of treatment may not be optimal, its range as above will yield advances in primary and secondary prevention.

X 315

Health education

P. J. NEVILLE

The Leprosy Mission, London, England

Health education is widely recognized as one of the essential elements in any leprosy control programme. The author discusses the principles of health education and, in particular, the need to make a "community diagnosis" of the leprosy problem, in order to understand and gain the maximum participation of members of the community.

There are honest doubts amongst medical personnel as to the effectiveness of health education. Methods for assessing the outcome of educational activities and also reasons for failure are suggested.

Health education is presumed to be part of the normal duty of all health personnel. The quality of work done could be improved by better staff training in health education. The author outlines possible course objectives and appropriate teaching/learning situations.

Leprosy control schemes need long-term, sustained health education activities, and the role of the health educator is discussed both in planning programmes and maintaining their momentum.

X 316

The role of surgery in leprosy rehabilitation — a general overview

N. H. ANTIA

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J. J. Group of Hospitals, Bombay, India

A long-term survey of patients who had undergone plastic surgery at the Tata Dept. of Plastic Surgery and the Kondhwa Leprosy Hospital revealed the following interesting findings.

1. The previous social and economic status was the most important single factor in rehabilitation.
2. Half of the cases even with severe deformities were never dehabilitated.
3. Surgery was responsible for social rehabilitation in about 10% of cases and economic rehabilitation in another 10%.
4. Prolonged hospitalization tended to deprive patients of their aptitude for self-support.
5. About a third of the results of hand surgery deteriorated over a period of years. This was not the case with surgery of the feet and face.

While the initial enthusiasm for reconstructive surgery has waned, surgery can still claim a small but well-defined role in rehabilitation in leprosy.

X 317

The prevention of disability in patients with leprosy

J. J. ARVELO
Departamento de Rehabilitacion Medica, Caracas, Venezuela

The problem

Leprosy is also an important neurological disease which gives rise to deformities and which carries a great social stigma. One of the reasons for that stigma is the deformity affecting the face, the hands and the feet. Over the years there has been a public health aspect to the fight against leprosy. More recently there has been the development of rehabilitation. This is of limited scope and there are major obstacles in terms of cost and organization. We must therefore give priority to the prevention of disability, with the advantages of lower cost, easier organization and better cover.

We now have good technical and administrative knowledge. There are highly effective and sensitive methods derived from the social sciences, physiotherapy, occupational therapy and mechanical aids. We also have a practical administrative scheme derived from the principles of Health Planning. Nevertheless, it is necessary to increase technical and operational investigations and to develop so far as possible the fundamentals of prevention.

The training of personnel

It is urgent to improve the training of staff at all levels of the pyramid, defining the objectives and clarifying the methods in training. These must involve auxiliary staff and deal with the deficiencies in educational materials.

In short, we now consider that no programme for fighting against leprosy can be complete if it does not incorporate the area of prevention. This meets the needs of the patient and has a lasting effect, even if long-term in its onset, upon the social stigma.

X 318

Leprosy rehabilitation: a pragmatic approach in a developing country

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Leprosy poses a problem to mankind and it is causing untold miseries probably unparalleled in human history.

Leprosy brings about two kinds of stigma to individual sufferers, one from the disease itself and its neuropathic manifestations, and the other from its social overtones.

By rehabilitation, the patient's family ties are strengthened and self-respect and dignity are restored.

Against this background, the German Leprosy Relief Association launched a scheme with the following objectives:

1. To cater for the needs of disabled leprosy patients;
2. To speed social assimilation in order to abolish stigma;
3. To rehabilitate patients in their home environments through various services designed to suit their needs, capacities and aptitudes.

A scheme operates to give loans to patients to enable them to start some trade or profession. 153 patients and their dependents (numbering 500) have benefited by this scheme. Rs. 1.37.360 has been loaned, and of this Rs. 43.251 has already been paid back within 2 years.

The problems of leprosy are not merely those of the sufferers themselves, but are the concern of the society as a whole, for they constitute a real brake on the socio-economic progress of the entire world.

X 319

Medical and socio-economic rehabilitation of leprosy patients in Cuba

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The New Programme of Leprosy Control in Cuba has among its objectives the notification, registration and classification of leprosy cases, presenting with deformity, their treatment and the medical and socio-economic rehabilitation of the patients.

The classification of deformities was made in accordance with the World Health Organization classification.

Social reintegration of the patients is possible provided motivation is high. This motivation can be achieved by means of perseverance in

educating the patient, or if after treatment he finds productive work which helps him to integrate into society.

Since there is only one antileprosy hospital in the country, having 275 patients, it was decided to set up here different work therapy units undertaking ceramics, tropical fish breeding, rabbit breeding, and farming skills.

From the psychological point of view the patients involved in these activities have recovered the ability to lead an active life, and to exercise the capacity for work, since they feel socially useful.

Since this experiment has proved highly successful among inpatients, it will be extended to ambulatory patients already receiving treatment. They at present receive only social security benefits and are not involved in work activities.

X 320

Social rehabilitation of the patient with leprosy

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Since its foundation in Bogotá in 1951, the Colombian Institute of Social Security has carried out important work in the rehabilitation of patients with leprosy, as summarised below:

1. Out- and inpatient treatment in private clinics especially set up for leprosy patients, the first to use the ideas of R. Chaussinand.
2. Medical and surgical hospitalization in the Clinics of the Institute, from 1965 onwards.
3. Grants for temporary or permanent incapacity, under the same conditions as for other patients.
4. Consultation with ophthalmologists, orthopaedic surgeons and other specialists of the Institute.
5. From 1965 to 1972 outpatient treatment in private practice.
6. From 1973 onwards outpatient treatment in the Central Dispensary of the Institute in Bogotá, under the care of a part-time specialist in leprosy.

Affiliates are retired on the basis of duration of service and of age or for permanent incapacity but they continue to receive medical attention and leprosy supervision. Invalidity from leprosy is classified as partial and compatible with work, or as total. In both cases, in addition to the supervision of the leprosy clinic, the patients come under the Rehabilitation Department of the Institute.

Health education is carried out directly by the leprosy specialist, with the aid of illustrated publications in which the word *leprosy* and its derivatives are avoided.

There is a prophylactic service for the families of patients. It is run by a specialist in leprosy and by a social worker.

X 321

The place and importance of surgery in leprosy within a national programme of leprosy control

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This subject concerns all countries affected by the leprosy endemic. Thanks to Dr Depinay, who was Head of a large sector of Endemic Disease Control in Mali, we have been able to carry out a precise enquiry, which has enabled us to evaluate the percentage of patients requiring surgery in relation to the total number of patients treated.

X 322

Disabilities, displacement and the role of reconstructive surgery in leprosy

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This paper is based on a disability survey conducted among 1368 leprosy outpatients of Bisidimo Centre, Ethiopia. The project was sponsored by the Germany Leprosy Relief Association. The WHO disability grading system was used for the survey. The results are tabulated according to sex, age, classification and occupation.

Disabilities: Out of 1368 patients, 940 had disabilities which included WHO Grade I (68.7%). The largest age-group with disabilities is the 20 to 40 years age-group. There is no appreciable difference in number of disabled among tuberculoid and lepromatous groups.

Displacement from job and home, leading to patients becoming beggars and adult dependents, is highest in the group with Grade II or III

disabilities. In the group without disabilities the percentage of beggars is 6.1% whereas in the group with Grade II or III disabilities, the percentage of beggars is 29%. The greater the disability, the greater the chances of displacement.

Role of reconstructive surgery. In view of the above findings, it is argued that surgery, if made available at the right time, should help in the prevention of displacement and reduce the need for rehabilitation. In the final analysis, prevention of displacement through reconstructive surgery is more economical and beneficial to patients than the rehabilitation of displaced patients.

X 323

Twenty years of surgery at the Institut Marchoux at Bamako

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In the course of the past 20 years, 2817 surgical operations have been carried out on leprosy patients at the Institute at Bamako.

These comprised: amputations 625; skin plastic operations 326; operations on the tibial nerve and plantar nerve 630; treatment for the prevention of relapse of plantar ulcers 145. Palliative operations 1091, of which 574 were for claw hand.

The choice of operation is determined by the metacarpo-phalangeal stabilization test. Most of the standard operative procedures were used (Bunnel, Littler, Fowler, Riordan, Brand, Zancolli, Srinivasan). The surgical procedures favoured were: for *mobile fingers,* shortening of the metacarpo-phalangeal capsule with advancing of the pulley of the flexor tendons; or perhaps the operation of Giraudeau, with the long palmar tendon (Flexor carpi radialis), and rarely the operations of Littler or Brand. *For fixed fingers*, the operation of Bunnel, employing the two sublimis tendons.

Failure of opposition of thumb — 150.

Present emphasis is as follows: shortening of the metacarpo-phangeal capsule with advancing of the pulley of the long flexor tendon of the thumb, if the same technique is practised on the four remaining fingers.

—transplantation of a fifth tendinous tongue on the adductor of the thumb in the cases where the techniques of Brand or Giraudeau are used.

—transplantation of the distal half of the long flexor of the thumb onto the long extensor if the transplantation of a superficial flexor on the forefingers has been used.

—interphalangeal arthrodesis if the clawing is stiff.

Paralysis of opposition of the thumb — 197. Many techniques have been used (Bunnel, Steindler, Ney, Thompson, Brand, Zancolli, Phallen and Miller, Chouhy, Aguire, Burkhalter, Gosset). The usual technique has been a variation of Thompson's operation.

Verus equinus foot — 170. Either the operation of Carayon or that of Giraudeau was employed.

X 324

Neuropathic foot in leprosy

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The study sets out the findings acquired from 1975 to the present day, in the solution, prognosis and treatment of lesions present in the leprous foot.

Follow-up of patients was made only of those examined during 1971 and followed up until 1977. Immediately apparent is the incongruity between the treatment of Hansen's disease and the appearance of the sequelae produced by neurological, vascular and skin deficiences. In short, the patient is cured of Hansen's disease, succumbs to the secondary sequelae, is cured of these and then is socially unacceptable.

The results of treating 112 patients are evaluated. In 71 cases surgery was carried out. Surgery for Hansen's disease is recommended only when carried out by specialists highly qualified to do this. The need to prevent sequelae is emphasised, together with conservative and atraumatic use of surgery, which can only be achieved through teamwork.

X 325

The protection of anaesthetic limbs of patients living in rural areas in developing countries

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The purpose of this paper is to emphasize that the application of neem oil (*Aladirachta indica*) to the extremities will prevent bites from rats,

ants and other insects among leprosy patients, especially those who live in underdeveloped countries with few facilities.

Before beginning our study, we made an analysis of this oil at the Christian Medical College and Hospital, Vellore, and the findings will be presented.

Since neem oil complied with the standards given in the Indian Pharmacopoeia — 2nd Edition, it can be used for medicinal purposes.

The study also records a simple method of giving patients packets of sterilized dressing which include Mag. sulph. and glycerine gauze pieces, cotton balls and dispensable bamboo forceps. The patient is taught how to clean ulcers with saline and apply the dressing over the wound. This helps the patient considerably, avoiding the need to walk long distances to the nearest clinic, particularly in a village situation. It also leaves the doctor free to attend to such conditions as infected ulcers, enlarged glands and raised temperature.

X 326

A method for standardizing physiotherapy assessments

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A method of standardizing the assessment of sensation, muscle strength, range of motion and deformities is described using carefully pre-arranged and pre-typed questions, instructions and answers on two separate index card systems — one for instructions and questions and one for answers. Each card gives specific instructions and/or asks a specific question which requires a specific answer. The answer that is selected determines the path for further questioning or investigations. The greater the deviation from normal, the greater the number of questions. Each answer has a numerical value, and also gives specific instructions on how to proceed further. Each number represents a specific answer which is pre-typed on a separate answer index file. The assessor simply compiles a list of numbers corresponding to the answers selected. This list is then translated (usually by a secretary) into sentence answers by referring to the appropriate numbers in the answer index file.

Advantages of this method are:

1. standard assessment techniques;
2. no chance to omit required information;
3. helps to compensate for less skilled assessors;
4. format is easily adjustable to provide more simple or more complex information as desired;
5. writing of final report can be done by clerical staff;
6. can be computerized.

X 327

Hand lesions in Hansen's disease

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A number of patients diagnosed as having Hansen's disease in different forms was studied at the outpatients' department of the Hospital Juarez de la SSA y Zoquiapan.

They are chronic patients, already studied, under special treatment by leprosy doctors and trained personnel (mainly nurses).

The present study aims firstly to show the hand lesions that the patients develop during the illness; secondly, depending on the severity of the lesion, to devise reconstructive and plastic surgery to improve hand functioning.

The study is based on comparative clinical observation (physical examination) of the hands, with the help of laboratory and research library facilities: oblique X-ray examination of the hand and A.P. electromyography were performed.

For each patient an analysis of hand function (skin function, muscles, tendons, etc.) and a clinical photograph was taken. Observations, results, conclusions and comments.

Parameters to follow: *Hand*: dorsal and palmar surface. hand function, skin (surface, fat, etc.), blood supply, nails, nerves, muscles, tendons, bones and joints, electromyography. *Other parameters*: sex, age, place of residence, origin, development, sickness in the family, related histories of illness (diabetes, neoplasms).

X 328

Compression neuropathy of the radial nerve in leprosy

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A series of 203 cases of acute neuropathy observed in a group of 431 leprosy patients attending an Orthopaedic Clinic in a Leprosy Service during a period of 3 years and 8 months is reviewed, with special reference to the topography and clinical features of 19 cases of acute radial neuropathy.

The main etiological factor responsible for this syndrome was identified as an extrinsic compression of the nerve in the supinator tunnel of the proximal third of the forearm, the anatomy of which is discussed.

The physiopathology of the disease process is analysed and a therapeutic approach according to the different stages of its natural history is proposed, including a discussion of the surgical technique for radial nerve release in cases not responding to conservative treatment.

X 329

Surgical treatment of ulnar nerve paralysis in leprosy

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99 consecutive ulnar nerves associated with varying grades of paralysis due to leprosy were treated by nerve surgery together with routine medical treatment. The selection was according to predetermined criteria, including paralysis of up to one year's duration, and inadequate relief of signs of nerve compression and of paralysis with medical treatment including Prednisolone. Adequate data and follow-up were available in respect of 64 operated nerves in 58 patients. Findings from these are analysed in detail, results assessed objectively during the follow-up period of 1 to 7 years, and associations worked out between the clinical and operative findings, treatment and the results. These findings are presented and discussed in this paper.

The overall results were: improvement in 32, no further nerve damage in 11, and worsening in 6, while 15 nerves with severe pre-operative nerve paralysis showed no recovery. The recovery shown at 1 year was maintained or improved consistently with time in the majority of cases. Out of 10 nerve abscesses, 3 showed recovery and 2 no further damage. The lepromatous cases showed better overall nerve recovery than those on the tuberculoid side of the spectrum. The shorter the duration of the pre-operative paralysis, the better was the result. Worsening of nerve function postoperatively was mainly associated with ENL episodes.

X 330

Decompression in leprosy neuritis as a therapeutic and preventive measure

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Leprosy cripples millions of people, mostly in Afro-Asian countries. Its stigmata are seen on face, hands and feet. The deformities of hand (the claw hand) and feet (foot drop) and late Charcot-like destruction of the tarsus with absorption of digits handicap a person physically, psychologically, economically and socially.

The surgery of leprosy deformities and rehabilitation of the patients consistute a great challenge.

Neuritis is a very common manifestation of leprosy which produces many lesions, from an anaesthetic patch to gross deformities. If the neuritis can be tackled by medical or surgical means, much stigma hampering vocational and social rehabilitation can be prevented.

A simple operation by the author reported in 1964 to decompress effectively the portion of the nerve by longitudinal incision, without removing the sheath and disturbing its blood supply, done within 2—3 years of the onset of this deforming disease, has both a preventive and therapeutic aspect and will thus save many problems in rehabilitation.

Compression by external fibrous bands as at the elbow, wrist, and ankle may also be relieved.

The follow-up as regards sensation and muscle power recovery will be reported.

X 331

Adaptation of decompression methods to the clinical form of neuritis

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Treatment of neuritis in leprosy is as follows:

Chemotherapy of *M. leprae* by itself is uncertain and may lead to aggravation of the condition

(rifampicin for L or BT neuritis, DDS controversial). Clofazimine is preferable, combined with another anti-inflammatory agent in reactive neuritis.

The *steroids* are effective in the two types of reactive neuritis, thalidomide only in ENL neuritis but with less certainty than upon the nodes and the systemic features.

Neurosurgery has two objectives:

Haemodynamic decompression aims to relieve circulatory obstruction and stagnation and to allow the drugs to reach the area.

Decompression of nerves depends upon the type of neuritis present:

To be avoided in BT microangiopathic neuritis, conservative neurolysis in LL and ENL forms (in case of failure of medical treatment).

Intrafascicular neurolysis in the BT forms, resistant to medical treatment.

Neurolysis with stripping of sheath and fasciculotomy in advanced BL neuritis.

X 332

Nerve surgery in leprosy

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Nerve damage is in leprosy the major cause of disabilities. Prevention and treatment are therefore of utmost importance. Medical treatment is often sufficient, but some nerves deteriorate even under theoretically adequate medical treatment. Many surgeons claim success from nerve release operations; however their results do not convince the majority of leprologists. Therefore we investigated the merits of nerve release using the previously described objective method for assessing nerve function, the "nerve deficit index".

We compared operated with non-operated nerves in the same patient; medical treatment was continued. Surgical treatment was considered to be an addition.

Our assessment showed that careful surgery did not cause any further nerve damage but, on the contrary, reversed the damage. Indications for nerve release and methods to perform these relatively simple procedures will be discussed.

X 333

Neuropathy in leprosy: results of surgical treatment

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The results of operations carried out by different surgeons, using various techniques in different conditions and at different times have been analysed. The treatment was at a specialist hospital. There were 150 operations and a comparison was made with a similar group of patients selected randomly and not treated surgically.

The results were assessed with respect to pain and to physical signs: muscular power, weakness, paralysis and wasting.

The most significant finding was the relief of pain in cases of nerve compression.