PONTIFICIAE ACADEMIAE SCIENTIARVM SCRIPTA VARIA

72

WORKING GROUP

ON

IMMUNOLOGY, EPIDEMIOLOGY AND SOCIAL ASPECTS OF LEPROSY

May 28 – June 1, 1984

EDITED BY

CARLOS CHAGAS

PONTIFICIA
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SCIENTIARVM

EX AEDIBUS ACADEMICIS IN CIVITATE VATICANA

MCMLXXXVIII

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Casina Pio IV

INDEX

SCIENTIFIC PAPERS

FOREWORD

The Pontifical Academy of Sciences, in organizing a Working Group on leprosy, has complied with one of its objectives, i.e., to render more visible some of the dire human sufferings which need a scientific, cultural and compassionate approach.

While discussing with some friends from different countries, social levels and professions, I was surprised to see that they thought that leprosy was no longer a real danger. Of those conversations I will always remember the vivid impression I had when, during my stay in the hinterlands of my country, I visited the isolated huts where, thrown out of the rather poor society of the village, the leprosy-infected human beings lived. My companions were surprised that I could stay with them and take the coffee cups they offered me, not knowing the great effort I had to make to be with them.

In 1980 I visited the leprosy colony of Marituba, during the visit His Holiness John Paul II made to Brazil. More than a thousand patients were there, some cured, some disfigured, some without a trace of infirmity, but in all of their faces, hardened by their suffering, the brightness of hope appeared in their eyes when they heard the comforting words of John Paul II. Talking with some of them I understood what it means in loss of dignity to be marginalized by your brethren.

These talks in Marituba led me to reflect on the neglect by public health authorities of many countries of the disease produced by M. leprae. *Maybe this neglect, I thought, was due to the relatively scarce number of patients, afflicted with other infectious diseases, whose number would call for a great economic effort. But the human element in that case cannot be neglected. Only those who have been in touch with a leprosy patient or have seen the dramatic effects the appearance of a case in a family produces, can judge the human element it involves. My thoughts became still more poignant when in writing recently the biography of my father I remembered his dedication to this problem at the end of his life (1934), when he tried to establish a center at the Oswaldo Cruz Institute for new therapeutic agents against Hansen's disease.*

The new perspectives opened by the use of the armadillo as a model for the disease and the new approaches to the immunology and therapeutics of leprosy, together with the need to obtain an overview of the integration of a cured patient into society, showed me the need to organize the Working Group, whose information report is now published.

The meeting could not have been held were it not for the authoritative way in which Professors Barry Bloom and Jacinto Convit organized it. I am profoundly grateful for what they did for the Pontifical Academy of Sciences.

This volume of the Scripta Varia is published with a rather long delay. It took me a long time to decide on its publication. It was the fact that the incidence of leprosy is increasing in the Third World, even if in a mild way, which made me feel that the discussions held at the Academy can bring fruitful advice to governments and public health authorities, clinicians and sociologists involved in this very dramatic health problem..

I want to extend my gratitude to all those who have left their laboratories and their countries to spend in Rome five days of hard work. I believe that the words of His Holiness John Paul II in the address to the Participants of our Working Group showed his interest in the subject and his gratitude for the effort the Participants have undertaken to achieve our objective.

Finally, I wish to express my thanks to Father Enrico di Rovasenda, Chancellor of the Academy, to Mrs. Michelle Porcelli-Studer, Mrs. Gilda Massa and Mr. Silvio Devoto, whose solicitude and zeal make our meetings a pleasant activity.

CARLOS CHAGAS

President of the Pontifical Academy of Sciences

LIST OF PARTICIPANTS

LYGIA M.C. ANDRADE, Fundaçao Oswaldo Cruz, Laboratorio de Hanseniase, Av. Brasil, 4365 Manguinhos, CEP 21040 Rio de Janeiro, Brazil.

OTTO BIER, Rua Dona Veridiana, 220/apto. 71, Santa Cecilia, CEP 01238 Sao Paulo, Brazil.

BARRY BLOOM, Dept. of Microbiology and Immunology, Albert Einstein College of Medicine, Yeshiva University, 1300 Morris Park Avenue, Bronx, N. Y. 10461, USA.

JACINTO CONVIT, Director, Instituto Nacional de Dermatología, San Nicolás a Providencia, San José, Apartado de Correos 4043, Caracas, Venezuela.

TORE GODAL, Laboratory for Immunology, The Norwegian Radium Hospital, Montebello, Oslo 3, Norway.

MICHEL F. LECHAT Université Catholique de Louvain, Ecole de Santé Publique, Epidémiologie - UCL 30.34, Clos Chapelle aux Champs 30, 1200 Bruxelles, Belgique.

NELSON F. MENDES, Depto. de Microbiologia, Immunologia e Parasitologia, Escola Paulista de Medicina, Caixa Postal 20300, Ag. Vila Clementino, Sao Paulo, Brazil.

WAYNE M. MEYERS, Chief, Division of Microbiology, Armed Forces Institute of Pathology, Washington, D.C. 20306, USA.

R.K. MUTATKAR, Department of Anthropology, University of Poona, Pune 411007, India.

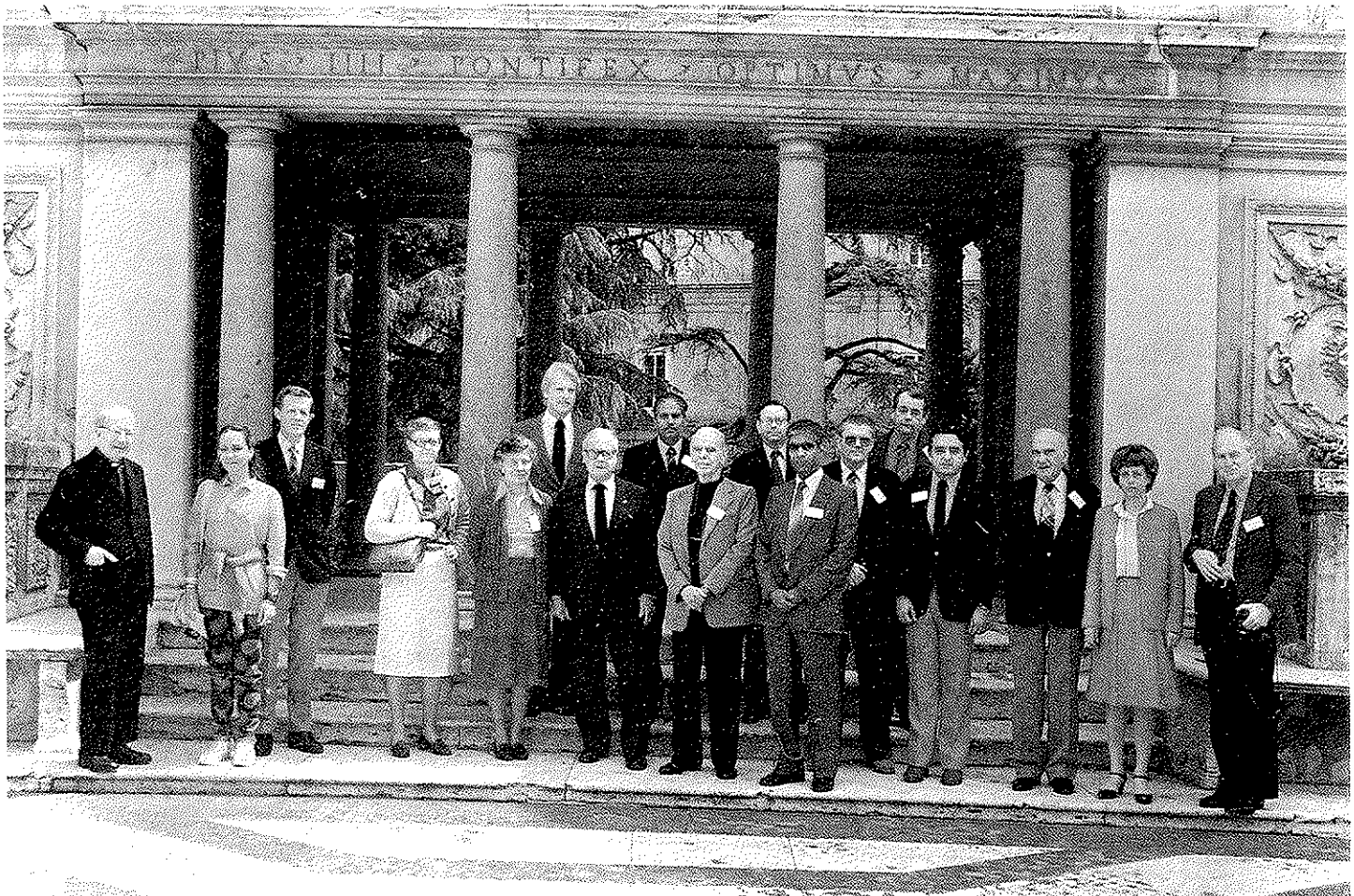
S.K. NOORDEEN, Secretary, IMMLEP & THELEP Steering Committee, World Health Organization, 1211 Geneva 27, Switzerland.

F.E. RABELLO, rua Senador Vergueiro 14/301, Rio de Janeiro, Brazil. (Professor RABELLO was unable to attend, but his paper appears on page 31.)

MARIAN ULRICH, Instituto Nacional de Dermatología, Apartado 4043, Caracas, Venezuela.

G.P. WALSH, Chief, Experimental Mycobacteriology, American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D.C. 20306, USA.

RICHARD YOUNG, Department of Biochemistry, Stanford University Medical Center, Stanford, California 94305, USA.



Participants in the Working Group

AUDIENCE OF THE HOLY FATHER

The participants in the Working Group on the theme "Immunology, Epidemiology and Social Aspects of Leprosy", accompained by the President of the Academy, His Excellency Professor Carlos Chagas, and by the then Director of the Chancellery, Rev. Father Enrico di Rovasenda, were received by His Holiness John Paul II on June 1st, 1984.

At the beginning of the Papal Audience Professor Chagas delivered the following address:

Your Holiness,

When you so greatly honoured me by your invitation to join you during your visit to Brazil, I never thought that I would attend a spectacular event where such joy, gratitude, happiness and emotion were present in the face of the 22 millions of Brazilians who saw you.

Even in the eyes of those whom a badly conceived socio-economic policy has thrown into poverty, one could perceive hope and thankfulness.

However, no emotion has been greater than the one experienced by all of us during your visit to the Leper Colony of Marituba near Belem. More than 1500 patients of all kinds had assembled to meet you. Among the patients one could see many nuns, priests and lay missionaries. After your homily a patient in a wheelchair was brought to you. He was affected by that type of leprosy which has haunted humanity for centuries: his face was completely disfigured and his hands were both without fingers. After reading a speech from a sheet of paper held by charitable hands, he offered you an envelope. It contained a collection gathered among the lepers of Marituba. In giving it to you he asked that it should be used for the benefit of others more needy than himself and his companions. Tears filled my eyes, as I learned in that very instant, as never before, how generous a human being can be.

My knowledge of the subject the Study Group has discussed is far from being that of a specialist, but my interest is very great and common to all those who cannot avoid thinking about human suffering and believe that scientific research can improve the quality of life and help to restore human dignity.

Permit me, Holy Father, to affirm at this point, that not enough effort has been made to increase and accelerate the basic research necessary to ensure a full combat against leprosy. It may be that this is due to the false assumption that leprosy is a disappearing pestilence; it may also be that leprosy placed in an economic perspective should not receive a high priority. How anti-human this concept would be! But I wish to praise with all my heart those who have given resources and made benevolent efforts to obtain hospitalisation of lepers and to improve their treatment. Their efforts are paralysed because progress can be achieved only when more research and development are undertaken.

Let me, Holy Father, praise again the men and women, who as religious or as lay persons, missionaries, doctors or nurses, have devoted their lives to help lepers. They are an example for a world where unselfishness and munificence are lacking.

Your Holines, it is for me a great honour and joy to present to you the members of the Working Group the Pontifical Academy of Sciences has assembled for the study of "Immunology, Epidemiology and Social Aspects of Leprosy".

All of its members have devoted their lives to the study of leprosy, working for years in the field, in tents or barracks, in hospitals, in laboratories, being thus directly involved in one of the most dignifying tasks a human being can undertake. They are the Samaritans of our present world. The participants of the Study Group have contributed to the opening of a new era in the treatment and prevention of leprosy. They are using for this new endeavour in science the armadillo, which rather recently has been shown to be able to simulate the major aspects of this human disease and may be found in nature harbouring the Mycobacterium Leprae. *This is a real breakthrough in the study of leprosy. The experimental model will allow a wider application of the new knowledge and techniques developed by modern immunology and reinforce the scrutiny of the defence mechanisms against the invasion of Hansen's bacillus or of the failure of the same system.*

This immunological knowledge will also permit the obtaining of more precise methods of diagnosis with particular reference to the very early stages of the infection. It will also allow for great improvements in the therapeutic approaches used up to now or suggest new ones, and in times which I am convinced are not far away, the immunological methods will lead up to a vaccine. It is my belief, Your Holiness, that it may be possible to eradicate leprosy from our world before the middle of the coming century. But in order to obtain this, Holy Father, governments, international organizations, industries, philanthropic institutions and wealthy women and men must strongly increase their support of basic studies, fundamental research and field work in leprosy. It is also necessary

that those who suffer from this disease should know that the upgrading of the quality of their life is a constant concern of many doctors, nurses, scientists, nuns, priests, missionaries and men and women of good will. But society must also become aware that leprosy is not a divine chastisement and must understand that lepers are human beings, our brothers in God, and that it is our obligation to integrate this abandoned flock into the realm of our lives so that it will be able to love, smile and enjoy the gifts of friendship.

Your Holiness, no voice in the world has your authority to herald this appeal. All of those who have participated in this extraordinary Working Group humbly ask you to do it. Your appeal will change the destiny of millions of people who suffer and need the comfort of your blessings.

The Holy Father answered with the following Discourse:

Mr. President, Ladies and Gentlemen:

1. *Today's meeting is a source of deep interest for me, as the theme which you are studying during these days recalls to my heart, no less than to yours, the terrible sufferings of a large number of our brothers and sisters, those who are afflicted by the dreaded disease of leprosy, and especially those in whom it has caused irreversible loss of limbs.* My interest *is matched by my* sincere administration *for the careful and untiring researches which you conduct for the purpose of fighting this illness and saving many human lives.*

At this moment my thoughts go to various meetings which Jesus had with lepers. I wish to quote from just one, as told by Saint Mark in the first chapter of his Gospel. The sacred text reads: "And a leper came to Him beseeching Him, and kneeling said to Him: 'If You will, You can make me clean'". At this request Jesus "stretched out His hand and touched him, and said to him: 'I will; be clean'. And immediately the leprosy left him, and he was made clean" (Mk 1:40-42).

By touching the leper's sores with His hand, Jesus knocked down the barrier *separating the untouchables from the human community, and by this miraculous cure He opened a path of hope that religion and science have to follow. Neither for the one nor for the other can any person henceforth be called unclean, but every individual will have to be respected and helped to regain the good health worthy of the human person.*

2. *The sense of universal brotherhood proclaimed by the Gospel evoked from followers of every faith a* generous eagerness to assist sufferers from leprosy, *and leper colonies and hospitals were set up in every part of the world. In every place there was a widespread movement to provide voluntary aid, an*

"unexpected gift of private mercy" on the part of those who, "strong in courage... moved by pity, took upon themselves and virtuously maintained the care to which they were not called by their duties", as happened during the plague in Milan described by Alessandro Manzoni in his famous novel I Promessi Sposi (Chapter 32).

Among the apostles of the lepers who appeared among the Christian missionaries, both Catholic and Protestant, I cannot fail to mention Father Damien De Veuster *of the Picpus Fathers, who has been honoured throughout the world as the most generous example of Christian charity towards lepers. Together with him I wish also to mention among the lay apostles Marcello Candia, who made a total gift of himself and his resources to the sufferers from this disease.*

However, the care given by generous volunteers, and the institutions subsequently set up by governments, could not have been effective on the health-care level had not science offered and provided means and methods of diagnosis and therapy.

3. *As in every other field, so in the sphere of the treatment of the widely differing forms of disease, feelings of brotherhood and* scientific research *link hands in order to rescue humanity from its needs and afflictions. The help of charitable volunteers and the scientist's work both call for powerful spiritual energies. Scientific research is not only a magnificent use of the mind; in the words of my predecessor Paul VI in a speech to the Pontifical Academy of Sciences, it also demands "the exercise of lofty moral virtues, which confer upon the scientist the aspect and merit of an ascetic, sometimes of a hero, to whom humanity must pay a great tribute of praise and gratitude"* (Discourse of 23 April 1966).

Eminent moral virtues and the assistance of the Spirit *are needed by the scientist who not only devotes himself to research but also wishes to exercise the charity of knowledge. When reason, tired and perhaps disillusioned in the efforts of study, seems to give in to the temptation of abandoning its undertaking, the Spirit comes to the aid of those who wish heroically to persist in the efforts they are making for love of neighbour, and at the highest point of the mind it lights a spark that brings a sudden intuition of the truth, whence research resumes its path and reaches the longed-for discovery.*

4. *Ladies and Gentlemen, you are following the path traced out by Gerhard Hansen, who through the perseverance of reason and the spark of the Spirit discovered the cause of leprosy:* Mycobacterium leprae. *Through your enlightened scientific work, in harmonious collaboration with wise doctors and*

generous volunteers, and through the farsightedness of governmental and private institutions, leprosy has diminished in many parts of the world. But there are still millions of our brothers and sisters *who suffer its terrible consequences. For the sake of these people efforts must be everywhere increased to ensure that those who are still condemned to a sort of civil death* can rediscover life, *improve its quality, and find in society a place corresponding to their human dignity, for like all other people they are made in the image and likeness of God. There is no reason at all why those have been cured should not be fully reintegrated into society.*

Mr. President, in your address you have rightly stated that science when directed towards peaceful purposes can lessen the world's ills, improve the human condition, and help to raise the quality of life, especially of those who are humblest and the most neglected among human beings.

5. I therefore call upon governments, international institutions and philanthropical associations *to make increasing contributions to the work being done by research scientists, doctors and volunteers in order to free leprosy patients from their sickness and from their humiliating and tragic rejection by society.*

Mr. President, you mentioned my apostolic pilgrimage to Brazil and in particular my visit, accompained by yourself, to the leprosarium at Marituba. There, and also, more recently in Korea, I have had the opportunity to express my solidarity personally with those who suffer and to assure them of the love and concern of the universal Church.

Ladies and Gentlemen, continue your research and your therapy, and be assured that the Church fully supports your work, for like you she has received Christ's command, written in the Gospel, to "heal the lepers", and she knows that lepers who have been cured are a sign of the Kingdom of God (cf. Mt 10:8; 11:5). *Help to build up the Kingdom of God, which is also the kingdom of humanity. Be dispensers of justice and love to all those who, in the most desolate corners of the world, are waiting to receive* a message of hope *from today's society.*

May God bless you and your research in the service of His people.

SCIENTIFIC PAPERS

The opinions expressed with absolute freedom during the presentation of the papers and in the subsequent discussion by the participants of the Working Group — although published by the Academy — represent the points of view of the participants and not necessarily those of the Academy.

RECOMBINANT DNA AND FUTURE VACCINES

RICHARD A. YOUNG
Department of Biochemistry
Stanford University School of Medicine
Stanford, California 94305, U.S.A.

INTRODUCTION

New advances in recombinant DNA technology have provided powerful tools for basic and applied research in human health problems. Two components of vaccine research can benefit significantly from current recombinant DNA technology: the identification and isolation of genes which specify antigens potentially relevant to immunity, and the large-scale production of the antigen in relatively pure form. Genes that encode antigens of interest can be isolated by using antibodies to identify the products of individual foreign genes in *E. coli* host cells. Thus, using this technology, genes which specify parasite antigens can be simultaneously identified and isolated by using antibodies from patients afflicted with the parasite. The isolated genes of interest can be expressed in procaryotic or eucaryotic hosts to produce (hopefully) large amounts of antigen, which can be used for research, diagnostic or vaccine purposes. This manuscript briefly reviews recent advances and current limitations in the use of recombinant DNA in vaccine research.

RECOMBINANT DNA STRATEGY FOR SURVEYING PARASITE ANTIGENS

A means to survey the protein components of a pathogen for potential immunogens would be a useful prerequisite to selecting a polypeptide vaccine candidate for further study. Recombinant DNA technology offers an effective strategy to thoroughly examine the

antigens encoded in a pathogen genome when antibodies are available for use as probes [1, 2]. Part of the power of this approach lies in the potential to express all possible coding sequences in the genome of interest, even those which may not always be expressed *in vivo*. Moreover, inherent in this recombinant DNA methodology is the ability to simultaneously identify immunogens — in this case, antigens against which humans have mounted a humoral antibody response — and clonally isolate the DNA which specifies the polypeptide.

The antigen coding capacity of a pathogen genome can be systematically examined by using a recombinant DNA expression library. In principle, fragments of the pathogen genome are expressed under the control of procaryotic gene signals located in the vector; sufficient numbers of these recombinant molecules should exist in a library to represent redundantly the pathogen genome. To construct such a library, DNA is mechanically sheared to produce random endpoints, and these DNA fragments are inserted into the expression vector λgtll. Sufficiently large numbers of recombinants are produced to obtain inserted DNA endpoints at each base pair within each gene in the pathogen genome. Antigens produced by the recombinant λ phage plaques are screened, using serum or monoclonal antibody probes, as shown in Figure 1. The complete library, and thus all antigen coding sequences, can be examined in a single experiment (10^6 recombinants can be probed in a single experiment). Recombinants identified by the antibody of interest can be clonally isolated.

Requirements for a recombinant DNA expression system

A systematic examination of foreign polypeptide antigens in *E. coli* is possible if the factors which influence production of detectable levels of each of many different kinds of proteins are adequately considered. There are three major problems associated with obtaining expression of foreign DNA as a stable antigen. The first problem is that most foreign DNA does not contain the transcription control signals required for expression in *E. coli*. Thus, the foreign gene must be placed under the control of an *E. coli* promoter that is efficiently recognized by *E. coli* RNA polymerase.

The second and probably most serious problem is that unusual polypeptides are efficiently recognized and degraded in *E. coli* [3-6]. The severity of the problem differs with each antigen; some foreign proteins are quite stable, some appear highly unstable. While the

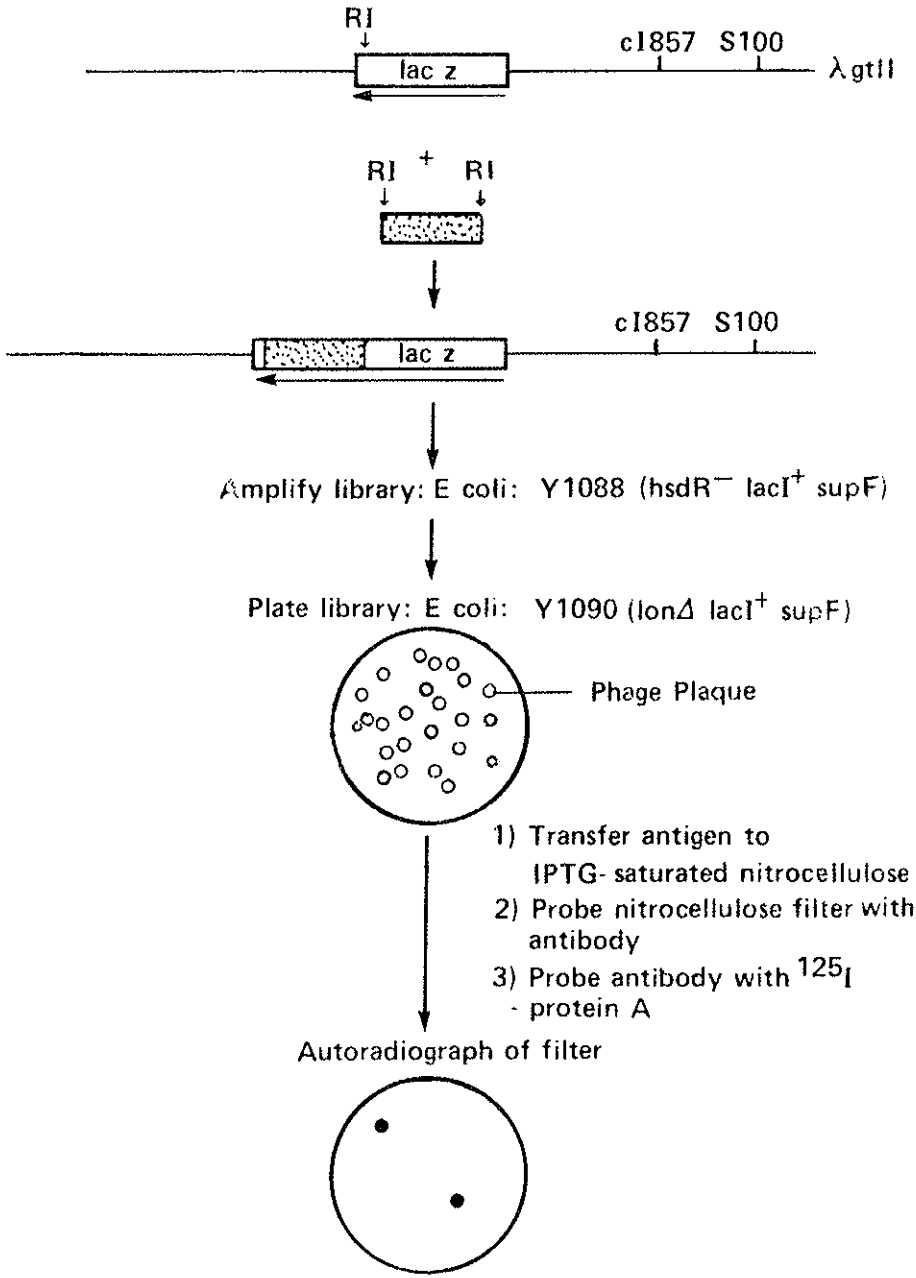

RI
lac z
cI857 S100
λgtII
RI + RI
cI857 S100
lac z
Amplify library: E coli: Y1088 (hsdR⁻ lacI⁺ supF)
Plate library: E coli: Y1090 (lonΔ lacI⁺ supF)
Phage Plaque
1) Transfer antigen to IPTG- saturated nitrocellulose
2) Probe nitrocellulose filter with antibody
3) Probe antibody with 125I - protein A
Autoradiograph of filter

FIG. 1

problem of antigen instability is rarely addressed directly in the literature, the difficulty in accumulating foreign proteins is revealed by the techniques used to detect the polypeptide. Thus, enzymatic activity or immunoprecipitation of pulse-labeled proteins are commonly used approaches [4-6].

The instability of foreign antigens can be reduced in most cases by fusing the antigen to a stable host protein and by using host mutants deficient in proteolysis [1]. Fusion of unstable foreign antigens to the carboxy-terminus of the stable *E. coli* protein β-galactosidase has been shown to enhance the stability of some foreign proteins [1, 6, 7]. More importantly, the stability of the fusion product of β-galactosidase and eucaryotic antigen can be markedly increased (>100-fold in some cases) in *lon* mutants of *E. coli*. *lon* mutant strains are deficient in one of the ATP-dependent proteases which are responsible for the destruction of abnormal proteins [3]. This particular protease deficiency is especially useful since the presence of the mutation does not appear to alter the normal growth properties of the cell and because the *lon* protease appears to have some specificity for the class of abnormal polypeptides of which β-galactosidase fusions are a member [1].

The third major problem with foreign antigen synthesis in *E. coli* is that the presence of these unusual proteins is often harmful or even lethal to the cell. Demanding high levels of gene expression can compound this problem, since constitutive high level expression of even normal components of the cell can often be lethal [8]. A suitable solution to this problem has been to ensure that expression of the foreign antigen is transient. Thus, the expression of the DNA encoding the foreign protein is repressed during early log-phase growth of the host cell culture. Near the end of this period, when the transcriptional and translational apparatus are still fully active, the expression of the foreign protein is induced, and satisfactory levels of the antigen are produced before cells become unviable.

These concepts, designed to improve the levels to which foreign antigens can accumulate in *E. coli*, have been incorporated into the λgtll expression vector-host system [1]. The λ phage expression vector was constructed to permit insertion of foreign DNA into the β-galactosidase structural gene *lac* Z under the control of the *lac* operator. The recombinant DNA can be propagated lytically or lysogenically (efficient lysogeny is obtained with *hfl*A [high frequency lysogeny] mutant hosts). In either case, expression of the foreign DNA is

repressed by the presence of the *lac*I gene product. Production of the foreign antigen fused to β-galactosidase can be rapidly induced by the addition of isopropyl-β-D-thiogalactoside (IPTG) to the culture medium. The presence of the *lon* mutation permits accumulation of otherwise unstable novel proteins to levels which facilitate detection by immunological or physical (i.e., polyacrylamide gel) analysis. Figure 1 outlines the experimental scheme which we have used to isolate eucaryotic DNA sequences which specify antigens of interest [1, 2]. Details of the procedure can be found in reference 2.

Surveying Mycobacterium tuberculosis *Antigens*

The λgtll expression system is being used to investigate specific antigens encoded by *M. tuberculosis*. *M. tuberculosis* DNA (isolated by Grosskinsky and Bloom from Erdman strain, TMC § 107) was sheared to generate random endpoints and was inserted into λgtll to produce an expression library of 10^7 unique recombinant phage. *M. tuberculosis* DNA insert lengths ranged from 2.5 to 8.5 kb with an average length of approximately 4 kb. The number of recombinant phage in this library exceeds the number of base pairs in the pathogen's genome by approximately 3-fold; it is, therefore, highly likely that the library has the capacity to express all *M. tuberculosis* DNA in both orientations and in all three translation frames.

Attention is now being directed to two questions: Can clones be isolated which express antigens that are bound by monoclonal antibodies with unique specificity to *M. tuberculosis* proteins? Against what protein antigens do humans produce serum antibodies when they successfully mount a protective immune response? Experiments which address the latter question may provide antigens which are useful vaccine candidates not only because they are immunogens, but also because the DNA which encodes them is identified and can be isolated directly.

Limitations to a Recombinant DNA Survey of Subunit Vaccine Candidates

The λgtll expression system provides a means to thoroughly and efficiently survey the potential immunogens of particular pathogens. The method, however, is designed to detect protein antigens which lie within a contiguous polypeptide chain. It obviously cannot be used to identify nonprotein components which might contribute to a

protective vaccine. Moreover, antigenic sites which are created through intermolecular interactions are excluded from such a survey using recombinant DNA technology. The importance of this latter consideration is unclear since the contribution of this type of antigen to an organism's immunogenicity is as yet unknown.

Large Scale Production of Foreign (Parasite) Gene Products

Many different gene products have been produced in foreign hosts through the use of recombinant DNA expression vectors. The successful production of foreign proteins is dependent upon overcoming the same problems encountered in the system discussed above for the expression and isolation of recombinant DNA clones. However, while these are general problems, their solutions are best recognized on a case by case basis; what works for the production of good yields of one foreign product may not work well for another.

Variations in the level of accumulated foreign protein can occur if (1) foreign DNA sequences interfere with efficient transcription or translation, (2) the mRNA is unstable (as is often the case if it is poorly translated), (3) the polypeptide product is rapidly proteolyzed and/or (4) the product is toxic to host cells. Some of these problems have been understood for some time, others have been recognized only recently. Solutions to all of them exist, even if they are primitive or are in the early stages of development. For example, transcriptive interference by foreign DNA may be minimized by changing vectors. If mRNA instability is caused by poor translatability, efficient translation initiation signals can be provided. If the protein product is toxic to the host cell, its production can be suppressed until a time propitious for obtaining satisfactory yields. Most importantly, it is now recognized that the major factor in obtaining poor yields from recombinant DNA in foreign hosts is the ability of most cells to efficiently recognize and degrade protein that is "unusual". Thus, an exciting new development is the isolation of *E. coli* strains which are defective in many different proteolytic functions (9). Preliminary evidence indicates that these strains are precisely what is needed to produce good yields of a wider variety of foreign proteins than previously possible.

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LEPROSY AS A ZOONOSIS

GERALD P. WALSH, WAYNE M. MEYERS, CHAPMAN H. BINFORD

Armed Forces Institute of Pathology
Washington, D.C. 20306

ROBERT H. WOLF, BOBBY J. GORMUS, LOUIS N. MARTIN, P. J. GERONE

Delta Regional Primate Research Center
Covington, Louisiana 70433

and

JOEL R. LEININGER

University of Minnesota
St. Paul, Minnesota 55108

Historically, leprosy has been considered a disease confined to humans and the patient with lepromatous leprosy the sole source of *Mycobacterium leprae*. In the last ten years we have studied naturally-acquired leprosy in three different animal species: the nine-banded armadillo (*Dasypus novemcinctus*), a chimpanzee (*Pan troglodytes*), and a mangabey monkey (*Cercocebus atys*). These studies demonstrate unequivocably that animal reservoirs of the disease exist and enzootic infection could be a significant factor in epidemiologic studies in areas where human leprosy is endemic.

Naturally-Acquired Leprosy in Nine-Banded Armadillos

Background and present status

The discovery in 1971 of the susceptibility of the nine-banded armadillo to leprosy provided a laboratory animal model for the study of experimental lepromatous leprosy [28]. Armadillos inoculated with

M. leprae develop lesions as early as 6 months after inoculation, and by 18 months, dissemination to all major tissues and organs has occurred [29]. The bacillary load, the extent of the infection, and the absence of any detectable cell-mediated immune response in the majority of inoculated animals indicate that armadillos are more susceptible to leprosy than humans [32]. We believe that the hypersusceptibility of the armadillo is responsible to a large degree for the development and perpetuation of naturally-acquired leprosy in wild-caught armadillos.

The first armadillo with naturally-acquired leprosy was found in 1974 while collecting tissues from normal, recently captured animals. The only gross pathologic change in this animal was enlarged inguinal lymph nodes. Tissue smears of these nodes contained large numbers of acid-fast bacilli (AFB) which were later found to be non-cultivable on mycobacterial media. Histopathologic examination of formalin-fixed tissues revealed a disseminated mycobacteriosis indistinguishable from that seen in armadillos experimentally infected with *M. leprae*.

In the ensuing 12 months, a total of 7 armadillos captured in three different locations in southern Louisiana were found with the disease [30]. Later studies of large numbers of animals from Louisiana showed prevalence rates ranging from 4% to 29.6% [31].

To date we have found a total of 105 armadillos with naturally-acquired leprosy, 104 of which were captured in Louisiana and one was found in northeast Texas. Most of the positive sites in Louisiana are swampy areas which have dense foliage and harbor large numbers of insects.

Fourteen of the animals had clinically apparent disease at the time of capture. The remaining 91 were detected by ear specimen examination.

Naturally-infected armadillos have been reported by four other centers. In 1976 a naturally-infected armadillo was found near Natchez, Mississippi [11]; Smith *et al* in 1978 reported the disease in two armadillos in southern Louisiana [26]; in 1978 two armadillos with naturally-acquired leprosy captured near College Station, Texas, were reported [1, 5]; and Smith *et al* in 1983 [27] completed an extensive survey of armadillos captured along the Texas Gulf Coast and found 21 naturally-infected armadillos among 451 animals examined, for an overall prevalence of 4.6%. The local prevalence ranged from 1.0% to 15.4%, and the authors concluded that because the rates of infectivity were highest in southern Texas, it was unlikely that the disease had originated from any of the research centers in Louisiana where armadillos were being used in leprosy studies.

Because naturally-acquired leprosy had never been diagnosed in any animal species, great emphasis was placed on confirming the identification of the etiologic agent isolated from infected armadillos. In 1968 at the 8th International Leprosy Congress, several criteria were proposed for identifying an isolate as *M. leprae*, and since then more have been added. These criteria have been used to identify the agent causing natural armadillo leprosy. These studies have been reported in detail and are only summarized here:

a. *Histopathology:* Large numbers of AFB, frequently arranged in packets or globi, staining more intensely with the Fite-Faraco stain than with the Ziehl-Neelsen method, and the invasion of peripheral nerves, all are consistent with the identification of the organism as *M. leprae* [3].

b. *Microbiology:* The etiologic agent is not cultivable on standard mycobacterial media even though several cultivable species of mycobacteria (*M. avium-intracellulare, M. scrofulaceum*, and *M. gordonae*) were isolated, primarily from the lymph nodes of a small number of animals [3, 27]. Acid-fastness is pyridine extractable [3]. Base ratios and DNA homology with *M. leprae* show that the etiologic agent is identical to the leprosy bacillus [27]. The natural agent, like *M. leprae*, is unusually sensitive to Dapsone [12].

c. *Immunology:* Lepromin prepared from tissues of naturally-infected armadillos, and standard human lepromin gave similar reactions in leprosy patients [19]; concentrations of antibodies to mycobacterial antigens 2, 5, and 7 in sera of naturally-infected armadillos are similar to those seen in experimentally-infected armadillos and in lepromatous patients [13]. Fluorescent antibody studies show that the natural agent is indistinguishable from *M. leprae.*

d. *Animal passage:* Normal armadillos inoculated with the natural agent developed disseminated leprosy [33]. The growth patterns in the mouse footpad were similar to *M. leprae* [20].

e. *Ultrastructural studies:* Freeze-etch and thin-section preparations revealed no differences between tissues from armadillos with the natural infection and those with experimental leprosy [18].

The results of all these studies thus demonstrate that the organism isolated from armadillos with naturally-acquired leprosy is *M. leprae.*

Origin and significance

Armadillos have not been domesticated and it is unlikely that they acquired leprosy directly from lepromatous patients; however, contact with contaminated fomites such as clothing and bandages must be considered as a possible source of the infection. Such contact would have been possible in the pre-sulfone era, when patients living at home in rural areas would have discarded such items. Leprosy bacilli have been shown to remain viable in dried nasal secretions for up to 7 days [6] and in moist soil at room temperature for up to 46 days [25]. Because armadillos commonly encounter insects, these also must be considered as sources of the infection in armadillos.

Once introduced into the armadillo population, animal-to-animal transfer of leprosy, either by direct contact or by inhalation of contaminated soil in burrows, could have resulted in the disease becoming endemic in this species. In addition, we have detected *M. leprae* in the milk and mammary glands of lactating armadillos, so transmission via mother's milk to newborn armadillos is a definite possibility [21].

Leprosy in humans has been endemic in Louisiana for more than 150 years [9]. Armadillos migrated into the state in 1926 and therefore are not responsible for introducing leprosy into Louisiana. A study by the Centers for Disease Control published in 1977 failed to show any association between human leprosy patients and contact with armadillos [10]. However, a report in 1983 by researchers at Baylor College of Medicine implicated armadillo contact as the most likely source of the infection in five patients diagnosed with the disease [16]. A sixth patient has been found since the publication of that report [17]. In the United States, indigenous human leprosy is concentrated in two states: Louisiana and Texas. In Louisiana, of the 38 cases reported in the period 1967-1976, 34 (or 89%) were native-born individuals [8]. In 1980, of the 32 cases reported in Texas, 15 (or 47%) occurred in native-born persons [2]. By contrast, California reported 91 cases in 1980, of which only 1 was from the indigenous population.

The prevalence of the disease in armadillos in Louisiana, and the more recent report of prevalences as high as 15.4% in armadillos captured in Texas, require that armadillos be considered as a reservoir of the disease in these areas.

Naturally-Acquired Leprosy in a Chimpanzee

Background

Naturally-acquired leprosy in a nonhuman primate, a chimpanzee, was first reported in 1977 [7]. The animal was obtained from a primate import company who had purchased it from local trappers in Sierra Leone. Two months after arriving at the University of Iowa, the animal was inoculated, along with 7 other chimpanzees, with bovine leukemia virus. Two months after the inoculation, lesions appeared and spread over the entire trunk and limbs of the animal and within 6 months, the ears had become markedly thickened. A biopsy specimen of the ear revealed a diffuse infiltration of macrophages containing large numbers of AFB. In the 14 months that followed, lesions developed on the lower lip, nares, eyebrows, and scrotum. AFB were present in peripheral nerves, and nasal smears contained large numbers of acid-fast organisms.

Thirty-three months after the appearance of the initial lesions, the animal died following anesthesia for a routine surgical procedure. Necropsy revealed disseminated leprosy involving the liver, spleen, lymph nodes, testes, lungs, eyes, and nasal mucosa [15]. Microbiological studies confirmed the identification of the AFB as *M. leprae* [14].

Source and significance

We speculate that this chimpanzee acquired the infection from a patient with multibacillary leprosy. In some African countries, chimpanzee mothers are killed and the young animals are raised by villagers until they are sold to animal exporters. Human leprosy is highly endemic in Sierra Leone and it is possible that this animal was in close contact with patients with untreated lepromatous disease prior to export to the United States. It is very unlikely that exposure to leprosy occurred after arrival in the United States.

It has not been possible to establish any relationship between the inoculation of bovine leukemia virus and the development of leprosy in this animal. All of the chimpanzees in the study had serological evidence of infection by the virus. It is possible that the experimental virus infection could have compromised the animal immunologically, permitting a latent leprosy infection to progress.

The frequency of naturally-acquired leprosy in chimpanzees in the wild is not known, and therefore it is not possible to determine the potential role of chimpanzees in the epidemiology of leprosy in humans.

Chimpanzees are found throughout the tropical rain forests of Africa, where there are numerous leprosy-endemic areas, and the information that natural leprosy can occur in this species could be of great importance. In earlier studies, chimpanzees inoculated with *M. leprae* did not develop progressive disease [4]. The discovery of naturally-acquired leprosy in a chimpanzee suggests that the susceptibility of this species should be re-evaluated, using inocula containing large numbers of viable *M. leprae* such as those prepared from leprosy-infected armadillo tissues.

Naturally-Acquired Leprosy in a Mangabey Monkey

Background

This animal, commonly known as a "sooty" mangabey monkey, was imported to the United States from West Africa in 1975. The first lesions of leprosy were seen in September 1979, consisting of firm nodules on the face and ears. It was never inoculated with *M. leprae* and was on a cholesterol metabolism study at the time the disease became apparent.

Four months later, following a histopathologic diagnosis of lepromatous leprosy made at the Armed Forces Institute of Pathology in Washington DC, the animal was transferred from the Gulf South Research Institute in New Iberia, Louisiana, to the Delta Regional Primate Research Center, Covington, Louisiana. At that time, the face was heavily infiltrated and many of the lesions were ulcerated. There was nodular thickening of the ears and on the extensor surfaces of the forearms. Peripheral nerves were not enlarged, and no paralytic deformities were detectable at that time.

Microbiologic, immunologic, histopathologic, and electron microscopic studies have shown that the infecting organism is *M. leprae*. Details of these studies have been published [22, 23, 24] and are only summarized here.

a. *Microbiology:* Non-cultivable AFB with loss of acid-fastness after treatment with pyridine; oxidation of D-DOPA; 100% homology with DNA from *M. leprae*.

b. *Immunology:* Presence of antibodies to mycobacterial antigens 2, 5, and 7 in concentrations similar to those seen in lepromatous patients and experimentally-infected armadillos.

c. *Histopathology:* Presence of histiocytes containing AFB frequently arranged in packets or globi, with invasion of dermal nerves by AFB; the AFB stain more intensely with Fite-Faraco stain than with the Ziehl-Neelsen technique.

d. *Electron microscopy:* Demonstration of macrophages containing foamy structures composed of bacilli surrounded by spherical droplets.

Paralytic deformities

Approximately 16 months after the cutaneous lesions were first seen, paralytic deformities developed in this mangabey monkey. The intrinsic muscles of the foot and hand, as well as the peroneal muscles of the foot, were paralyzed, with accompanying deformities. To our knowledge, this is the first leprosy-infected animal that has manifested paralytic deformities like those seen in human leprosy.

Response to therapy

Soon after the deformities were observed, the general health of the mangabey deteriorated. Treatment was started with Rifampin (RFM) at 10 mg/kg *per os* for a period of 28 days, followed by injection of a repository form of Dapsone (DADDS) at a dosage of 20 mg every 77 days. Within 30 days after the start of treatment, the general health of the animal had markedly improved, and smears from skin lesions and the nasal mucosa contained no solidly-staining AFB. Bacilli taken from lesions at this time failed to multiply in the mouse footpad, confirming effective chemotherapy. Over the ensuing 12-16 months, there was gradual resolution of the lesions. After that time, however, there was a gradual re-exacerbation of the disease, and organisms isolated from a persistent lesion below one of the nares multiplied in the mouse footpad. RFM therapy was re-instituted, with a favorable response. Drug sensitivity studies have shown that the mangabey isolate is partially resistant to Dapsone [24].

Passage studies in normal mangabeys and other nonhuman primates

Leprosy has been transmitted to normal mangabeys inoculated with either the mangabey isolate or with human *M. leprae* passaged in

the armadillo. Rhesus monkeys and African green monkeys have also been found to be susceptible to leprosy. It appears at this time, however, that mangabeys may prove to be the most suitable model of all the species studied thus far.

Significance of spontaneous leprosy in a mangabey monkey

The discovery of naturally-acquired leprosy in a mangabey provides additional evidence that leprosy can exist in nonhuman species and is not exclusively a disease of humans. While it is reasonable to assume that this animal was infected following contact with an untreated lepromatous patient, the possibility that it became infected following contact with another mangabey with lepromatous leprosy cannot be excluded. The results of the passage studies showing that mangabeys as a species are susceptible to leprosy lend credence to this possibility.

The finding that normal mangabeys as well as other nonhuman primates are susceptible to leprosy is of great significance. Studies of the susceptibility of mangabeys and other nonhuman primate species were prompted by the discovery of naturally-acquired leprosy in a mangabey monkey, and the information obtained so far indicates that primates can now be used as experimental models of this disease.

SUMMARY

We have studied naturally-acquired leprosy in three animal species. The prevalence of the infection in wild armadillos in the southern United States necessitates that armadillos be designated as reservoirs of the disease in this area. Although the prevalence of leprosy in chimpanzees and mangabey monkeys in the wild is not known, the discovery of naturally-acquired leprosy in these species requires that they be considered as possible reservoirs of the disease in geographic areas where these species are found. The infection in all three species has been of the lepromatous or near-lepromatous type and therefore is highly bacilliferous and contagious. The role that each species may play in the transmission of leprosy to man must now be ascertained.

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THE ANTIBODY RESPONSE IN LEPROSY

MARIAN ULRICH, JACINTO CONVIT AND MARTA CENTENO,
Instituto Nacional de Dermatología,
Caracas, Venezuela

Overwhelming evidence that cell-mediated immune reactions provide the basis for an effective protective response to infection by *Mycobacterium leprae*, together with rapid technological advances in the evaluation of T-lymphocyte reactivity, have led to important advances in our understanding of cell-mediated activity in leprosy. Circulating anti-mycobacterial antibodies, in contrast, do not play a direct role in protection, and their measurement has not been useful for diagnostic or prognostic purposes. The role of antibody-mediated hypersensitivity phenomena, such as erythema nodosum leprosum appears to be well established, but these phenomena are normally managed at the clinical level. Antibody- or immune complex-mediated modulation of cell-mediated responses has not been clearly established *in vivo*. With relatively few exceptions, leprologists and investigators have not concerned themselves with antibody responses in leprosy during the last decade.

Perhaps four factors have been fundamental in stimulating a renewed interest in the evaluation of anti-mycobacterial antibody activity in leprosy:

1. *The isolation and characterization of phenolic glycolipid I and the demonstration of its highly specific serological reactivity* by Patrick Brennan and his colleagues [1]. This fundamental contribution has provided the basis for the development of specific tests which are not handicapped by the extensive cross reactivity with environmental mycobacteria which has characterized anti-mycobacterial serology.

2. *The widespread application of enzyme-linked immunosorbent (ELISA) techniques for antibody measurement.* These techniques are

highly sensitive, employ stable reagents and a minimum of sophisticated equipment, and are readily adapted to the study of large numbers of small serum samples. ELISA procedures are particularly suited for use in those areas of the world with endemic leprosy, where resources are often severely limited.

3. *The development of hybridoma technology and its application to leprosy.* The production of antibodies specific for simple antigenic molecules and individual epitopes on complex molecules offers the possibility of detecting a specific antigen-antibody reaction within a complex system by suitable inhibition tests, isolating single antigens or detecting their presence in tissues, and elucidating possible mechanisms of antibody-mediated immunomodulation, among others. These types of study are still in quite early stages in leprosy, but several *M. leprae*-specific epitopes and antigenic molecules can be identified by the monoclonal antibodies produced by Buchanan [2], Ivanyi [3] and Bloom. Monoclonal antibodies have of course been used with great success in characterizing the cell-mediated response in leprosy, both *in vitro* and at the level of organization and functional activity in the granuloma.

4. *Renewed interest and new approaches to leprosy control*, stimulated by the activities of the Special Program for Research and Training in Tropical Diseases of the UNDP/World Bank/WHO as well as independent centers. Leprosy control still depends on early detection of clinical disease and effective treatment. Field trials in prophylactic vaccination are being initiated in several areas which may introduce fundamental modifications in the strategy of leprosy control, and the determination of anti-mycobacterial antibodies may play an important role in this strategy.

The availability of suitable immunological tools for serological study allows the definition of very clear areas of interest for the application of these studies. These areas can be divided into studies in clinical leprosy and in subclinical infection, immuno-epidemiology and related fields.

Studies in clinical leprosy with more traditional approaches as well as newer applications permit several fundamental generalizations. Anti-mycobacterial levels appear to depend rather closely upon the bacterial load; specific as well as cross-reacting antibodies are present in relatively low titers at the tuberculoid end of the clinical spectrum of leprosy and increase across the spectrum, reaching maximum levels in

lepromatous leprosy. Within each clinical category there is, nevertheless, considerable individual variation. No clear qualitative differences have as yet been demonstrated in different clinical forms of leprosy; it has not been possible to ascribe possible *in vivo* antibody-mediated immunoregulatory functions to antibodies of a particular specificity. Interestingly enough, Mehra has demonstrated that monoclonal antibodies to phenolic glycolipid I (PGL-I) block the suppressor activity induced by this antigen *in vitro* [4]; to my knowledge, the relevance of this mechanism *in vivo* has not been evaluated, though the information to do so would be readily available.

We have determined levels of IgG and IgM antibody to PGL-I in serum samples from lepromatous and borderline lepromatous patients who showed significant histopathological changes, including reversal reactions and shifts toward more resistant forms of leprosy by the Ridley-Jopling criteria, and patients who did not show such changes. As shown in Tables 1 and 2, we could not demonstrate any relation between the initial levels of antibody of either class and the subsequent response to immunotherapy. Antibody levels did not show dramatic changes in a period of two years after the initiation of immunotherapy, though many decreased.

Antibody titers decrease after chemotherapy; studies by Melsom and collaborators [5] report the most rapid decrease in the IgG class of antibodies, while our studies [6] as well as those of Brennan's group [7] show a more rapid decrease in antibodies of the IgM class to glycolipid as well as to a complex soluble extract which contains PGL-I (Figs 1 and 2). Yoder *et al.* [8] have reported an increase in antibody titers prior to relapse in borderline tuberculoid leprosy. All of these studies taken together indicate that serological studies may provide a useful approach to the evaluation of chemo- and immunotherapy in clinical leprosy, to the early detection of relapse or drug resistance, and to the possible detection of persisting viable organisms. All of these studies are of relatively long duration and require close collaboration between clinical and laboratory personnel. It would appear to be of great interest to include the storage of an initial serum sample from new cases of leprosy as part of the routine procedure in different areas of the world, since regional differences may be important and the necessary technology should be quite readily available.

The use of serological tests may be of even greater interest and potential importance in aspects of leprosy control related to early detection of disease, including subclinical infection, immuno-

TABLE 1

*Titer of IgM and IgG antibodies to phenolic glycolipid I in the sera of patients who showed histopathological changes after M. leprae-*BCG immunotherapy.

Patient	IgM		IgG	
	Initial	Two years	Initial	Two years
AMM	16000[a]	8000	1000	2000
SG	8000	8000	4000	500
JPV	8000	2000	2000	500
UM	8000	2000	1000	1000
EP	8000	2000	1000	500
AH	8000	2000	<250	<250
DC	4000	4000	1000	500
RE	4000	4000	1000	500
AJO	4000	1000	250	500
JJG	2000	2000	1000	500
SD	1000	4000	500	500
JC	1000	1000	250	250
HG	1000	1000	<250	<250
LP	500	500	1000	250
JHM	<250	<250	500	500
LR	<250	<250	500	250

[a] Reciprocal of the highest dilution giving an OD >.02 at 405 nm.

TABLE 2

Titer of IgM and IgG antibodies to phenolic glycolipid I in the sera of patients who did not show histopathological changes after immunotherapy.

Patient	IgM		IgG	
	Initial	Two years	Initial	Two years
JY	16000	16000	8000	2000
TC	16000	4000	500	250
GN	8000	1000	500	500
RV	2000	1000	1000	250
JLR	1000	1000	<250	<250
JR	500	250	<250	<250

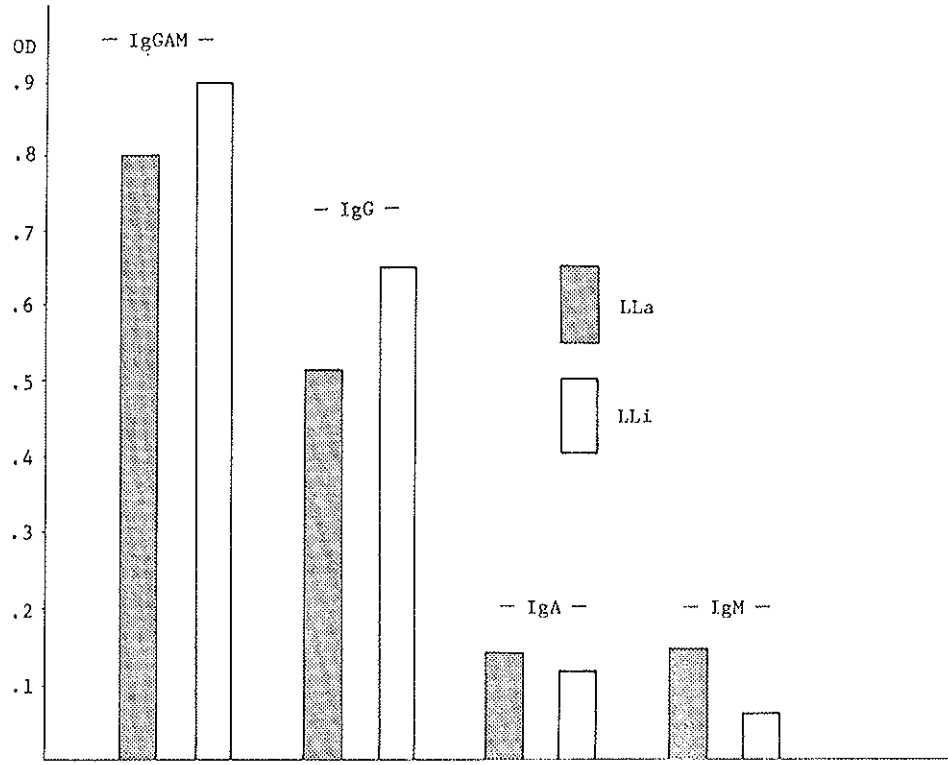

FIG. 1. Antibody levels to soluble extract of *M. Leprae* in active and inactive lepromatous leprosy.

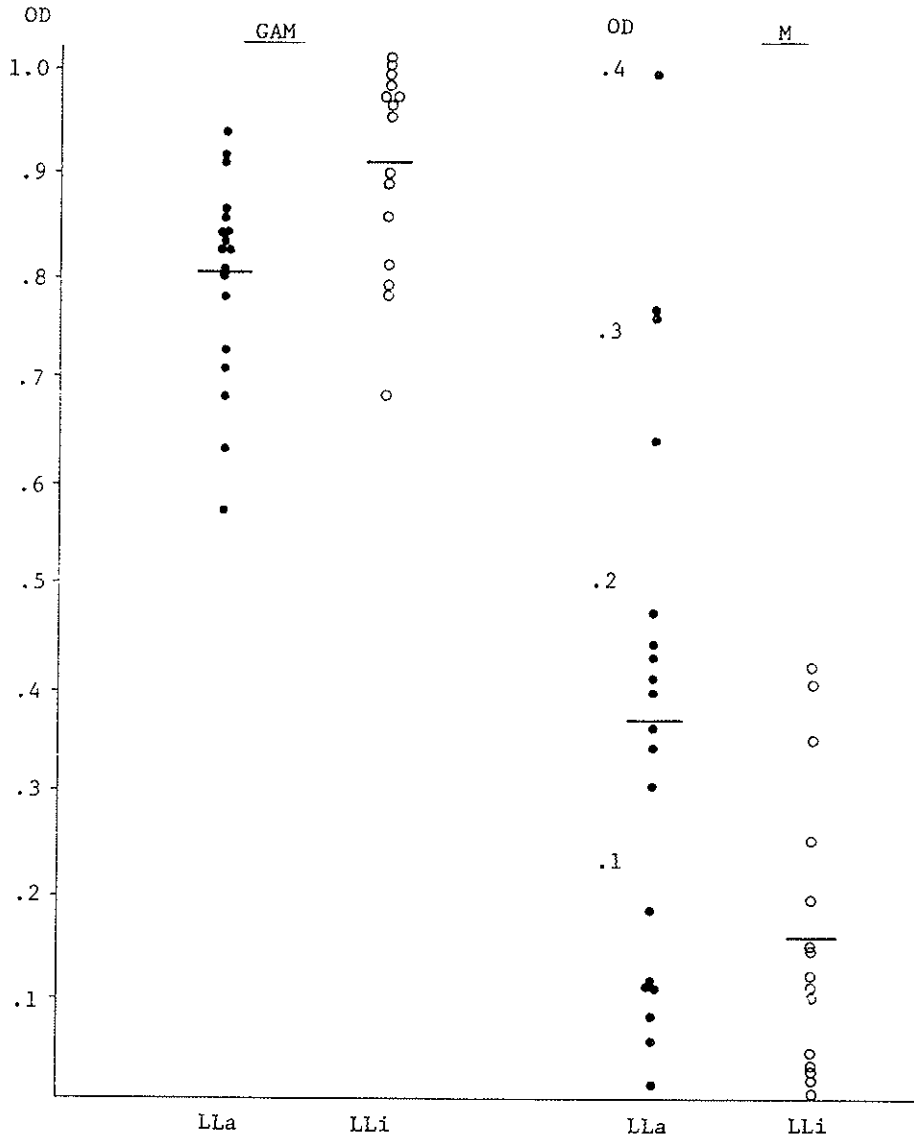

FIG. 2. Individual antibody responses to *M. leprae* soluble extract in active and inactive LL.

epidemiological studies and immunoprophylaxis. Progressive forms of leprosy with an average incubation period of several years may be the source of new infections in the community during a period when there is no clinical evidence of disease. The availability of a specific serological test for detecting infection by *M. leprae* may offer the only possibility for detection of potentially progressive disease during the incubation period, since cell-mediated reactivity to *M. leprae* is absent. Buchanan [9] has recently reported four cases of clinical leprosy (2 TT, 1 BT and 1 LL) in the follow-up of a group of 1096 household contacts from Sri Lanka; the contact who subsequently developed LL had exceptionally high levels of antibody to PGL-I. We have detected strong serological reactivity to PGL-I and to a complex antigenic extract of *M. leprae* in partially overlapping groups of about 3% of a group of 302 household and non-household contacts who gave negative skin tests to a soluble antigen of *M. leprae* (Figs. 3 and 4) [10]. Since these individuals are incorporated into an immunoprophylaxis trial and have been vaccinated, there is some question whether clinical disease will occur even if they now have subclinical infection. About 18% of the skin-test negative contacts with ELISA indices greater than 4 did not respond to vaccination, while the overall percentage of non-response was less than 3%. These results indicate that a small group of contacts possess immunological peculiarities similar to those observed in lepromatous leprosy—high anti-mycobacterial antibody titers together with negligible cell-mediated reactivity to *M. leprae*. The study of T-cell suppressor activity of the type described by Mehra and colleagues [4] will be of particular interest in this group.

There is some doubt whether the PGL-I system is ideal for detecting early infection by *M. leprae*. The concept of "original mycobacterial sin" [11] would suggest that the earliest antibody response to infection by *M. leprae* might be to common antigens shared with environmental mycobacteria; a specific antibody response may develop much more slowly. Additionally, glycolipids are not particularly strong antigens. The development of an appropriate inhibition test with monoclonal antibodies to a *M. leprae*-specific proteic epitope might offer a more sensitive tool for detecting early infection. Until the nature of the early response has been more clearly defined, there would appear to be justification for measuring both specific and non-specific anti-mycobacterial antibody, in conjunction with skin testing and, in selected individuals, *in vitro* studies of cell-mediated responses in contacts.

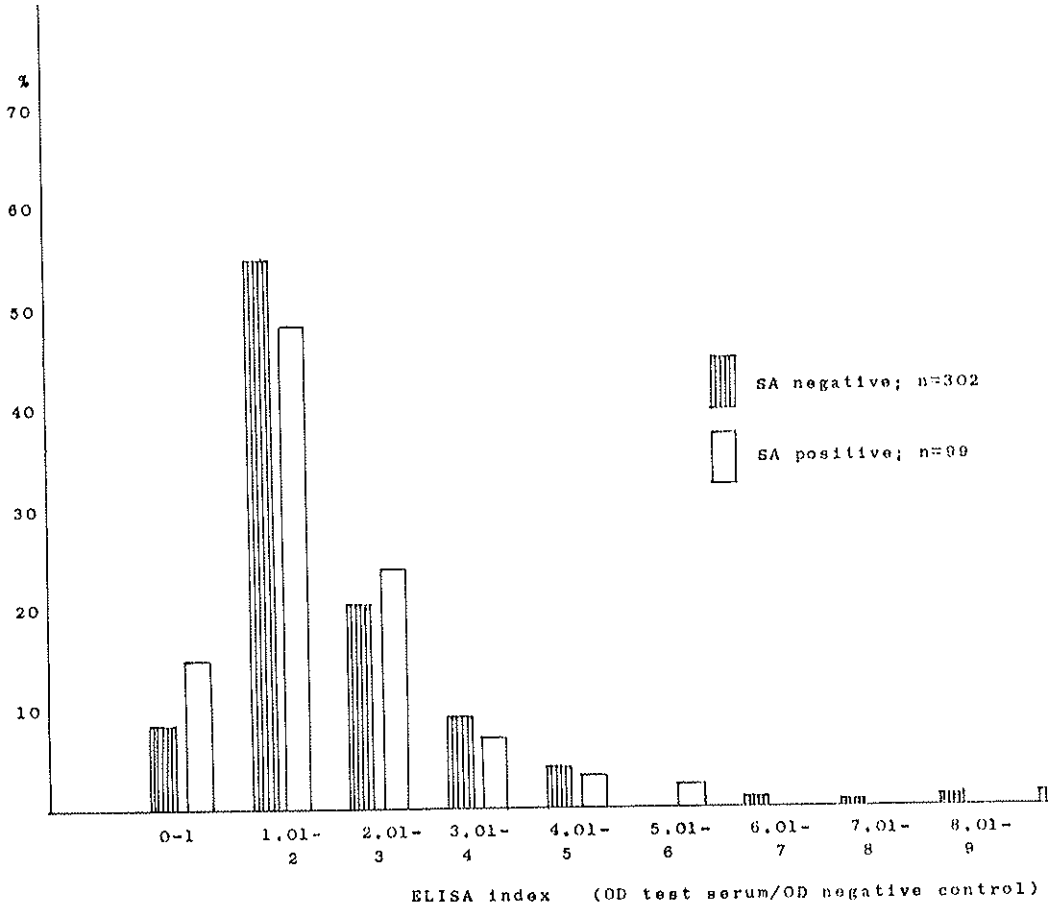

FIG. 3. Antibody levels in SA-negative and SA-positive contacts, measured by microELISA with soluble antigen from *M. leprae*.

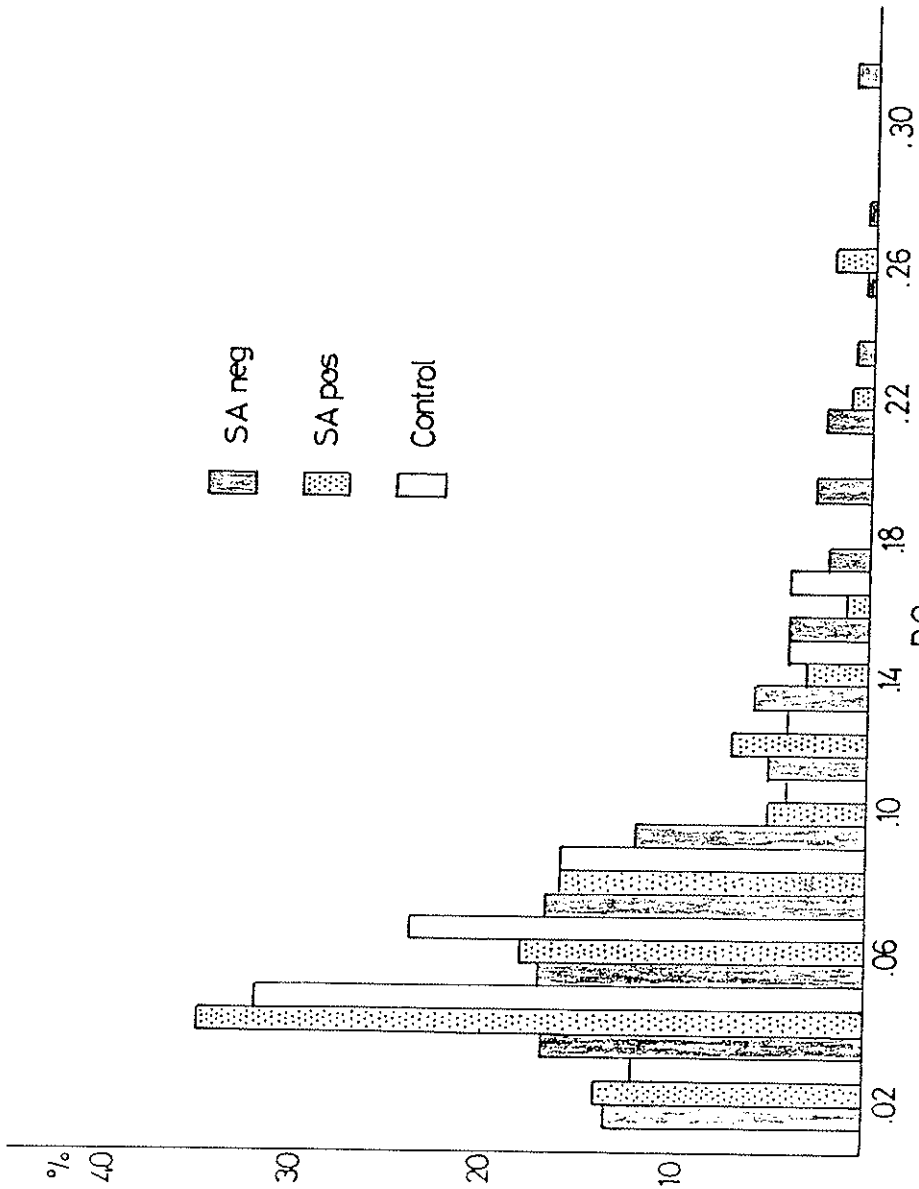

FIG. 4. Antibody levels to PGL-I in healthy contacts.

Bloom has suggested that the measurement of anti-PGL-I may offer useful information during the course of vaccine evaluation, since the *M. leprae* preparation being used (as well as BCG) would not be expected to stimulate the formation of these antibodies. If they were to appear during the course of follow-up, that would suggest the presence of active infection by *M. leprae* (and vaccine failure). The obvious corollary is that diminution or disappearance of anti-PGL-I antibodies in the vaccinated group but not in the controls would clearly suggest that vaccination possesses a therapeutic effect in subclinical infection.

In the relatively near future, serological tests could be used in leprosy to: (1) monitor the course of clinical infection and evaluate the response to chemo- and immunotherapy; (2) detect multibacillary infection during its subclinical stage. Combined studies of cell-mediated reactivity and serological activity may permit the definition of a susceptible population among apparently healthy individuals and contribute to the evaluation of immunoprophylactic procedures. All of these possibilities could contribute in one way or another to more successful programs of leprosy control.

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THE STANDING PROBLEM OF A VACCINE AGAINST HANSENIASIS: A NEW OPTION OFFERED IN TERMS OF IMMUNOPROPHYLAXIS AND IMMUNOTHERAPY

F. E. RABELLO
rua Senador Vergueiro 14/301,
Rio de Janeiro, Brazil

1 — VACCINE FOR THE OVERT DISEASE

In terms of procedure in Preventive Medicine as in terms of logical reasoning, a vaccine should be devised that may be capable of giving full pre-pathogenic protection to the incidents and accidents that characterize the disease, as known from clinical and epidemiological points of view.

However, particularly on account of the features of Hansen's disease, it is useful to invert the order of factors for a moment, due to the profound alterations that have been obtained by the vaccination findings of Dr. Convit and his collaborators (Convit *et al.*, 1982).

Out of a total of 351 active cases of the Virchowian group and type (BL and LL in the British system, which we have not adopted) vaccinated three or more times, no less than 62% show clearly defined and striking clinical and histopathological changes which, with fever, general discomfort and arthralgia, represent well defined cases of the Souza Lima-Tajiri phenomenon — that is to say, forms of Tuberculoid Pseudo-exacerbations: so-called Reversal Reaction (RR).

Curiously, this whole syndrome of clinico-pathological reactivity, in the majority of cases requiring no less than 5 or more vaccinations, occurs in no more than 32.1% of positive responses to the intradermic test to a soluble antigen — leaving therefore 67.9% of the patients still immune negative, despite the intensity of phenomena provoked by the vaccination.

Everything that occurred in this material almost duplicates exactly what is classically seen in the clinical and histological syndromes typical of the pathergic responses usually seen in the forms of the immuno-negative L(V) group. After many repeated vaccinations, all the patients still remain distant from the quiet states of normal immuno-response.

Although one still cannot openly accept a "movement" outside type L(V), such responses represent, without a shadow of doubt, examples obtained for the first time through vaccinal provocation, of *immunological modulations* like those already known to fit the "cellular history" of the disease, in the words of Dr. Abulafia (1982).

This could possibly represent the immunogenic production of small clones of T cells capable of recognizing specific antigens and hence capable of explaining the phenomena, such as those that occur in different situations during the course of malignant Hansen's disease. The following situations are pertinent examples:

1 — the episodes of pseudoexacerbation (Souza Lima, 1955) — RR — after the regression of the forms of the malignant group with sulfone;

2 — the small foci of "Tuberculoid Contamination" described by Wade (1963) in the histoid form of L(V);

3 — the very rare cases, like Ag. Pupo's *princeps* patient, and the two referred by Souza Lima and Souza Campos (1947) of L(V) patients burnt out at the cost of large mutilations, showing at necropsy compact tuberculoid granulomas in the nerve trunks and in the skin;

4 — finally, in the light of the preceding cases, the equally rare patients studied by excellent observers of the so-called "nerve abscess" during the course of Virchowian Hansen's disease. This being an exception to the rule that makes these cases a *Colliquative T neuritis*, a typical form of Tuberculoid Hansen's disease. A designation as proposed by myself in 1935-1938, seeming better and simpler than the one proposed by Job *et al.* (1980) — "Segmental Necrotizing Granulomatous Neuritis of Leprosy".

I insist on the scrutiny of those microscopic aspects because it appears to me that it is very encouraging to discover in the old devastatingly malignant "monolith" of Virchowian Hansen's disease

— the sadly celebrated "Lepra lepromatosa", as proposed by myself in 1937 — *evident signs of a restricted but undeniable stronghold of cellular resistance*, even in these malignant cases.

This is surely a "breach" still to be explored, now that the work of Convit and his group proposes the use of a composition of *profound antigenic impact*, with this vaccine of M. Leprae + BCG complex.

II — Vaccine for subclinical infection ("infeckt")

Criteria for establishing the concept of infeckt in Hansen's disease.

It will obviously be a major advance when, in the epidemiological field, cases can be found in which we are certain of the installation of a subclinical infeckt state of the disease.

In the near future, in the field of epidemiological and immunological enquiry, the states of "Leprosy-infection" (Souza Campos 1956), or of subclinical infection (Godal 1974, Fliess *et al.* 1975) will emerge at the very biological root of what we call the HI-Immature group, the apparent clinical matrix of the disease.

Only recognized as a stage in the natural history of Hansen's disease, these subclinical states of Hansenic infection have recently been viewed in concrete terms.

In the past, J. Jadassohn (1913-1928) made clear reference to these phenomena in his masterly presentation of the general pathology of the disease (his "Allgemeine Pathologie" — in *Lepra* from the Handbuch of Kolle-Wassermann): "First of all I would like to stress the existence of pure invasions in which there are no reactions on the part of the organism and, on the other hand, "infections" that, clinically speaking, remain totally latent or that produce such tiny symptoms that they remain unnoticed by the carrier".

Jadassohn recalls Beurmann *et al.* (1906), and especially Gougerot (1906), who proposed that a distinction should be made between "latent microbism" in which the bacillus that is present and hibernating, as it were, causes no reaction in the tissues, and the "veritable incubation" which is restricted to just a few months, in other words, the "germination" phase that precedes the disease itself.

It happens that in the particular case of Hansen's disease, we experience a preliminary difficulty in view of the well-known

amplitude of the initial *Latency or Primary* inapparent stage (so-called "incubation"), beginning by circumscribing the "infeckt", before the inauguration of overt disease.

In this context, and unfortunately with necessary reservations, we would like to present some more complete data:

a — We can find a more exactly based assessment in the classic work of Rogers and Muir (1946), in which they sought to encompass the problem more closely, by using data on 84 reliable cases from the literature (average time of 2 years 2 months), followed by data obtained from the Indian Census of 1921, in 326 infantile cases, with the latency time from 0 to 3 years of age.

From this they produced the thesis, later denied by the work of Brazilians and Argentinian writers, of the extreme susceptibility of the child. When today we know, to the contrary, about the well-defined resistance of the small child of 0-4 years of age, with approximately 80% of the T (TT of British writers) forms, until the pubertal crisis, when the L(V) forms begin to intervene.

The data provided by the Japanese authors: Y. Hayashi (1941) are much more exact in 15 selected patients finding periods of 3-8 years in 12 out of those 15 cases; and even lower periods observed by Yajima (1942) in 993 patients: an average of 2-3 years.

b — At the end of this period of time, these people are on the brink of the overt disease, presumably ready to finally experience the habitual signs and symptoms characteristic of the disease. In this way, still healthy carriers of the specific pathogens already form a living part of the pathological process.

The chronological and biological correlations throughout these stages of the process are not, unfortunately in the case of Hansen's disease, as well demarcated as in tuberculosis. It is surmised that the human recipient invaded by *M. leprae*: "the immune compromised host", still negative to lepromin, can shelter a heavy load of bacilli, a wealth of germs still without any clinical expression (cf. the old findings on bacilli present in the lymph nodes of contacts in endemic areas).

Probably it can also be accepted that, by sheltering so many bacilli, these human recipients — even *before* the action of immune mechanisms — become an unexpected and potent source of contagion to the community, by far exceeding the cases of overt disease (cf. the well studied data of Indian authors).

On the other hand, we know of the epidemiology of so many infectocontagious conditions that, to maintain this subclinical "infeckt", both cellulo-mediated or humoral response mechanisms may come into action. In this sense there may occur the possible detection of antibodies in patients even without ever having shown any clinical evidence.

This leads us to question the pertinence of the criticisms that have been made of the value of the sero-reactions of the FLA-ABS type in a recent *mise au point* by Abe *et al.* (1973) — a criticism that was in fact raised by the results obtained also by Sritharan *et al.* (1981) showing high indices of positivity already in contacts, when confronted with the indices obtained in defined cases of the overt disease.

In this respect, we should make some comments on the ideas recently produced by reliable Brazilian observers. Among others, we would like to mention the following points which deserve further careful study, possibly in greater depth.

1 — The idea that the whole process should start from a single root, the Immature group, recalls, curiously enough, a similar scheme proposed by R. Cochrane in 1940: "basic lesions".

2 — However, I believe that, together with what we have learned since that time from the classic Brazilian, São Paulo masters among others, several reservations can be formulated as far as this idea is concerned.

3 — Not only as to the point of departure I, but also concerning some of its developments.

4 — I am quite aware that a broad spectrum scheme for everything that comes from Group I does not imply any "sequential" idea in the British authors' sense. On the contrary, what is now being proposed is a fixity (in my opinion, still rather premature perhaps) for what are known as "other types". This puts an end to the British sequential proposal in terms of microscopic findings. And it is already a definite advantage over them.

5 — I confess, on the other hand, that I am not so sure that there is a single root — Group I — at the basis of the whole process. And this reservation is proved to a certain extent by what we know of specific granulomatous diseases such as the "inapparent" forms in syphilis, for example, and the "sub- clinical forms" in tuberculosis as mentioned above.

On this point, I would refer to the well thought out ideas in Gomez Orbaneja and Garcia Perez's old paper (1953).

This — besides the lack of precision as to the true beginning of the process that the immuno-pathological findings of Myrvang and Godal (1973) perhaps present as a possible raising of the veil — still unfortunately hides, for us, *the biological onset* of the whole process.

In any case, I believe that, as the Spanish authors we have mentioned point out, this onset includes *more than one form of beginning.*

6 — This is exactly what is suggested by Noussitou (1979), an author who, although distant from us and always original in his concepts, interprets the Asiatic material in the same way as Argentinian and Brazilian Hansenologists.

Commenting on Ridley's scheme (Ridley, 1977), Noussitou does not accept that the "TT AND BT" cases result from untreated immature cases, but come directly from sub-clinical infections — just as Ridley imagines for the "LLp" cases, that is to say, in this rather complicated terminology, full-polar type L(V) cases.

As for infantile cases T and TR, Noussitou argues — and this we already know from Noussitou himself and Bechelli *et al.* (1974) — that they do not appear to come from the immature clinical matrix because, in Burma, I children "whiten" rapidly or soon become MAT or T (in 750 new infantile cases between 1965 and 1973 there were no more than 25% I, and already 64% T).

7 — This leads us to enquire into the display of certain definitely primary T forms of response of the tissues in Hansen's disease. This is particularly so in the following situations:

7.1 — As in primary tuberculosis of the skin and its cutaneous lymphnode complex (cf. Bruusgaard, 1926), the fundamental finding of Souza Lima and Souza Campos (1947) of the "infantile nodular T" forms did not imply the need for any I root. They were, though rare today, clearly primary, and data from 1947 and also more recently those given by Pessoa Mendes (1956) confirm, without a shadow of doubt, the primary nature of these "Early infantile T infiltrates", avoiding with this designation the word "leprosy".

In these cases, Pessoa Mendes observed 7 out of 12 with more than three lesions, three of these cases having 8, 17 and 23 lesions (the latter being found in two sisters, contacts who perhaps received infinitely large doses of infecting bacilli).

A spontaneous healing was observed in 8 of the 12 cases, the rest being in a clear state of involution. Mitsuda was strongly positive in all of them with + + +, and only one case with + +. It is important to notice that the follow-up was between 5 and 14 years — in Souza Campos' material it was between 15 and 21, as a rule with stable scars and definite "vermiculate" appearance.

The histological picture, for which P. Rath was responsible, revealed an almost equal number of *torpid structures* in 4 cases, reactional in 5. It is curious that this reactional aspect was only microscopic, *never clinical*, and it did not coincide in the case of the little sisters, one with 23 lesions, and found to be torpid, and one with 17 lesions, with reactional findings. Only these cases with numerous lesions were a hint to probable hematogenic origin, while in the majority of these infantile T cases, the solitary nature of the lesions or their very limited number recalls the discussions about the possible exogenous origin of certain cases of Lupus Vulgaris.

We must therefore accept that there are primary forms, such as cases I, Infantile T, and TR, that dispense *before or after* any kind of lesions. We should notice that in Souza Campos' infantile cases, this careful observer has already pointed out that they were strongly

immunopositive — i.e., Mitsuda-positive long before the nodular T lesions, judging from the children who, living in the same conditions, clearly showed that they were suffering from sub-clinical infections, without any overt evidence of disease.

* * *

Knowing already the *main potentialities of persistently* immunonegative contacts, it is now the *lieu et place* to examine them in the light of the findings of Dr. Convit and his group.

Small children 0-4 years of age will not be included, with an option limited almost only to the group and type T (BT or TT according to British authors); as well as school children between 6-10 years of age with options still limited to the forms T and to the group I — "Immature" Hansen's disease.

It is precisely the groups of young contacts between 12 and 19 years of age, vaccinated with the proposed Vaccine of *M. Leprae* + BCG, that are of interest, because there one can find human recipients who, as is known, still have a chance of displaying resistance.

It is well known that in endemic countries, individuals who remain immunonegative to the Mitsuda test, from 16 to 20 years of age, are already considered as potentially dangerous and of high risk.

This situation is now being challenged by the vaccination efforts of the Convit proposal, with *results* still limited by the as yet small number of people vaccinated: 25 to 357 vaccinated between the ages of 12 to 14, and 15 to 19.

These are, however, promising results, as besides the immunological reversal, respectively from 89.8 to 92.9%, there did not occur *any apparent disruption* in the *statu quo ante*, i.e., without clinical sign of progression towards any form, even T, of the overt disease. As to the immunological level, Rotberg, who repeatedly studied this subject in 1934 and between 1937 and 1944, provided observations about the immunological root of the overt disease. As is well-known, Rotberg (1937) established that Mitsuda anergy results from a congenital incapacity to respond to lepromin, due to the lack of a congenital protection factor — Factor N (or better called, perhaps, NR for native resistance).

Hence, the corollary idea of the existence of an "anergic margin" at the root of L(V) forms a circumstance fortunately limited to only some 20% — which has now been corrected in a more precise estimate by Convit's figures to *no more that 8-10%* — of vaccinated contacts.

There would then be a "ceiling" for the appearance of L(V) forms as was suggested, on the epidemiological level, by Kajpoor in India (1963). Another piece of evidence in favour of this limit of the anergic margin is shown by the well-known fact that even for those in very close contact (husband and wife) a persistent negative Mitsuda does not necessarily mean an ominous future because it is quite possible, especially for the woman, to stay "healthy" indefinitely, although immuno-negative: living in a condition of subclinical infection, enjoying a native and/or acquired resistance, which I have proposed to call resistance with a small *r*.

This is ideal material for future enquiries which, in terms of sub-clinical infections, may help us to discover the *biological matrix* of the disease, and in the near future a possible field of choice for immuno-prophylactic attempts on the lines of Dr. Convit's *M. leprae* + BCG vaccination.

Access to discovery in the field of scientific research lies, as in other areas of thinking, in achieving "new forms to new contents".

The work being elaborated by Dr. Convit and his group had been following a careful Pastorian methodology.

The irreversibility, still always claimed, of the immuno-negative status vis-à-vis *M. leprae*, although fortunately limited in compromised hosts, shows more than one vulnerable point whether in spontaneous conditions or, as has now been demonstrated by Dr. Convit's findings, with the use of a powerful immuno-therapeutic challenge.

For this reason, all of us Hansenologists in Latin America are following with enormous interest the efforts of our Venezuelan colleagues to launch an attack on the hitherto inaccessible set of states that may lead to Virchow's leprosy, now finally vulnerable at its very roots.

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EPIDEMIOLOGY OF LEPROSY

S. K. NOORDEEN
Leprosy Unit, World Health Organization,
Geneva

1. Introduction

The control of leprosy through a better understanding of the epidemiology of the disease is beset with several problems, some relating to the inadequacy of the tools for use in the field, and others resulting from the peculiarities of the disease itself. Furthermore, the lack of standard terminology for defining the disease and its classes, the need for long-term investment in efforts, and the generally low priority given to the disease in several countries have added to the frustration of the epidemiologist in this field.

2. Distribution of Leprosy in Space and Time

2.1 *Geographic distribution*

The geographic distribution of leprosy in the world is shown in Figure 1. The estimated total number of leprosy patients in the world varies from 10 to 12 million. The last estimate made by WHO in 1975, was about 10.6 million (Sansarricq, 1981). Since then, in spite of variations in certain countries, the total estimate for the world appears to remain at about the same level.

Of the estimated cases, Asia contributes to the largest share with about 62 per cent, followed by Africa with about 34 per cent, South America with about 3 per cent, and the rest of the world with about 1 per cent. However, in terms of intensity of the disease in the population, that is, mean prevalence by continent, the problem is about

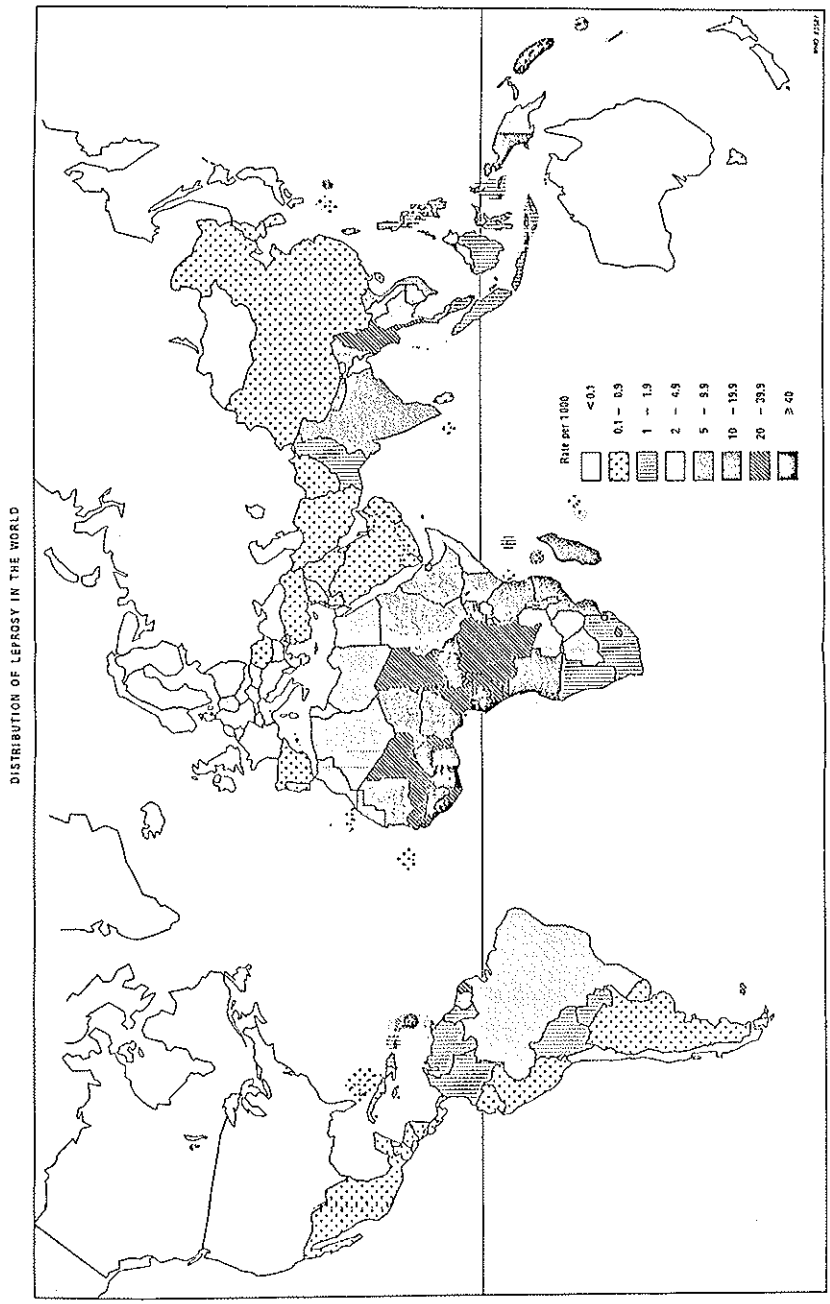
DISTRIBUTION OF LEPROSY IN THE WORLD
Rate per 1000
< 0.1
0.1 – 0.9
1 – 1.9
2 – 4.9
5 – 9.9
10 – 19.9
20 – 39.9
≥ 40

FIG. 1

three times as intense in Africa as it is in Asia. Almost one billion people in the world live in high endemic areas where the prevalence of leprosy is at least one per 1000.

In countries where leprosy is endemic, the prevalence rates show marked variations, with rates ranging from below one per 1000 to over 50 or more per 1000. Considerable variations in prevalence are known to exist within countries and even between adjacent areas. In fact, the uneven nature of the distribution of the disease appears to be a characteristic of leprosy.

An interesting feature of leprosy is the geographic variation seen in the occurrence of lepromatous leprosy, as indicated by the proportion of lepromatous cases over total cases, and often expressed as lepromatous rate. This rate varies from below 5 per cent to over 70 per cent in different parts of the world.

2.2 *Age Distribution*

Leprosy is known to occur at all ages, ranging from early infancy to very old ages. The youngest case seen by the author was in an infant of two and a half months, where the diagnosis of tuberculoid leprosy was confirmed by histopathology. Occurrence of leprosy, presumably for the first time, is not uncommon even after the age of seventy.

Figure 2 shows the age-specific incidence rates in a part of South India where leprosy is highly endemic. The pattern is very similar to that seen in many high endemic areas, where there is a clear peak at ages 10-14, followed by a depression which in turn is followed by a rise and a plateau covering ages 30-60. The bimodal curve in high endemic areas suggests the possibility of two distinct experiences, one among children and the other among adults. In the absence of specific immunological tools to measure subclinical infection, one can only speculate on the assumption that the disease occurrence parallels the acquiring of infection. Even so, it is difficult to accept that a large number of persons in high endemic areas acquire infection and disease for the first time at a late age. There are two possible explanations for this. One is that the incubation or latent period is very long in a proportion of infected individuals, resulting in manifestation of disease late in their lives, possibly somewhat similar to endogenous reactivation in tuberculosis. The other explanation is that leprosy in adult life in endemic areas is often the result of re-infection or superinfection among individuals who had previously been infected

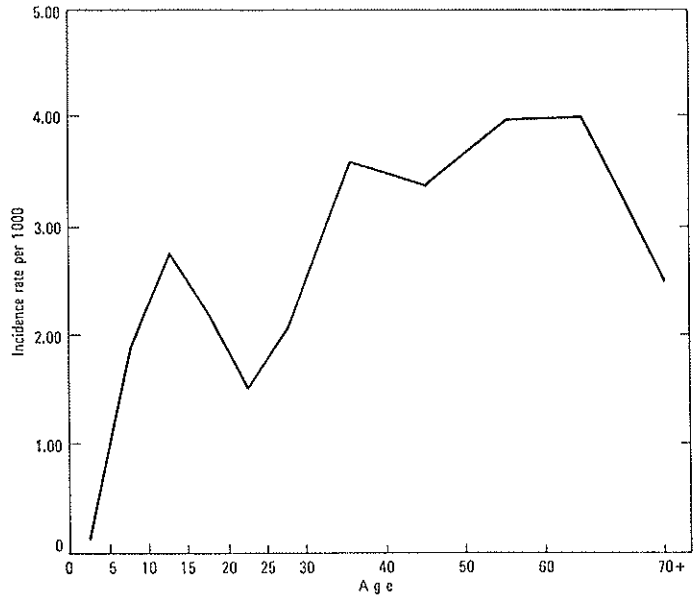

FIG. 2. Age-Specific Incidence of Leprosy in South India.

and whose immune response to leprosy had become inadequate as they grew older. In either case, in the absence of a specific method for identifying sublinical infection and strain variations of *M. leprae*, the hypotheses will remain untested.

2.3 *Sex distribution*

Although leprosy affects both sexes, in most parts of the world males are affected more frequently than females, often in the ratio of 2:1. This preponderance of males is observed in as diverse geographic situations as India, Philippines, Hawaii, Venezuela and Cameroon. Doull *et al*, from their studies in the Philippines, have also pointed out that the difference was a true difference due to higher incidence among males, and not due to differing duration of disease for the two sexes.

2.4 *Clustering of leprosy*

The more frequent occurrence of leprosy in certain clusters, particularly family clusters, is well recognized. However, the most debated point is whether this is due to the clusters sharing the same environment or the same genetic predisposition, or a combination of both. The occurrence of leprosy in clusters has been particularly observed in low endemic areas, and well documented in Norway and Louisiana.

2.5 *Time trends in leprosy*

Just because leprosy as a disease has a chronic course, it is often assumed that the epidemiological situation in any area remains static. In fact, the epidemiological situation is capable of a considerable amount of dynamic changes, and the factors that influence these changes are many. Both long-term and short-term trends have been studied with regard to occurrence of leprosy.

2.5.1 *Long-term trends*

In Northern Europe, continental United States, Venezuela, Japan and Hawaii, there have been well-documented studies on decline in incidence of leprosy leading gradually to virtual disappearance of the disease in the native-born population. In northern Europe the peak was reached in medieval times, with the decline occurring last in Norway during the 19th century (Irgens, 1980). Careful analyses of declining incidence rates in Norway, Hawaii and Japan reveal several features which are similar to those of tuberculosis under similar circumstances, including (a) a gradual increase in the mean age at onset of disease over time, (b) a decrease in age-specific incidence rates within successive cohorts associated with a fall in the mean age at onset, and (c) a gradually increasing proportion of the lepromatous type over a period of time among incidence cases.

2.5.2 *Short-term trends*

Among short-term trends the well-documented leprosy epidemic at Nauru Island in the Pacific is unique in many ways (Wade and Ledowsky, 1952). It showed that, although leprosy is generally an endemic disease, occasionally it is capable of reaching epidemic proportions when conditions are favourable. The disease was probably

introduced into Nauru for the first time in 1912 by a patient from the nearby Gilbert Island. By 1920 there were four known cases, and by 1924 at least 24 per cent of the population of 1200 were known to have been affected. The sudden increase followed an epidemic of influenza. The disease started declining after 1927 and by 1952 only 4 per cent of the population were affected, and this had declined to less than 1 per cent by 1981. Less dramatic outbreaks have been reported from Eastern Nigeria, New Guinea and the Pacific Islands of Ponape and Truk.

The short-term outbreaks reported so far have certain common features. They include occurrence of disease in an unselected manner throughout the community irrespective of age, sex and household contact status, and the type of leprosy which was mostly tuberculoid with a high tendency for spontaneous healing.

2.6 *Occurrence of deformities*

The occurrence of deformities in leprosy is one of the important concerns about the disease. About one-fifth to one-third of leprosy patients develop deformities of varying degrees. Deformity in leprosy is not only permanent, but in many instances also progressive even after the disease has become inactive. This is largely due to the component of sensory loss that occurs with the disease. The proportion of deformity is higher in lepromatous leprosy than in non-lepromatous leprosy, resulting from the progressive nature of the former type. In addition to physical deformities, and mainly as a result of them, leprosy patients in many societies suffer from an additional burden of social disability due to the stigma attached to the disease.

3. The Prevalence Pool

The prevalence pool of leprosy in a population in general is in a constant flux resulting from inflow and outflow. The inflow is contributed to by the occurrence of new cases, relapse of cured cases, and immigration of cases. The outflow is mainly through cure, death, and emigration of cases. Of the various factors that influence the prevalence pool, the importance of spotaneous inactivation of disease and mortality are less well recognized.

3.1 *Inactivation of Disease*

Where leprosy treatment facilities exist, inactivation or cure due to specific treatment is an important mode of elimination of cases from the prevalence pool. Even in the absence of specific treatment, a majority of patients, particularly of the tuberculoid and indeterminate types, tend to get cured spontaneously. A study in Culion Island in the Philippines showed that, among children, self-healing occurred in 77.7 per cent of cases (Lara *et al*, 1956). A later study in South India involving long-term follow-up of a high endemic population (Noordeen, 1975) showed that, among newly detected tuberculoid cases of all ages and both sexes, the rate of inactivation was 10.9 per cent per year, the bulk of inactivation in the study being spontaneous (Table 1).

TABLE 1 – *Inactivation of tuberculoid leprosy by age*

Age group in years	Total cases	No of cases inactive	Inactivation Rate per year %
0–9	47	24	14.6
10–19	72	24	9.5
20–29	41	18	12.5
30–39	45	14	8.9
40–49	30	11	10.5
50 and over	35	12	9.8
TOTAL	270	103	10.9

3.2 *Mortality in Leprosy*

Mortality in leprosy is often considered unimportant because the disease is rarely an immediate cause of death. However, leprosy patients are exposed to increased mortality risks due to the disease's indirect effects. In a study in Cebu, Philippines (Guinto *et al*, 1954), it had been found that the mortality rate for lepromatous patients was four times more than that of the general population, and that the situation for non-lepromatous patients was very similar to that of the general population. A comparative study of lepromatous patients,

non-lepromatous patients, and general population from the same rural area in South India (Noordeen, 1972) showed that the standardized death rate for lepromatous patients was three and a half times that of the general population, the non-lepromatous patients themselves having a mortality risk which was twice that of the general population (Figure 3). In that population, leprosy was found to contribute to about 1 per cent of all deaths.

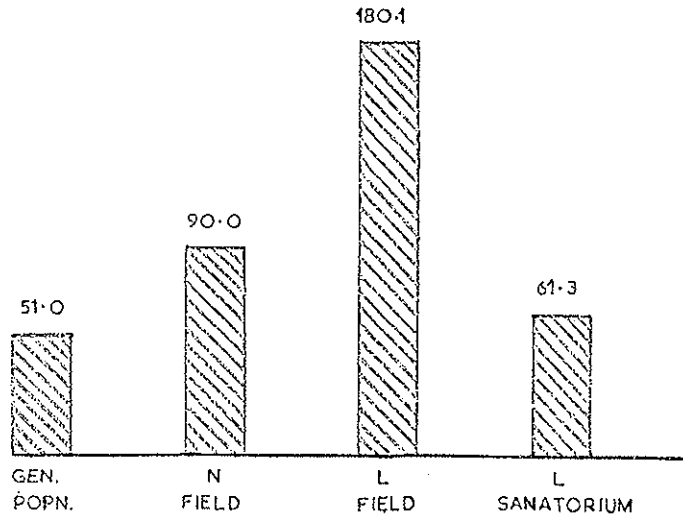

FIG. 3. Standardized death rates (per 1000 for 6 years) among general population, non-lepromatous cases (N) from the field, lepromatous cases (L) from the field, and lepromatous cases from the sanatorium.

4. Transmission Factors

4.1 *General Considerations*

There are several constraints in studying the transmission of leprosy. Unlike many other communicable diseases, in leprosy there is considerable difficulty in identifying the three reference points that are involved in the transmission of the disease, these being the onset points of exposure, infection and disease. The problem with the onset point of exposure relates mainly to the clear identification of the source of infection, which is not always easy. The problem with the onset point of the disease is related mainly to the insidious nature of the onset of the disease in most instances. The identification of the point of onset of infection is the most important and most difficult problem in the study of transmission. Although the future in this area appears to be very promising with the availability of specific and sensitive tests, at present there is no test dependable enough to measure sub-clinical infection with sufficient sensitivity and specificity for use in epidemiological studies. Until such a test becomes available the epidemiological picture of leprosy will remain incomplete.

4.2 *Reservoir of Infection*

The only known reservoir of infection in leprosy is the human being. However, a naturally occurring disease with organisms indistinguishable from *M. leprae* has also been detected among wild armadillos in parts of Southern United States (Walsh *et al*, 1981), though the epidemiological significance of the animal is generally considered to be negligible. Among human beings it is the lepromatous cases that carry the largest load of organisms, with the maximum load reaching over seven billion organisms per gram of tissue. Patients of non-lepromatous leprosy carry a very much smaller bacillary load, probably not exceeding one million organisms in total. In addition to clinically identified cases, occurrence of AFB in the skin (Figueredo *et al*, 1949; Chatterjee, 1976a) and nasal mucosa of healthy subjects (Chacko *et al*, 1979) have also been reported. The evidence that the AFB found on such "carriers" is *M. leprae* is not conclusive, although there is some evidence that persons who carry such AFB have a higher chance of developing the disease as was found during their follow-up (Chatterjee *et al*, 1976b).

4.3 *Portal of Exit of* M. leprae

The two portals of exit of *M. leprae* often described are the skin and the nasal mucosa. However, the relative importance of these two portals is not clear. It is true that the lepromatous cases show large numbers of organisms deep down the dermis. However, whether they reach the skin surface in sufficient numbers is doubtful. There is no doubt that when lepromatous patients have ulcers from the breaking down of nodules, or when they have other breaks in their skin, large numbers of organisms could be discharged. It is also possible that, apart from breaks in the skin, small numbers of organisms escape to the surface of the skin along with sweat and sebaceous secretions. Regarding the nasal mucosa, its importance had been recognized as early as 1898 by Schaffer (1898), particularly that of the ulcerated mucosa. The quantity of bacilli from nasal mucosal lesions in lepromatous leprosy has been demonstrated by Shepard (1960) as large, with counts ranging from 10,000 to 10,000,000.

4.4 *Portal of Entry*

The portal of entry of *M. leprae* into the human body is not definitely known. However, the two portals of entry seriously considered are the skin and the upper respiratory tract.

With regard to the respiratory route of entry of *M. leprae*, the evidence in its favour is on the increase in spite of the long held belief that the skin is the exclusive portal of entry. Rees and McDougall (1977) have succeeded in experimental transmission of leprosy through aerosols containing *M. leprae* among immune-suppressed mice, suggesting a possible similarity among humans.

4.5 *Subclinical Infection in Leprosy*

Although reliable tools for a routine study of subclinical infection in leprosy have yet to be made available, limited studies based on measuring immune-response in healthy subjects have indicated that a much larger proportion of persons exposed to leprosy than those seen with the clinical expression of the disease acquire infection.

Godal in 1973 was the first to measure CMI response through the lymphocyte transformation test among different categories of persons exposed to leprosy. He found that the test was showing a gradation of

response among Europeans visiting Ethiopia according to the period of their stay and their proximity to leprosy patients. Contacts of leprosy patients also showed a high rate of response to LTT.

With regard to the humoural antibody response, Abe (1980) has applied his indirect fluorescence (FLA-ABS) test among different categories of the population of Okinawa. The test was found not only to be positive in 100 per cent of polar lepromatous and borderline lepromatous patients, 88 per cent of borderline tuberculoid patients and 77 per cent of polar tuberculoid patients, but also positive to the extent of 92 per cent among household contacts. None of the heatlhy non-contacts or patients with pulmonary tuberculosis were positive to the test.

In addition to the above, skin tests with various preparations of lepromin, and more recently with soluble antigens from *M. leprae*, have also provided useful information on the occurrence of sub-clinical infection, although the specificity of these tests, particularly of the integral lepromin, has been rather questionable. Zuñiga *et al* (1982), using the soluble skin antigen prepared by a method developed by Convit, have found that the skin test positivity in a part of Venezuela was 19 per cent among non-household contacts and 48 per cent among household contacts.

4.6 *Method of Transmission of Leprosy*

The exact mechanism of transmission of leprosy is not known. At least, until recently, the most widely held belief was that the disease was transmitted by contact between cases of leprosy and healthy persons. More recently the possibility of transmission by the respiratory route is gaining ground.

The term "contact" in leprosy is generally not clearly defined. All that we know at present is that individuals who are in close association or proximity with leprosy patients have a greater chance of acquiring the disease. However, it is the definition of contact by early workers with qualifications such as "skin to skin", "intimate", "repeated", etc., that has made it appear as if the disease could be acquired only under such conditions, and that the transmission involved some kind of "inunction" or "rubbing in" of the organisms from the skin of affected persons into the skin of healthy subjects.

There is considerable evidence that household contacts of leprosy are at high risk of infection and of disease. A large population-based

study in the Philippines was the first to provide age standardized attack rates for clinical leprosy per 1000 persons/years of observation according to type of primary case. In non-contacts, contacts of "neural" (non-lepromatous) and "cutaneous" (lepromatous) cases, the attack rates were 0.83, 1.6 and 6.23 per 1000 years of observation respectively (Doull *et al*, 1942). Later studies have confirmed this trend as was seen in South India (Table 2).

TABLE 2 – *Incidence by Contact State*

Contact State	Number Exposed	New cases in 5 years	Incidence per 1000 per year	Relative Risk
Non-Contacts	186,047	1,723	1.85	1
Contacts of non-lepromatous cases	11,173	379	6.78	3.7
Contacts of lepromatous cases	1,025	90	17.56	9.5
Contacts of both types	12,198	469	7.69	4.2

An interesting observation with regard to risk for contacts, is the exceptional situation in Europe, where immigrant cases and Europeans, who had returned home after acquiring leprosy in endemic countries, have failed to produce secondary cases among their contacts. There is as yet no plausible explanation for this. The other interesting observation in many studies is the observance of a relatively low rate of conjugal transmission.

In endemic areas, the observance of high risk for contacts should not lead to underestimation of the importance of the non-contact population in terms of their contribution to the total yield of new cases. Even with a relatively low risk, the non-contact population contributes to a larger share of new cases solely because of its large size in comparison with the contact population. Even in highly endemic areas, the contact population contributes to less than 15 per cent of the total population, and even with the increased risk its contribution to the total new cases is less than 25 per cent, the rest of the 75 per cent or so of new cases coming from the non-contact population, which has a relatively low risk.

With regard to contacts of non-lepromatous cases, although they have a low risk relative to contacts of lepromatous cases, their risk is still higher than that for non-contacts. Even with a relatively low infectivity, non-lepromatous cases contribute to as many or more new cases as lepromatous cases. This is because of the much larger proportion of non-lepromatous cases which, therefore, contribute to a much larger share of the total contact population. Thus, the collective potential of non-lepromatous cases as sources of infection should not be underestimated.

5. Factors Determining Clinical Expression After Infection

5.1 *General Considerations*

There is sufficient evidence in leprosy to show that all people who get infected do not develop the disease. The factors that determine clinical expression after infection appear to be as important as the factors that determine infection after exposure. Of the many possible factors that determine clinical expression of disease, a few are discussed below.

5.2 *Genetic Predisposition*

Although the relative contribution of genetic host factors versus environmental factors is still far from clear, both twin and family studies indicate an important contribution of host genetics to the type of disease developing after infection. Whether genetic factors also contribute to differential susceptibility to infection with *M. leprae*, or to the development of clinical leprosy irrespective of the type, is less clear. There is now ample evidence that HLA-linked genes influence the development of tuberculoid leprosy (de Vries *et al*, 1981) and evidence has recently been presented for HLA-linked control of lepromatous leprosy (van Eden, 1983). These HLA-linked genes do not seem to control susceptibility to clinical leprosy *per se*, but rather to determine the type of disease to develop.

5.3 *Route of Infection*

Recent studies by Shepard *et al* (1982) in the mouse foot-pad model suggest that the route of entry of the organism may, to some extent, determine the occurrence of leprosy. This is based on the

observation that while intradermal administration of killed *M. leprae* sensitizes the animal, intravenous administration of killed *M. leprae* tends to tolerize the animal as studied through skin test reactivity. This also raises the possibility of tuberculoid and lepromatous leprosy being the result of different routes of entry of the organisms.

5.4 *Re-infection*

The occurrence of leprosy, presumably for the first time, in older individuals in endemic areas has raised the possibility of re-infection in these individuals, as it is difficult to believe that they remained uninfected for such a long period in an endemic area. However, this occurrence in the older ages can also be explained by the possibility that the disease in these persons represents reactivation of old undetected primary disease following waning of previous acquired immunity. As there is no evidence of a distinct primary disease occurring in leprosy as in tuberculosis, the hypothesis of re-infection gains some importance. Further, the occurrence of relapse in lepromatous leprosy also suggests, at least in a proportion of relapsed individuals, the possibility of re-infection. There is nothing against these immune deficient inactive patients living in endemic areas succumbing to fresh infection. In the absence of a method for identification of strain variations of *M. leprae*, the hypothesis on re-infection will remain untested.

5.5 *Prior Infection with Other Mycobacteria*

There is some evidence that prior infection with the atypical environmental mycobacteria and possibly *M. tuberculosis* influence the occurrence of leprosy. BCG vaccination itself is known to provide a degree of protection against leprosy as shown in Table 3 (Sundaresan, 1982; Scott *et al*, 1982; Stanley *et al*, 1981; and Tripathy, 1983). This is possibly due to the antigenic overlap between *M. leprae* and other mycobacteria. The varying degrees of protection given by BCG against leprosy in different geographic areas, and the limited protection seen among natural tuberculin positive reactors in the BCG study in Uganda (Stanley *et al*, 1981), support this possibility. Rook *et al*, (1981) have gone further and have suggested that the protective efficacy of BCG in different areas may get enhanced or diminished, depending upon the local environmental mycobacteria, some acting synergistically with BCG and some antagonistically.

TABLE 3 – *Major Field Trials with BCG*

Country	Control			BCG			
Number of Study Subjects	Person-Years	New Cases	Incidence ‰ per year	Person-Years	New Cases year	Incidence 0/00	Protection %
BURMA (28 220)	151 060	831	5.5	151 415	663	4.4	20.4
NEW GUINEA (5 544)	27 100	172	6.3	29 300	100	3.4	46.0
UGANDA (10 990)	42 800	192	4.5	43 300	37	0.9	80.9
INDIA (181 400)	240 000	2 301	9.6	488 000	3 602	7.4	23.0

6. SUMMARY AND CONCLUSIONS

A critical review of the past progress in the field of epidemiology of the disease reveals several features unique to leprosy. These include study of the disease by traditional leprologists often isolated from the mainstream of developments elsewhere, the relative scarcity of hard information in published literature, the extensive use of ill-defined and non-standardized tools such as lepromin for epidemiological reasoning, and the widespread confusion in the application of terminology relating to disease states. Nonetheless, the fact remains that leprosy is one of the most challenging of diseases from the point of view of both its understanding and control.

The progress in basic research in leprosy in recent years has opened or promises to open a wide vista of opportunities for the epidemiologist. With the imminent availability of dependable and easily applicable immunological tools to measure humoral as well as cell-mediated immune response, the time has now come to formulate appropriate hypotheses to be tested under a variety of conditions

utilizing standardized methodology. The choice of hypotheses to be tested, at least to begin with, should focus on those directly relevant to disease control.

While measurement of infection state through immunological tools, as against measurement of disease state, could be very valuable in identifying risk factors for infection, it should not be forgotten that in leprosy disease determinants after infection are probably equally or even more important than determinants for infection. Again there could be a degree of interaction between these two sets of determinants.

The relationship between infection and disease in leprosy does not appear to be a constant one as seen from the finding that age-specific incidence of infection does not appear to parallel age-specific incidence of disease. For instance, the occurrence of new disease among significant numbers of older adults in high endemic areas cannot be explained simply as resulting from recent infection, as is the case among younger children in the same area. It is difficult to accept that the older individuals who develop the disease had remained uninfected for long periods in such high endemic areas where *M. leprae* infection is so ubiquitous and opportunities for exposure so frequent. Issues such as these need to be studied with appropriate tools to explain better the natural history of the disease and to explore possibilities such as re-infection.

In the past, the study of disease determinants appears to have focused more on genetic predisposition than on other factors. In this context the experience of the host with regard to exposure to other mycobacteria prior to infection with *M. leprae*, and the subsequent experience of the host with regard to repeated doses of *M. leprae* after a primary infection, are questions which need to be studied in some depth. Studies on these need to be carried out not only in high endemic areas, as has been the common practice hitherto, but also in areas where leprosy has a low endemicity and in areas, as in parts of Europe, where autochthonous leprosy fails to occur in spite of the presence of active sources of infection in the immigrant population.

A very interesting feature of leprosy is the variety and gradation of response of the host to *M. leprae*. This response extends from subclinical infection as demonstrated by *in vitro* lymphocyte tests, skin test conversion, serum antibodies, and occurrence of AFB on healthy skin at the one end to lepromatous leprosy at the other end. In between one observes the early monomacular self-healing lesions as well as

well-characterized disease states such as tuberculoid and borderline leprosy. However, the factors that contribute to this wide gradation of response are not clear, whether they are mainly genetic or environmental or a combination of both. While genetic predisposition has been demonstrated both for the tuberculoid and lepromatous leprosy through HLA markers, its importance vis-a-vis the environmental influences is still to be determined. In this context the occurrence of divergent types of leprosy among monozygotic twins, at least among some, is a case in point.

Regarding the transmission process itself, although direct man-to-man transmission is the well accepted view in leprosy, whether through respiratory or skin route, the possibility of extra-human reservoirs existing in close proximity to man cannot be excluded. In any case there appear to have been very few attempts to search for these. The contribution of an extra human reservoir can possibly explain some of the unexplained features of leprosy, such as the very uneven geographic distribution of the disease, the uneven risk of leprosy in different geographic situations even for household contacts, the rapid rise and fall of leprosy in certain situations, and the non-occurrence of secondary cases among contacts of immigrant leprosy cases in parts of Europe.

A major problem facing leprosy research is how to evaluate the efficacy of tools for intervention such as vaccines in a reasonable period of time. The present approach of measurement of outcome through disease occurrence is not only an indirect measure of transmission of infection, but also one that requires follow-up of populations for very long periods of time. Therefore, there is an urgent need to develop tools that could serve as dependable intermediate markers in the measurement of outcome in such intervention trials. In addition there is a need for the development of appropriate epidemiometric models to predict and compare the different methods of intervention, as had been demonstrated by Lechat *et al* (1977) earlier.

Lastly, it should be pointed out that any investment in the study of epidemiology of leprosy can be justified only through its potential utility for disease control, whether direct or indirect. In this connection, an area that needs emphasis is health services research in relation to leprosy. There is also a need to recognize the importance of social and economic aspects of leprosy and to study these by employing an interdisciplinary approach in which epidemiology could play a significant role.

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SOCIAL ASPECTS OF LEPROSY

By

R. K. MUTATKAR

Department of Anthropology,
University of Poona,
Pune 411 007, India.

Leprosy is known as a 'great disease' by common people. Scientists interested in leprosy find it challenging. Medical practitioners find it uninteresting. Social scientists do not consider leprosy as their domain. Administrators are interested in the prevalence and incidence rates. Social workers try to focus on the rehabilitation of patients. Men of religion treat leprosy with compassion. Leprosy is thus differently perceived, but least understood. People are afraid of it since it brings social death and changes the identity of a person. Leprosy control programmes are greatly concerned in developing technology to prevent transmission and ensure cure with a view to reduce the pool of infection. But the situations connected with delivery of technology to people lead to various problems such as drug resistance. People are more concerned with clinical manifestations of the disease than with bacteriological condition and they are mortally afraid of deformity.

Social aspects of leprosy have been conventionally understood as dealing with socio-economic and rehabilitative problems of leprosy patients. Humanitarian work of sheltering leprosy patients in leprosy villages has been designated as great social work and is lauded as service to God. Till the International Congress of 1984, sessions on Social Aspects used to be concurrent sessions and the workshop was designated as on Human Aspects relating to treatment of leprosy patients. Shift in the emphasis from patient to community emphasizes the role of social sciences in preference to humanitarian social work. Researches presented at the Social Aspects session at the XII Congress related mainly to the need and methods of health education, the role of

migration of people, the burden experienced by families of leprosy patients, the problem of drop-outs, attitudes of people about leprosy, problems of rehabilitation, and self-developed colonies.

These types of researches have been attempted by (1) those social science students who have no understanding of the medical problem of leprosy, and (2) the para-medical staff in leprosy control establishments to seek solutions to the problems of compliance.

Health education has also been misunderstood, in practice, as a tool to ensure compliance of people with leprosy control strategies.

The social aspects thus continue to be misunderstood as dealing with the rehabilitation of patients and socio-economic reasons for non-compliance. For people the disease threatening social death continues to be dreaded and stigmatised. They do not understand:

(1) Why one gets it. Knowledge of immunology does not reach them through health education programmes.

(2) How does it spread?

(3) Why their doctors do not confidently diagnose it but refer them to places like leprosy clinics which are 'haunted' places.

(4) Why long treatment is given which does not bring about any perceptible change in a reasonable period and usually no duration of treatment is prescribed.

(5) Why one gets deformities.

Answers to some of these questions are not known to anybody and if they are tried to be explained to common people, it may put more fear in their minds, knowing more uncertainties about the disease. In spite of widespread literacy programmes, people occupying decision-making or opinion-making positions such as law givers, administrators, teachers, religious leaders are equally ignorant about leprosy and nurture prejudices handed down by tradition.

The scientists, on the other hand, are engaged in developing better drugs and vaccine against leprosy in order to control the disease. DDS is still considered an effective drug but the problem of compliance has led to drug resistance issues. MDT is now considered effective but how would its delivery to people be ensured when DDS could not be delivered to the people? Smallpox vaccine has taken 200 years to produce results; polio vaccine is still ineffective in the sense that most orthopedic disabilities are due to polio.

Thus, tools developed under laboratory conditions may be ideal, but unless their use by people is ensured, they are ineffective. Common people, whose perceptions of organised and disorganised life are culturally patterned, do not possess enough motivation to take care of their health, particularly in case of chronic ailments like leprosy which do not require immediate attention. Those illnesses are cared for by people who hinder their playing of effective social roles, who hinder their efforts in fulfilling social obligations. In leprosy, that stage is reached when a person's identity as a member of a social group is threatened and when remedial action is difficult.

The term social aspects used in leprosy should actually include, in social science terminology, social, cultural, economic, political, psychological and religious issues. It would thus refer to the interplay of forces that act on the patient, the family, the community, health workers and the drug industry. This broad understanding of social aspects would give better insights into the role of these aspects in the transmission and control of leprosy.

The crux of leprosy control programmes, from the people's point of view, should aim at preventing deformities. People are afraid of leprosy because of deformities. Deformity threatens personal identity by threatening social death. The close association of the word leprosy with deformity prompts a person not to accept the diagnosis, since its acceptance threatens social rejection. However, nerve damage research has so far not produced any preventable solution. The success of the programme can therefore be measured in terms of deformity rate.

The problems of case finding and case holding have been identified, and solutions have been suggested through health education, community participation and better management techniques.

A policy statement about health education adopted at the Post-Congress workshop on Health Education spells out the broad objectives: "Health Education refers to the process of assimilation of scientific health knowledge, attitudes and behaviour in the health culture of people. Health Education in leprosy aims at ensuring community participation in leprosy control programmes. Health education therefore addresses itself to the patients, their families, to the community and all components of health services".

The importance of listening to people and discussion is being more realised now in preference to one-way talk from the health education worker to pass on 'wisdom' to the people. Community participation is also getting its due importance, which would mean (i)

involvement of the community in the utilisation of services, (ii) participation in decision-making to meet the objectives: (a) increase the social acceptability and effectiveness of leprosy control, (b) increase cost effectiveness. Indicators of success of community participation would mean (i) deformity rate reduction, (ii) voluntary reporting, (iii) utilisation of services, and (iv) rehabilitation.

Although the transmission process is not conclusively known, transmission from one human to another calls for an understanding of the cultural habits of the people. Environments producing respiratory infections and the habits of spitting and sneezing by people are relevant for understanding droplet infection. Habits like tobacco-chewing need to be understood for their relevance. Contacts in all cultural groups are socially defined and are related to caste, class and kinship affiliations. Large-scale migrations and settlements in industrialised cities or at development sites have relevance for epidemiological studies. In cities like Bombay, the prevalence rate has become high due to migrations. The intensity of interaction in both sexes needs to be studied by variation according to sex.

In every society, the rules of endogamy and exogamy regulate mating patterns. These rules, having been followed for centuries, coupled with varying food habits and other cultural patterns, must have given rise to varying genetic compositions in various ethnic groups. Studies in population genetics may therefore be relevant in leprosy transmission. It is felt that not enough attention is given to strains amongst human beings as amongst strains in bacteria.

Multi-drug therapy has been liked by people since it has shown quick results in the clinical manifestations of the disease. The disappearance of nodules and change in skin colour have helped to regain the social identity which was being lost. Studies of the impact of MDT on the attitudes of patients, their families and health workers would be useful in a situation where MDT has been administered only to lepromatous and where it has been given to all patients.

Needed Research

The social sciences possess tools for quantitative as well as qualitative research. Usually a judicious combination of quantitative and qualitative methods is recommended for valid and reliable results. Research areas in social aspects could be broadly divided into (a) those

having a direct bearing on control programmes, and (b) those supporting epidemiological and immunological studies. This classification is, no doubt, arbitrary and not mutually exclusive, but it may give some guidelines for providing priorities or forming research teams.

In the first category, the following research areas could be included:

(1) Operational problems in case finding. Comparative study in high and low prevalence zones could be attempted from the standpoint of people and health workers.

(2) Case holding. Studies of absenteeism in high and low endemic areas. Case studies of regular people to understand motivational forces are necessary.

(3) The perception of leprosy by health workers at different levels.

(4) An evaluation of the effect of MDT on patients, and its relevance to Health Education, community and health workers.

(5) Action research or participatory research in community participation.

(6) The role of community health volunteers and traditional birth attendants in leprosy control and rehabilitation in the context of Primary Health Care.

(7) Studies in migration and leprosy, with special reference to ethnic groups from endemic areas.

(8) The perception of stigma by the community and patients and the degree of stigma actually experienced.

(9) Studies of cured persons accepted back by the community to understand the reversibility of stigma.

In the second category, the following research areas could be included:

(1) Contact studies with reference to extended kin group, including consanguineal and affinal kin.

(2) Correlation studies of leprosy with crowding, personal hygiene habits and environmental sanitation.

(3) Attitudes of people about other vaccination programmes.

(4) Studies in social structure to understand mating patterns, rules of endogamy and exogamy, patient interaction with other members of the group, and rules of physical proximity.

(5) Studies of local physical environment with special reference to micro-environment of patients in terms of daily mobility, eating, drinking and sleeping habits, etc.

(6) Relevant studies about morbidity, with particular reference to skin, nervous and respiratory disorders.

It would be necessary to associate social scientists as members of multi-disciplinary research teams giving them equal status. This would also ensure understanding of relevant research issues by social scientists. Social scientists are good in evaluation research. They are also good at providing background social and economic information about the community as well as about the perceptions of people which is necessary before planning MDT or vaccine trials.

The traditional cultures of people do not equip people for precision management. Sophisticated tools require precision and a high degree of motivation. Life styles of various groups vary and keep changing, which may add to variables in immunology and epidemiology. Unless people are equipped to accept and use tools, they by themselves do not come forward. It is thus the business of social sciences to understand the process of culture and social change in the context of leprosy. Health education has a big role to play in changing people's responses, provided it is done with the help of community participation. The social aspects of leprosy thus involve the understanding of social, cultural and economic forces which have evolved historically and which keep on changing under the impact of technology.

ANIMAL MODELS FOR MULTIBACILLARY LEPROSY

W. M. MEYERS, G. P. WALSH and C. H. BINFORD
Armed Forces Institute of Pathology (AFIP)
Washington, D.C. 20306

R. H. WOLF, B. J. GORMUS, L. N. MARTIN, G. B. BASKIN
Delta Regional Primate Research Center
Covington, LA 70433

I. INTRODUCTION

Even though there have been outstanding advances in many areas of research in leprosy in recent years, there remains an urgent need for better animal models for studying the disease. The ideal model would be an immunologically unaltered animal that would manifest the entire spectrum of clinical forms of leprosy, reactional episodes, and peripheral neuritis with the deformities seen regularly in humans. No reported animal model satisfies these requirements. Most studies in the chemotherapy, epidemiology and pathogenesis of leprosy in humans have focused on the patient with multibacillary leprosy. Because of the importance of these areas of interest, this discussion will emphasize studies on those animals that have potential as models for multibacillary leprosy, i.e., borderline-lepromatous (BL) to polar lepromatous (LL) in the Ridley-Jopling (1966) system of the classification of leprosy.

II. HISTORICAL BACKGROUND

On February 28, 1873, Hansen took "magnificent nodules" from the alae nasi of patient Jobs Gil, scraped the cut surface of the nodules with a knife, and observed brown rod-shaped bodies in wet unstained

amounts of the tissue fluid thus obtained (Hansen, 1880). Although a transmissible etiologic agent of no other chronic disease of humans had yet been reported, and contrary to the prevailing view that leprosy was inherited, Hansen believed that leprosy was infectious and courageously announced that these rods were the cause. He undertook two avenues of study on this agent to prove his hypothesis: (1) he tried to grow the organism in artifical media, and (2) he tried to induce the disease in animals by the direct inoculation of animals. He was unsuccessful in both endeavors. During the next eighty years there were numerous additional attempts to transmit leprosy to many animal species, including cats, rabbits, monkeys, dogs, guinea pigs, rats and hamsters. Occasionally success was claimed; for example, Soule and McKinley, in 1932, believed that they had produced rapidly progressive leprosy in monkeys, when, in fact, they had merely elicited a spectacular Mitsuda reaction.

There was no rationale for the selection of species of animals or the site of inoculation of these experimental animals. In 1956, at the First Carville Conference on Progress and Potentials in Leprosy Research, Binford "elaborated the numerous details which support the thesis that in man the leprosy bacillus has a natural preference for anatomic sites of lower body temperatures and he expanded upon methods of applying temperature selection to animal experimentation." On making the observation that temperature might influence the growth of the leprosy bacillus, Binford began large scale studies in the ears and testes of animals, notably hamsters, and his findings were first reported in 1959. Further experiments, reported in 1965, demonstrated that there was regular (20 out of 21 experiments) invasion of nerves in the ears of hamster by *Mycobacterium leprae*; however, dissemination was never observed.

In 1960, Shepard reported the growth of *M. leprae* in the footpads of normal mice. This model, because of its reproducibility, has been highly useful in the detection of the viability of *M. leprae*, screening of antileprosy drugs, the detection of drug-resistant organisms, and studies on the antigenic properties of *M. leprae*. Rees *et al* (1967) produced disseminated leprosy in thymectomized and irradiated mice, but without immunologic manipulation or genetic deficiencies, the infection in mice is localized and self-healing, and does not resemble any of the established forms of leprosy in humans.

III. Animal models of disseminated leprosy

1. Armadillos

A. *Nine-banded armadillos* (Dasypus novemcinctus)

Storrs, while at the Gulf South Research Institute (GSRI), New Iberia, Louisiana, introduced the nine-banded armadillo into leprosy research. Storrs was impressed by the emphasis being placed on the hypothesis that *M. leprae* grew best in the cooler areas of the human body, and in experimental animals. Knowing that the core body temperature of the nine-banded armadillo was 30-35°C, she undertook studies on the transmission of leprosy in this animal (Storrs, 1971). In the initial study, four armadillos were inoculated intradermally in the abdomen and ears with a suspension of *M. leprae*. Approximately 15 months later, infiltrated lesions appeared at the sites of inoculation. Histopathologically, the infiltrations resembled lepromatous leprosy and there was invasion of nerves (Kirchheimer and Storrs, 1971). At necropsy there was widespread disease with extensive involvement of the lymph nodes, liver, spleen, lungs, bone marrow, meninges and other tissues. The infection was much heavier than usually seen in humans (Kirchheimer *et al*, 1972).

In the early studies at GSRI (1970-71), of 59 nine-banded armadillos inoculated, all intracutaneously, 24 (41%) developed disseminated leprosy. The salutary effect that this discovery had on research in leprosy is well known to medical science; however, it is amazing how little systematic research there has been on the development of the nine-banded armadillo as a model for the investigation of the pathogenesis, immunology, epidemiology and chemotherapy of leprosy.

Minimal infective doses of *M. leprae* have not been established, but the route of infection is important. Kirchheimer (1978) reported that 93% of armadillos receiving 10^8 *M. leprae* intravenously had disseminated leprosy within 550 days. Walsh (1978) points out that armadillos inoculated intravenously succumb to disseminated disease much earlier than those inoculated intracutaneously. In our recent experience at the AFIP, animals inoculated with 10^8 organisms intravenously develop heavy infections of the liver, spleen, and lymph nodes, but only small quantities of subcutaneous leproma. Animals

frequently become obtunded at 12 months. Approximately 90% of the animals that survive up to 15 months develop disseminated leprosy.

Apart from the low body temperature, the factors that render this animal susceptible to leprosy are unknown. Morphologically, the lymphoreticular system is intact and well-developed (Purtilo *et al*, 1975); however, lymphocytic function appears to be impaired at the body temperature of the armadillo (Purtilo *et al*, 1974). Lysozyme levels are low (Rea *et al*, 1979).

The Concanavalin-A responsiveness of mononuclear cells from armadillos is suppressed by antigens of *M. leprae* (Shannon *et al*, 1984) in a similar manner to the induced suppressor cell activity in patients with leprosy (Mehra *et al*, 1979). With rare exception (Job *et al*, 1982), only lepromatous leprosy has been observed in nine-banded armadillos. In clinical and histopathologic evaluations of more than 600 infected nine-banded armadillos, we have never observed a delayed-type hypersensitivity reaction to *M. leprae*, nor have we ever seen spontaneous regression of the disease. *D. novemcinctus* in South America appear to be more resistant than those from North America to infection by *M. leprae*. Opromolla *et al* (1980), however, have reported limited success in infecting this species in Brazil.

B. *Seven-banded armadillos* (Dasypus hybridus)

Only one study has been reported in which *Dasypus hybridus* was experimentally infected with *M. leprae*. Storrs *et al* (1975) inoculated each of two animals that originated from Argentina with 3.4×10^7 *M. leprae* intracutaneously at two sites on the abdomen. One of the armadillos developed a nodule at a site of injection at 14 months and the animal was killed at 24 months. There were lepromatous infiltrations in the skin, sciatic nerve, liver, spleen, and bone marrow. The remaining animal was clinically free of disease 13 months post-inoculation.

This armadillo regularly produces 8-16 monozygous offspring and should be an excellent model for the investigation of genetic influences on susceptibility and pathogenesis, but to our knowledge has not been further utilized.

C. *Eight-banded armadillos* (Dasypus sabanicola)

The eight-banded armadillo inhabits the savanna areas of Venezuela. Convit *et al* (1978) have reported the results of inoculation

of 93 *D. sabanicola* with *M. leprae*. A total of 35 animals developed clinical disease. Lesions appeared in several animals, and one armadillo had a hypopigmented area on the abdomen. There was histopathologic evidence of delayed-type hypersensitivity granulomas in some animals; however, in most, the disease was smiliar to that seen in *D. novemcinctus*. The potential of *D. sabanicola* for the study of its ability to produce lesions covering the spectrum of the forms of leprosy has not, to our knowledge, been pursued.

2. Primates

In the late 19th century, there were repeated unsuccessful attempts to infect monkeys and chimpanzees (e.g., Nicolle, 1905; Marchoux and Bourret, 1908). Collier, in 1940, claimed successful transmission of leprosy in monkeys fed a diet of the tuber *Colocassia antiquorum*, but Cochrane (1947) could not confirm this finding. In Malaysia, in 1976, Waters *et al* (1978) necropsied a white-handed gibbon that they had inoculated with *M. leprae* in 1961. Although there was no clinical evidence of disease, histopathologically, there were early disseminated lepromatous infiltrations.

A. *Chimpanzee*

Gunders, in 1958, reported findings in a chimpanzee he had inoculated intravenously with *M. leprae* in Liberia. At 11 months there were nodules rich in acid-fast bacilli in the skin of the extremities and ears. When last observed, 14 months post-inoculation, these lesions were regressing. From our own evaluation of tissues on file at the AFIP, we interpret the disease in this animal as borderline leprosy (BB-BL). We believe this is the first well-documented experimental disseminated infection of an animal by *M. leprae*.

In 1965, Binford began collaborative studies with the Delta Regional Primate Research Center, Covington, Louisiana, on the transmission of leprosy to chimpanzees by the intradermal and intravenous inoculation of large numbers of *M. leprae*. A total of 24 chimpanzees were inoculated. Among these were two young animals born in the chimpanzee colony. These animals received suspensions of *M. leprae* intravenously and intraperitoneally shortly after birth, in an attempt to induce tolerance. After six months the animals were inoculated with *M. leprae*. Approximately one year later, lesions

developed at inoculation sites on the ear and lower forearm. In one animal, borderline leprosy was diagnosed histopathologically, and there were acid-fast bacilli in histiocytes and in small nerves. In the other animal, a histopathologic diagnosis of tuberculoid leprosy was made. There was intraneural involvement. Within six months, the lesions in both animals had healed, and the animals were lepromin positive.

There were no further reported studies on leprosy in the chimpanzee until 1977, when Donham and Leininger detected naturally-acquired leprosy in an animal imported from Sierra Leone. They studied this chimpanzee extensively, and the clinical, microbiologic and histopathologic features were those of borderline-lepromatous leprosy. The etiologic agent could not be differentiated from *M. leprae* (Leininger *et al*, 1978), and at necropsy there was wide dissemination of the disease (Leininger *et al*, 1980). Acid-fast bacilli from this animal were inoculated into a number of other chimpanzees in 1976 and 1977. These animals remain under observation, but have no lesions (Leininger, 1983).

B. *Mangabey monkey*

In December 1979, in collaboration with George Imes, D. V. M., of the Veterinary Pathology Department of the AFIP, we made a histopathologic diagnosis of lepromatous leprosy (LL-BL) in a biopsy specimen of skin from the muzzle of a young adult female sooty mangabey monkey (*Cercocebus atys*), then housed at GSRI (Walsh *et al*, 1981; Binford *et al*, 1982). The animal, imported in 1975, originated in West Africa and was on dietary cholesterol studies. She had never been experimentally inoculated with *M. leprae*. Thirteen months after diagnosis, there was extensive progression of the cutaneous lesions over the face, ears, limbs and tail, and there were paralytic deformities of the hands and feet.

The etiologic agent in this index animals was undistinguishable from *M. leprae* (Meyers *et al*, 1980). The animal's general health deteriorated, and combined therapy with rifampin and dapsone was started 14 months after diagnosis. Clinical and histopathologic responses to therapy were good, and the animal is alive and well today.

We transmitted this disease to other sooty mangabey monkeys. Initially, we inoculated two male mangabeys with suspensions of organisms separated from tissues of the index monkey. Each animal received 3×10^8 bacilli into each of 5 sites in the skin of the ears and

muzzle, and 1.2×10^9 bacilli intravenously. Nodules were first noted at the inoculation sites 4 months later. By 17 months, these nodules had enlarged and there was dissemination to uninoculated surfaces of the body, including the limbs and tail, and particularly the scrotum. Histopathologic changes in the scrotum included extensive infiltrations of macrophages containing large numbers of acid-fast bacilli. There were occasional patches of lymphocytes, but most of these were associated with intracutaneous lymphoid nodules rather than delayed-type hypersensitivity granulomas. Acid-fast bacilli invaded the smooth muscle of the scrotal wall and nerves.

One of these animals died unexpectedly at 46 months post-inoculation. Death followed anesthesia. At necropsy there were extensive lepromatous infiltrations of the skin of the face, ears, front and hind limbs, tail, scrotum and testes. Peroneal nerves were enlarged. Histopathologic analysis revealed extensive lepromatous infiltrations at all these sites, including nearly complete replacement of the peroneal nerve. Inguinal lymph nodes contained large numbers of acid-fast bacilli in histiocytes, and the paracortical areas of peripheral lymph nodes were largely replaced by bacilli-laden histiocytes. The liver and spleen showed minimal infiltration. Thus, the pathologic changes in this animal closely resemble those seen in humans with early advanced lepromatous leprosy. The second mangabey monkey, inoculated in March 1980, is now under chemotherapy, and is responding favorably. Two sooty mangabey monkeys were inoculated in December 1980 with suspensions of *M. leprae* of human origin passaged once in armadillos. Inoculations were by the intravenous and intracutaneous routes. Thirty-two months after inoculation, there is active progressive disease at all inoculation sites, and both animals have acid-fast bacilli in nasal smears. Histopathologically, the nodules in the skin of both animals are in the subpolar lepromatous (LLs) area of the spectrum of the disease.

Twenty-two mangabey monkeys have been inoculated with, or otherwise exposed to, *M. leprae*. Clinical, histopathologic and immunologic observations indicate that leprosy in this species simulates lepromatous leprosy in humans in most respects tested. Mangabey monkeys with advanced lepromatous leprosy show declining responses to Concanavalin-A, and there is an associated increase in suppressor T-cells (OKT8).

The sooty mangabey monkey seems to offer the best promise as an ideal model for multibacillary leprosy. Although only preliminary observations are available, the following clinical features are noted:

bacteremia, dissemination to cool area of the body, variable clinical forms of the disease, and neuropathic deformities. There has been a favorable response to chemotherapy. Harboe (1981) has suggested that the mangabey monkey may serve as a suitable model for testing the efficacy of candidate vaccine for leprosy, but these studies have not yet been possible. The longevity of 20.5 years (Napier and Napier, 1967) for mangabey monkeys in captivity would make long-term observations possible. Mangabey monkeys breed readily in captivity.

C. *Rhesus monkeys*

In one of two rhesus monkeys (*Macaca mulatta*), leprosy developed 14 months after the intravenous and intradermal inoculation of large numbers of *M. leprae*. The disease in the early stages resembled borderline leprosy, but now, at 30 months post-inoculation, the disease is near to polar lepromatous with wide dissemination. Eighteen rhesus monkeys have now been inoculated with *M. leprae*. Two of the additional animals show early dissemination of the disease.

D. *African green monkeys*

Three African green monkeys (*Cercopithecus aethiops*) were inoculated intravenously and intradermally with large doses of *M. leprae*. Nodules developed on the ears of all three animals, beginning approximately 3-25 months after inoculation. Smears from the nasal mucosa of all the animals contain acid-fast bacilli. The histopathologic changes in the nodules on the ears are those of lepromatous leprosy. One of the animals has widely disseminated disease.

3. ATHYMIC RODENTS

A. *Nude mouse*

Prabhakaran *et al*, in 1975, were the first to study the growth of *M. leprae* following inoculation into the footpad of the nude mouse (nu/nu). They concluded that such mice did not develop generalized infection, but had observed the animals for only six months post-inoculation. Colston and Hilson (1976), however, continued their observations on the growth and dissemination of *M. leprae* for up to 322 days. At the end of this period the inoculated hind footpads contained 10^9 organisms and there was dissemination to testes, nose,

tail, forepaws, liver and spleen. There was no dissemination in nu/+ littermates and the footpads contained only 10^6 organisms. Kohsaka *et al*, and Nakamura and Yogi, in 1979, further developed the nude mouse model under specific pathogen-free conditions and were able to maintain the animals for up to 22 months. They noted dissemination to lung, liver and spleen.

Hastings *et al*, in 1980, showed the regular spread of *M. leprae* infections in nu/nu mice to the liver and spleen, between approximately 100 and 280 days. Job *et al* (1982) reported their observations in nu/nu mice for up to 565 days after inoculation of *M. leprae* into the hind footpad. There was dissemination from day 273, and at 565 days there were lepromatous infiltrations in all organs except the brain. Despite high body temperatures, there is marked proliferation in the viscera, even in the parenchymatous cells of liver, kidney and other organs and tissues. Preliminary studies suggest that the therapeutic efficacy of DDS in nude mice may be variable (Kohsaka *et al*, 1981).

B. *Nude rat*

Fieldsteel and coworkers (1971, 1976, 1980, 1981) have developed the neonatally thymectomized Lewis rat as a model of multibacillary leprosy, and later extended their studies to congenitally athymic rats. *M. leprae* infections in thymectomized rats proved to be unpredictable; however, infections in congenitally athymic rats were more uniform. There was dissemination of the infection beginning about 8 months after inoculation into the footpad (Dawson *et al*, 1983). Dissemination was limited to the cooler parts of the rat (tail, footpads, snout and ears), peripheral lymph nodes and bone marrow. There were a few AFB in the liver, but these disappeared at about 15 months post-inoculation. Cutaneous nerves contain small numbers of organisms, but the sciatic nerve is not affected. Of particular interest is the limitation of the infection in the congenitally athymic rat, even though thymic-dependent T-cell function is lacking. This host has been relatively little studied, and further observations are needed.

IV. Summary

Disseminated multibacillary leprosy has been reported in unaltered subjects in three species of armadillos, chimpanzees, sooty mangabey monkeys, rhesus monkeys, African green monkeys, nude rats and nude

mice. The chimpanzee has not been shown to be regularly susceptible, and, thus, requires much more study to establish its potential usefulness. Armadillos, by virtue of their accessibility, at least in the Western Hemisphere, have great potential for experimentation, but their usefulness in nearly all areas of experimentation remains almost untested. Nude mice and nude rats have the advantage of being readily available to appropriately equipped laboratories; nevertheless, husbandry is tedious, maintenance is expensive, and these animals are relatively short lived. Infections in nude mice appear to be overwhelming and are, like those in the armadillo, usually more severe than in most leprosy patients. Moreover, these rodents, although not artificially altered, have an established genetic immunologic deficiency, in contrast to the immune system of individuals susceptible to leprosy. The mangabey monkey, although still in an early stage of experimentation, appears to offer great promise today as a model of many of the clinical manifestations of leprosy. The most important disadvantages are: the relatively short supply of this animal and the expense of maintenance. An overriding advantage is the close species comparability to humans.

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LEPROSY CONTROL

MICHEL F. LECHAT
Catholic University of Louvain in
Brussels, Belgium

1. Objectives of Leprosy Control

The objective of leprosy control is three-fold:

a) The main objective is in the long run to decrease incidence (that is the annual number of new cases as related to the total population) to an acceptable level. This level should be set arbitrarily according to what is considered in each country as an acceptable reduction of the problem, taking into consideration other health needs and availability of resources. Except in very exceptional circumstances, it seems unreasonable to aim at the eradication of the disease.

b) Second, control should efficiently prevent deformities. Control measures such as chemotherapy will prevent deformities only to the extent that the patients are treated at an early stage.

c) Beyond these public health oriented objectives, the treatment, cure, and rehabilitation of the individual patients are part and parcel of control.

2. Epidemiological Basis of Leprosy Control

The epidemiological determinants of leprosy which are relevant to control are the following:

(1) man is the single (or at least the only) significant reservoir;

(2) transmission is assumed to be direct from infected to susceptible individuals;
(3) specific environmental factors regulating transmission have not been identified.

Under such conditions, there are only three possible approaches to control:

(1) elimination or removal of the reservoir (segregation);
(2) elimination of the agent in the reservoir (chemotherapy);
(3) protection of the susceptible population (chemoprophylaxis, vaccination).

3. Strategies of Leprosy Control

Segregation has been practiced on a large scale as long as no specific medicaments were available. With the discovery of the sulfone-drugs in 1941, chemotherapy became available. For the last thirty years, it has been the keystone of leprosy control.

Chemoprophylaxis, which has been recognized as relatively effective in population trials, is not applicable on a large scale.

Active research is carried out in order to develop a specific leprosy vaccine. Possible availability of a vaccine in the future would overturn the approach to control of the disease.

Since at present control is universally based on chemotherapy, only this method will be considered.

4. Chemotherapy

The aim of control through chemotherapy is to sterilize the agent (*M. leprae*) in the reservoir (man), through treatment of all infectious cases.

The basic requirements are therefore:

(1) the availability of a potent drug efficient in all cases of the disease;
(2) early diagnosis;
(3) complete, or as complete as possible, treatment coverage.

4.1 *Available drugs*

Until recently, the only drugs active against *M. leprae* were the sulfones, principally the parent-compound, dapsone. Synthetized around 1908, the sulfones were first used in leprosy by Faget, at the Carville leprosarium, in the U.S.A., in 1941. This is a major example of how the lack of laboratory models has hindered leprosy control. It strongly illustrates the need for research. If a laboratory animal or a growth medium had been available at the time of discovery of the sulfones, the patients would have benefited 30 years earlier from a specific medicament.

The availability of the sulfones made possible the large-scale development of ambulatory treatment. Patients, at least the tuberculoid patients, and soon all the patients, were treated in their community. Mobile teams were organized where no basic medical facilities were available. The sulfones were particularly adapted to this mode of treatment. They were cheap, the cost of treatment for one patient was estimated at some 2 dollars per year. They were given by mouth, which makes in-the-field administration easy and requires no special equipment. Their toxicity is low at the usual dosage, which calls for a minimal medical supervision. They are effective when administered weekly, which makes organization of control convenient and allows treating a large number of patients with a relatively modest staff. They have a long shelf-life, which reduces the possibility of logistic difficulties.

Millions of patients were treated on an ambulatory basis, especially in Africa and Southeast Asia. When the footpad model became available (Shepard, 1960), it was shown that the sulfones make a lepromatous patient non-infective in a couple of months. This strengthens the argument to leave all patients in the community and make do without isolation.

This observation was confirmed by epidemiological observations in Hong-Kong and in Venezuela. Attack-rates for leprosy in children of untreated, or not yet treated, lepromatous parents on one hand, and parents under treatment on the other, showed considerable differences.

Over the last decade, however, sulfone-resistance of *M. leprae* has been recognized in an increasing number of patients. Resistance, both primary and secondary, is now widespread worldwide. This has required the addition of new drugs, namely rifampicine, clofazimine, and ethionamide or prothionamide.

4.2. *Early diagnosis*

In order to reduce the period of dissemination of bacilli by untreated patients, it is necessary to detect and treat patients as soon as the first manifestations of the disease are apparent. This requirement, however, raises a number of difficulties, both theoretical and practical.

From a theoretical point of view, it is not known whether some persons in the latency stage, before the onset of overt clinical manifestations, constitute a source of infection. Studies conducted in highly endemic areas have demonstrated bacilli in the skin in a significant proportion (up to 10%) of apparently normal contacts.

Practically, due to the conditions prevailing in countries with high prevalence, there is always a delay between the onset of disease and treatment. This delay may reach years. A detection of 75 per cent of the cases within one year after onset is often the best one can expect.

The importance of early detection has increased with the emergence of primary resistance. Besides its importance for control, early detection is essential to prevent deformities.

Modes of detection of leprosy patients can be classified in several categories: systematic population survey, voluntary reporting, surveys of specific population groups, surveillance of high-risk groups, combined multi-disease detection, consultation at health services, such as skin clinics, health centers, etc. ...

It should be stressed that there is no leprosy control without organized detection. Haphazard referral of casually diagnosed cases has no part in leprosy control.

Systematic population surveys were an essential part of leprosy campaigns in many countries, mostly in Africa in the pre-independence days. Whole villages were examined at periodic intervals for a number of diseases, such as sleeping sickness, yaws, and leprosy. Although there is no doubt that such a method, compulsorily enforced, was highly effective to detect cases, it is most questionable that it could still be implemented today. Such systematic examinations of whole villages, however, still have their place in prevalence epidemiological surveys.

Voluntary reporting covers a whole range of types of detection, from the isolated cases seeking treatment from some specialists to the systematic organization of a surveillance system integrated into primary health care. Its efficiency depends on the motivation and education of the population and the degree of development of health services. It can

be integrated into a structure for primary health care (horizontal), or specially organized in the framework of a specific leprosy service (vertical) including treatment and case-management.

Surveys of specific population groups are often recommended: school children, workers in factories or plantations, army, etc.... Sometimes this mode of detection can be applied at a specific time in life (school entrance, recruitment in the army, new employment). The efficiency and effectiveness of such surveys depends very much on the relative prevalence found in such groups as compared to the general population. Furthermore, some population groups, such as army conscripts or workers, are deliberately or implicitly selected for good health. In some countries, schooling is unequally available, attendance at school being associated with a higher socio-economic level.

Contacts, and especially household contacts of multi-bacillary cases, constitute an exposed group of persons, characterized by attack-rates higher than the general population, as demonstrated in studies conducted in the Philippines (Doull *et al.*). In many countries, detection is mainly based on contact examination, with as a result a high yield of cases at relatively low cost. The efficiency and effectiveness of detection through contact examination depend, however, on the prevalence of leprosy.

Detection of leprosy in skin-clinics (called "*dispensarios de dermatología sanitaria*" in Latin America) has been widely practiced in a number of countries having a large problem of public health dermatology together with a significant leprosy prevalence. It is especially worth considering in countries where a psychological stigma is still attached to leprosy, for patients can then receive specialized services without drawing attention.

4.3. *Coverage and drug-delivery*

Chemotherapy will be efficient to the extent that the largest part of the reservoir of infection is rendered negative, i.e., an adequate coverage of effective treatment.

However, coverage is seldom satisfactory. In many countries, the estimated prevalence may considerably exceed the apparent prevalence; in other words, the number of undetected patients is much greater than the number registered. This is due not only to delay in detection, but also to many patients absconding from the health services. That fact is

confirmed by the high number of old cases with extensive deformities among the newly detected patients.

Poor attendance to treatment is another drawback. Since sulfone-monotherapy must be continued for years (even for life in multibacillary patients) in order to achieve bacterial negativation and prevent relapse, the rate of defaulting is high, and it may happen that a majority of patients are abandoning after a few years.

5. Drug-Resistance

Since the inception of sulfone-based mass treatment campaigns, a major problem has appeared; that is, the resistance of *M. leprae* to the drug. Curiously enough, the possibility of resistance emerging with prolonged sulfone-treatment has been overlooked for a long time. The first WHO Expert Committee on Leprosy, held in 1952, mentioned that there was no clinical indication of resistance. Clearly, after a couple of years of treatment, it was too early to judge. The Second and Third Expert Committee, respectively in 1960 and 1965, recommended initiating sulfone treatment with very low doses and a very gradual increase before reaching full dosages. It was conjectured that this could reduce the incidence of reactional episodes in lepromatous patients at the beginning of the treatment. The existence of resistance as a problem was negated. It is only in 1970 that the possibility of selecting strains of *M. leprae* resistant to sulfones was mentioned, in relationship with recent recommendations then made for a decrease in the usual dosages.

Meanwhile, the techniques of footpad inoculation made it possible to investigate a number of pharmacological aspects of leprosy treatment, such as the minimal inhibiting concentration of drugs, the effectiveness of drugs, and resistance.

Dapsone-resistance has come to be today the major problem of leprosy control. Secondary resistance to dapsone has now been reported from more than 25 countries and its prevalence is steadily increasing. Primary resistance is also being reported with increasing frequency from several countries. In some areas, primary resistance affects 30 per cent of the new multibacillary patients. It has been observed that the prevalence of primary resistance was particularly high in those areas where control activities were conducted intensively and for a long time, which is only normal because under such

circumstances, with a large coverage of early detection, patients treated for long and having developed secondary resistance will constitute the main source of infection.

If adequate measures are not taken, namely multiple drug therapy, the emergence of drug-resistance could jeopardize in many countries the results obtained by leprosy control over the last decades.

Simulation of resistance using epidemiometric models (Lechat *et al.*, 1985) has shown that, with a 3 percent annual incidence of secondary resistance, the prevalence of total resistance among the total of surviving multibacillary patients reaches some 34 per cent after 15 years; with a 2% annual incidence it reaches 26%, and with a 1% annual incidence it reaches 15%.

Conversely, the effect on incidence of an increasing reservoir of infective resistant patients can be calculated for different rates of secondary resistance. Whereas with current control measures, the decline in incidence is markedly reduced, occurrence of secondary resistance at a rate of 1 per cent per year leads to a stabilization in the number of new cases after 32 years. With a 3 per cent rate, the declining trend of incidence is reversed after 11 years, and after 16 years with 2 per cent.

The answer to resistance is multiple drug therapy, based on the following drugs in addition to dapsone: rifampicine, clofazimine, and ethionamide/prothionamide. However, resistance to rifampicine and, exceptionally, clofazimine, has now been reported.

The emergence of resistance has changed the face of leprosy control. Replacement of monotherapy by multiple therapy is much more, however, than a shift in the type of tablets. It implies a complete change in the management of the patients. Drug-delivery has to be modified. Rifampicine, for one, has to be administered under strict supervision and under tight schedule. Adverse reactions are not infrequent and call for prompt diagnosis and referral to specialized care. Bacteriological follow-up is necessary to evaluate the improvement of the disease. Where sulfone monotherapy is still practiced, careful assessment of the bacteriological status is required to detect the emergence of resistance.

Due to drug resistance and to its necessary corollary, multiple chemotherapy, the treatment of leprosy, which for long was an easy matter, has become a very delicate affair indeed. The more hopeful side of the change is that, while sulfone-monotherapy of multibacillary patients was to be prolonged for life, multiple therapy permits to envisage a discharge after two years.

6. EVALUATION

It is now more than 30 years that large-scale campaigns based on systematic case-finding and mass sulfone treatment are carried out in a number of countries.

At the beginning of these campaigns, great expectations were entertained. The eradication of leprosy was even contemplated. That was the time when eradication was still a fashionable word. It seemed that all that was needed to achieve it was dedication and money.

Today, by contrast, it is commonplace to hear people question the results of the whole leprosy control as it has been conducted for three decades. Initial expectations have not been fulfilled. Leprosy is still with us, and each year brings its crop of new cases. Governments are raising doubts about the soundness and feasibility of the present strategy, the more so since there are many other health priorities in countries where leprosy is endemic.

There are no doubts that leprosy control based on monotherapy as practiced for some 30 years has totally changed the face of leprosy. Severely mutilated patients and burnt-out cases, a common sight before the sulfone, are exceptionally found any more. Still, there is much question about reduction of transmission.

The truth is that no proper evaluation mechanism had been incorporated in the leprosy control schemes from the beginning. Activities were mostly evaluated from a purely operational point of view. The questions asked were how many patients were put under treatment, how many discharged, how many people were examined for leprosy in the population.

The process of continuous evaluation requires the use of a method for collecting, processing and analysing information on the clinical, epidemiological and operational aspects of programs or projects. Moreover, it is generally recognized that the available information on leprosy in the majority of countries is poor or unsatisfactory. Also, owing to lack of uniformity in the definition of terms and concepts, the data obtained from different countries, and sometimes even from different areas in the same country, are hardly comparable; they consequently have little epidemiological value.

It results that a suitable system for collecting and recording data is essential for the planning, programming and monitoring of leprosy control programs, as well as to evaluate the outcome. Such a system is

also needed to gain knowledge on the epidemiology of leprosy, and judge the respective efficacy of preventive and curative strategies.

In order to permit comparisons of data, such an information system needs the definition of standardized technical terms. An information system must also be seen in a decision-making context. It should be simple in nature so that the necessary data can be collected by health service personnel at any level.

The OMSLEP Recording and Reporting System for Leprosy Patients (Lechat *et al*, 1981) represents an attempt at developing such a system. It is especially designed to facilitate the collection of data and the periodical retrieval of indices.

The system has also been adapted to make possible the use of microcomputers.

7. Types of Services

The implementation of leprosy control activities supposes three levels of services: (a) detection and case-management at the interface between health services and the population; (b) supervision; (c) referral.

It can be viewed as a pyramid, from the periphery to the more central, or from the less specialized to the more specialized levels.

These services can be arranged along two axes. At one extreme, there is a specialized leprosy service, dealing only with leprosy patients, with its own personnel and facilities (so-called vertical services). At the other extreme, the leprosy control activities are completely integrated into the general health services (horizontal services). There are many intermediate situations between these two. Each type of services has its advantages and disadvantages.

In the ideal situation of a well-organized extensive primary health care structure, there is no doubt that integration of leprosy control into it will assure its efficiency and decrease the cost. Moreover, it has the advantage that leprosy will not be singled out as a special disease, requiring special services, which can only add to the psychological and social stigma.

When basic health services are not so well developed, specialized services for leprosy control or activities, or part thereof, might remain the only way to actually deliver care to the patients. It is however costly, since it might require special personnel whose only

responsibility is leprosy control, together with its own transportation, proper supervision mechanism, and even particularized health facilities.

In a number of instances, the change from specialized services to integration has resulted in a collapse of all leprosy services, of no avail to general health.

Two remarks should be made regarding the (admittedly most desirable) progressive integration of leprosy services into the basic health services:

(1) when the leprosy service is well organized and has a wide coverage, and basic health services are poor or even inexistent, rather than integrating existing services into nothing, primary health care should be integrated into the leprosy services. That is to say: leprosy can be used as a catalyst and a nucleus to develop basic health services;

(2) integration should only be attempted when there is a reasonable expectation that it will not result in the downgrading or even collapsing of leprosy control.

Integration is a matter of good sense. It should be adapted to the local context, taking into account the local cultural patterns (psychological attitude of the population, acceptability), the level of training of the health personnel, the development of basic health services, and also history (in some countries, specialized services have a long tradition).

8. The Role of Voluntary Agencies

It should be clearly stated that the responsibility for leprosy control rests with national governments. It should also be honestly recognized that, while in a number of countries governments have made great efforts to fight the disease, in a number of others they have shown little or no concern.

The role of voluntary agencies, either national or international, as well as for foreign official agencies, has been determinant in stimulating interest, raising funds, promoting leprosy activities, implementing leprosy control and alleviating the suffering of patients throughout the world.

To quote the World Health Organization,

"With their flexibility and initiative, voluntary agencies are able to "introduce new approaches in leprosy treatment and control in the "light of their concern for the social components of the disease. Full "advantage could be taken of their training experience, literature, and "in-patient facilities both in general hospitals and in hospitals specially "catering to leprosy sufferers. They can provide a valuable "contribution to the development of the general health services, "especially in the early stages of development of rural and urban health "facilities.

"Voluntary agencies can also frequently initiate and develop certain "aspects of an antileprosy service, e.g., specialized physiotherapy units, "workshops for prosthesis, and re-education centres for handicapped "patients — which some governments cannot fully provide at present. "These, however, should: (1) be developed as part of the facilities for "all suitable patients, (2) not become so elaborate or expensive that "they cannot be incorporated into the government's programme if and "when desirable, and (3) serve as training centres wherever possible".

9. Legal Measures

The only desirable compulsory measures toward leprosy patients is medical examination and treatment. It is also the right of the patient.

Leprosy should be reported like other communicable diseases according to the requirements for an efficent implementation of control.

Special legislation should be repealed. Indiscriminate compulsory segregation is an anachronism and must be abolished. Discretionary authority could, however, be given to health authorities to require the hospitalization of presumably infectious patients or their temporary exclusion from work in those instances in which the prescribed therapy is neglected or ineffective.

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LEPROSY IMMUNOLOGY — SOME ASPECTS OF THE ROLE OF THE IMMUNE SYSTEM IN THE PATHOGENESIS OF DISEASE

by

TORE GODAL

Laboratory for Immunology,
The Norwegian Radium Hospital,
Montebello,
N-0310 Oslo 3, Norway

The immunology of leprosy has been a subject of extensive research for the last 15 years. Important progress has been made in a number of areas, including support for the overall concept that among those who become exposed to *M. leprae*, the great majority appears to develop an effective immune response sufficiently rapidly to arrest *M. leprae* infection before overt clinical disease is precipitated. This I will call subclinical infection. Only in a minority of subjects the disease apparently becomes clinically expressed. Towards the tuberculoid end, considerable evidence suggests that the immune response to *M. leprae* is the major cause of lesions, while towards the lepromatous end of the spectrum, accumulation of vast numbers of bacilli in infiltrating host cells plays an important role.

The precise detection of subclinical infection is of fundamental importance to a more complete epidemiological understanding of leprosy. This has not yet been achieved. However, significant advances have been made recently in this area by development of *M. leprae*-specific serological techniques as pioneered by Abe. More recently the employment of a chemically defined and unique antigen of *M. leprae*, namely the phenolicglycolipid 1 identified by Patrick Brennan and his co-workers, appears promising. In this and related areas the development of monoclonal antibodies is rapidly becoming important to leprosy immunology.

There is no time during this presentation to consider in detail all the different aspects of leprosy immunology. Thus, I will here focus on two aspects: namely, nerve damage in borderline and tuberculoid patients, and the nature of the immunological deficiency in lepromatous leprosy.

Nerve damage in leprosy is of key importance, since this is a major cause of deformity. Deformity often results from loss of sensation and loss of motor nerve function. If one looks histopathologically at damaged nerves in borderline and tuberculoid patients, the regular cablelike structure may be completely broken down by infiltrating inflammatory cells. Actually, there often is granuloma formation within the nerves. A considerable body of evidence suggests that this granuloma formation within the nerves with lymphocytes, macrophage and epithelioid cells results from immunological attack from the host on leprosy bacilli hiding within the nerves. Thus, whenever recognized by the host immune system, T lymphocytes will become attracted to these sites and release various factors called lymphokines, which in turn will attract and activate monocytes to kill bacteria that they will engulf. However, this attack will, as an unfortunate side effect, also distort and damage nerve fibers and function. It is important from a clinical point of view that this type of nerve damage in leprosy may occur very rapidly. This is especially seen in reversal reactions, where there may be a rapid build-up of immunological attack on leprosy bacilli. It is therefore very important to treat such patients adequately as soon as possible; that is, they really have to be considered as emergency cases, otherwise nerve function may be permanently lost.

Let us now turn to lepromatous leprosy. The central question here is; what is going wrong in lepromatous leprosy? Why does the host system fail to attack the leprosy bacilli, which are thriving in the tissues in vast numbers?

It is well known from earlier studies that this immunological defect is remarkably specific to leprosy bacilli. The patient's T-cells may respond strongly to BCG or PPD, but be completely negative to *M. leprae*. Thus, the defect is what we immunologists call antigen-specific. Since it is well known from a large number of studies, including studies on T-cell deficient animals, that it is the T-cell that has the capacity to mediate specific immunity to intracellular bacilli such as the leprosy bacillus, one has for a long time suspected that T-cells play a central role in the defect of lepromatous leprosy. The

mechanisms involved in T-cell activation and T-cell-mediated intracellular killing of mycobacteria have advanced considerably during recent years and allow a more detailed analysis of the defect in lepromatous leprosy. Thus, we will here now first consider the basic concepts of T-cell activation and then discuss recent findings, which suggest more precisely the nature of the defect in lepromatous leprosy.

T-cell response may be subdivided into three parts, the afferent limb or inductive phase, the central or regulatory phase or level, and the efferent limb or effector phase. With regard to the afferent limb, we have known for a number of years that T-cells do not see the antigen alone, but that the antigen is presented to the T-cell by other cells, so-called antigen-presenting cells, which include monocytes, macrophages or dendritic cells. The Langerhans cells of the skin also belong to this cell category.

How antigen-presenting cells interact with T-cells is not yet a fully understood process. It looks like they actually talk to each other, that is to say, it is a mutually dependent, highly sophisticated process. The antigen-presenting cells have on their surface the antigen derived from, in our case, *M. leprae* and high concentrations of HLA-DR molecules, both of which are required for T-cell activation. In addition there is evidence that the antigen-presenting cell produces a factor, interleukin 1 (IL-1), which is required for T-cell activation. However, the production of IL-1, as well as the level of HLA-DR expression, may actually be under T-cell control.

The activation of T-cells leads to two clearly distinguishable phenomena:

(1) some T-cells start to produce a factor required for T-cell proliferation and production of lymphokines. This factor is called interleukin 2 (IL-2).

(2) Other T-cells, will develop receptors for IL-2 and are thereby able to respond to IL-2.

This part of the immune response, the *afferent limb*, sets the stage for T-cell proliferation and interleukin production, which may be called the *central level* of the immune response. The central level may also be called the regulatory level, because T-cells are controlled by other T-cells, so-called suppressor cells, and this regulation is often called the suppressor circuit. These suppressor cells may have the T4 or the T8 phenotype and are thus not limited to T8 cells. Suppressor

cells may interfere with T-cell activation in various ways; for example, by blocking induction of IL-2 receptors or by blocking IL-2 production.

Let us now consider the third part of the T-cell response, the so-called *efferent limb*. How do T-cells effectuate their attack on *M. leprae* and related organisms? It appears that T-cells mainly orchestrate or conduct the attack by production of lymphokines, some of which have chemotactic properties and attract monocytes from the blood into the sites where *M. leprae* has been detected, and other lymphokines (one called macrophage activation factor, MAF, probably identical with γ-interferon) activate the macrophage to kill and digest the bacteria they have internalized.

We may now return to the question of what is going wrong in lepromatous leprosy. It would be apparent that there are many places where things could go wrong:

(1) The antigen-presenting cells may be compromised.

(2) T-cells may lack receptors for *M. leprae* antigens.

(3) Patients may have developed an overwhelming suppressor circuit that could suppress IL-2 receptor induction or IL-2 production. And finally;

(4) There could be a defect in the efferent limb.

Time does not allow a detailed consideration cf the experimental data, which may be in favour of or against any of these possibilities. However, data have steadily accumulated in recent years that provide further evidence that the defect is located at the central or regulatory level. Several investigators, especially Mehra and Bloom, have detected suppressor cells in lepromatous leprosy. Finally, Dr. Haregewoin in Addis Ababa, in collaboration with Salim Mustafa and myself, has shown that lepromatous T-cells fail to produce IL-2, but if given IL-2 from external sources to lepromatous T-cells, the T-cells will now mount a proliferative response to *M. leprae*.

Combined, these findings suggest that suppression of IL-2 production may be of central importance. They are encouraging because they suggest that these studies on the immunological nature of defects, in lepromatous leprosy may lead to new approaches for restoring immunological competence in such patients. Hopefully some day termination of chemotherapy and prevention of drug resistance may become feasible in such patients.

In conclusion, the immune system is of central importance to the pathogenesis of various disease manifestations in leprosy. The main contribution of leprosy immunology so far has been at the conceptual level. But the stage is now set in a number of areas for exploring more direct contributions to leprosy control.

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INVESTIGATIONS ORIENTED TOWARD THE DEVELOPMENT OF A VACCINE AGAINST LEPROSY

JACINTO CONVIT
Instituto Nacional de Dermatología
Apartado de Correos 4043, Caracas, Venezuela

Leprosy is a chronic, endemic, infecto-contagious disease which affects the most heavily populated areas of the world. The global number of patients with leprosy in the world is estimated at 14 to 15 million people; 90% of these patients are found in the Asiatic and African continents. Introduction of leprosy into the Americas was relatively late, occurring in the post-Columbian period. At present, it constitutes an important public health problem in Brazil and Colombia and, on a smaller scale, in Peru, Argentina, Bolivia, Paraguay, Venezuela and the Guianas. Autochthonous cases have not been reported from continental Chile. In Europe, small residual foci persist in the Balkans, Russia, Italy, Spain and Portugal.

In endemic areas, leprosy represents an important health problem not only because of its extreme chronicity, but because of the elevated percentage of physical incapacity which it causes, varying from 30 to 50% of the cases. The heavy burden of prejudice associated with leprosy compounds its physical consequences.

The campaign against leprosy has been based fundamentally on early diagnosis of the disease, public health education and treatment of cases. This approach requires the development of an extensive infrastructure in the field, which must be maintained for long periods of time; its effectiveness is measured in terms of decades of labor. This has frequently led to the abandonment of leprosy control programs because of a lack of sustained effort and continuity.

In the last two decades, two phenomena have been clearly demonstrated which exercise a negative effect in control programs: (a) the development of secondary resistance to *Mycobacterium leprae* and, subsequently, the appearance of cases of primary resistance. This problem is undoubtedly the consequence of the use of sulfone monotherapy in irregular and often insufficient doses during the last forty years. (b) Important internal migration of the population of countries with endemic leprosy from rural areas to urban centers. This leads to the possibility of the creation of new foci of infection, which can only be controlled by modifications in present leprosy control programs. This problem is compounded when migration is not limited to internal movements of the population, but includes migration to bordering countries.

The establishment a decade ago of the Special Program for Research and Training in Tropical Diseases (TDR) by the UNDP/ World Bank/WHO has changed the perspectives for leprosy control. The IMMLEP program has defined two high priority objectives, which are the development of a preventive vaccine for leprosy and the development of simple procedures for early diagnosis which can be easily adapted to field conditions. To achieve these goals, an intensive scientific program has been developed which includes research in the areas of immunology, epidemiology, molecular biology and genetics.

As a chronic, endemic, infectious disease, leprosy possesses singular characteristics which must be considered in the development of a vaccine. First, though the infection of the population in endemic areas is very widespread, only a relatively small percentage of that population is susceptible to the development of progressive clinical disease. In terms of percentages, approximately 80% of the population possesses a high degree of resistance and does not develop progressive disease. The susceptible group who does not develop resistance to infection by *M. leprae* is found in the remaining 20% of the population. The number of new cases per year (incidence) is generally quite low, rarely exceeding 2 to 4 per thousand, while the number of accumulated cases (prevalence) shows considerable variation, to 5, 10, 20 and even 30%, depending upon the intensity of the endemicity.

Another important characteristic of leprosy is the fact that patients with progressive disease and susceptible healthy individuals show a defect in the phenomena of cell-mediated immunity (CMI), which appears to be highly specific and limited to *M. leprae*. This observation is widely accepted by investigators at present, and contrasts sharply

with the opinion widely expressed in the scientific literature during the sixties, which considered the defect to be generalized and non-specific, altering reactivity to various antigens. This aspect is of particular interest in the development of a vaccine, since the problems confronted in vaccine development presumably would be much greater if the defect were non-specific and generalized.

Our activities toward the development of an anti-leprosy vaccine have covered four stages.

The first stage was to develop a test to detect the defect in CMI which affects non-reactors, a group which includes patients with borderline lepromatous and lepromatous leprosy, persistently Mitsuda-negative patients with indeterminate leprosy and persistently Mitsuda-negative contacts. This group represents a scale of intensity in the immunological defect which progresses from the Mitsuda-negative contacts to the BL-LL group. The test developed to detect this defect consisted of the intracutaneous injection of 0.1 ml of human Mitsuda antigen containing 6.4×10^8 *M. leprae*/ml and subsequent histological evaluation of the granulomatous response [1].

This injection induced the formation of a nodule 6 to 8 mm in diameter at three weeks in the group of non-reactors to standard Mitsuda. Histological study showed that the nodule consisted of a granulomatous lesion formed by non-differentiated macrophages containing numerous intact intracellular bacilli. In contrast, the reactions in positive reactors were characterized by the development of tuberculoid-type immune granulomata and essentially complete elimination of the bacterial population. This test, then, permitted the visualization of the immunologic defect in CMI toward *M. leprae* in the group of non-reactors described above. A similar phenomenon has been observed in parasitic disease (leishmaniasis) and in deep mycoses toward their respective micro-organisms. Therefore, this type of response appears to characterize non-reactors with a CMI defect toward any parasite. The specificity of this defect is demonstrated by the fact that the group of non-reactors to *M. leprae* described above developed characteristic immune granulomata subsequent to the injection of other mycobacteria, such as BCG.

In this first stage, the response of the group of non-reactors to *M. leprae* was evaluated when they were injected with a mixture of killed *M. leprae* and live BCG [2]. In these experiments, the formation of an immune granuloma and the clearance of both mycobacteria were observed.

In the second stage of our research, we considered the possibility that the development of an immune granuloma subsequent to the injection of the mixture of *M. leprae* and BCG in non-reactors might result in the liberation of active immunogens that could induce specific CMI reactivity to *M. leprae* in these individuals. An immunotherapy protocol using the mixture of killed *M. leprae* and live BCG was applied to a group of six patients with inactive lepromatous leprosy, six with persistently Mitsuda-negative indeterminate leprosy and two Mitsuda-negative contacts (Table 1). This small group of 14 persons was observed from 1973 to 1983 and the following observations were made: the six LL patients became permanently Mitsuda-positive after 6 to 8 vaccinations, with reactions of 5 to 9 mm.; they have been without treatment for 6 to 10 years without suffering relapse.

The Mitsuda-negative patients with indeterminate leprosy were vaccinated 4 to 6 times. They all developed a papular rash with a tuberculoid structure, which disappeared after three months; one developed a plaque with a tuberculoid structure super-imposed on an old hypo-pigmented lesion of the right elbow, which also disappeared in three to four months. All became persistently Mitsuda-positive, with reactions of 6 to 12 mm.

The persistently Mitsuda-negative contacts became reactive to Mitsuda antigen (6 and 10 mm) after a single dose of immunotherapy in one and two doses in the other.

The control examinations made in this group between 1980 and 1983, after six to ten years without chemotherapy, showed all of the LL and indeterminate patients to be free of lesions.

The third stage of investigation, based on the promising results obtained with immunotherapy in the small group described above, consisted of immunotherapy in a group of 626 persons, of whom 481 had BL or LL disease, 61 with Mitsuda-negative indeterminate leprosy, 57 BB-BT cases and 27 Mitsuda-negative contacts.

Immunotherapy consisted of the repeated intradermal injection of a mixture of 6×10^8 purified, autoclaved *M. leprae* and from 0.02 to 0.2 mg. of viable BCG, depending upon reactivity to PPD. Vaccination was made in three sites on the deltoid regions and the upper back. A maximum of eight to ten injections were administered at two to three month intervals, depending upon the immunological, clinical and bacteriological changes observed.

Table 2 shows the clinical and immunological changes observed in the 626 persons who received from 1 to 10 vaccinations in the course

TABLE 1. — *Immunotherapy with the mixture* M. leprae *plus BCG in patients and contacts. Initial experience.*

Classification	Positivization Soluble Antigen				Lepromin 30 Days			
	Initial		Final		Initial		Final	
	Nº Persons	Average Induration mm	Nº Persons	Average Induration mm	Nº Persons	Average Induration mm	Nº Persons	Average Induration mm
LL	6	0	6	15,8 (12–22)	6	0	6	7 (5–9)
IL Lepromin neg.	6	0	6	16,1 6–36	6	1,3 (0–3)	6	10 (6–12)
Contacts Lepromin neg.	2	0	2	12,5 (10–15)	2	2,5 (2–3)	2	8 (6–10)

TABLE 2. — *Immunotherapy with the mixture* M. leprae *plus BCG in patients and contacts.*

Classification	Total Nº Persons	Positivization I. D. Tests				Histological Reversion Phenomena		Bacteriologically Negative	
		Soluble antigen		Lepromin					
		Nº	%	Nº	%	Nº	%	Nº	%
Active BL-LL	300	141	47,0	91	30,3	90	30,0	194	64,6
Inactive BL-LL	181	107	59,0	94	51,9	—	—	—	—
Active BB-BT	26	23	88,4	19	73,0	8	30,7	12	46,0
Inactive BB-BT	31	16	51,6	28	90,3	—	—	—	—
IL	61	58	95,0	58	95,0	—	—	—	—
Contacts	27	27	100,0	23	85,0				

of three to four years of observation. All of the patients simultaneously received chemotherapy with two or three drugs (DDS-rifampycin-Lampren).

The local reactions as well as the residual scar at the injection sites of immunotherapy were similar to the responses observed with BCG vaccination alone. Secondary reactional phenomena and neuritic reactions were no different from those which are observed in patients receiving chemotherapy alone.

The analysis of the results given in Table 2 shows that 185 of a total of 481 patients with BL or LL leprosy became Mitsuda-positive. In the other groups (BB-BT and indeterminate leprosy) the number of positive Mitsuda reactions was much higher. Of the 27 contacts, 23 gave positive reactions and the other 4 could not be tested because they did not remain in control. Biopsies were taken of the Mitsuda reactions from 55 of the BL-LL patients chosen at random; histological examination revealed the presence of an immune granuloma of variable intensity with complete clearance of the bacilli injected in the test.

The characteristics of the reversal phenomena observed are of particular interest, since they represent one aspect of the changes in CMI observed in these patients, the majority of whom had LL or BL leprosy. It should be borne in mind that these phenomena are exceptional in patients of this type who receive chemotherapy alone.

The clinical and histological forms of the reversal reactions were highly variable, and included the observation of histological changes characteristic of reversal reactions without apparent clinical modification.

Reversal reactions were of variable duration and usually were not accompanied by systemic manifestations. In exceptional cases, systemic reactions required the administration of corticosteroids for a period of six to ten weeks (4 to 8 mg. Dexamethasone). In 7 cases we observed a type of reversal reaction characterized by edema of the dorsum of the hands, feet and lower legs, which we interpret as the localization of the reaction in lymphatic vessels and nodes.

The influence of the reversal phenomena on the evolution of the disease was striking, and included regression of lesions — nodules, plaques and spots — with a notable and progressive reduction in the bacterial population. In this sense, these reversal reactions have a significance quite different from those few observed in cases which have received prolonged chemotherapy, and in which chronic lesions are very limited or do not exist. For these reasons, we consider reversal

phenomena during immunotherapy to represent a process which is of moderate duration of a few weeks and which is accompanied by notable improvement in the disease.

Positive reactions to soluble antigen of *M. leprae* were observed in 248 BL-LL cases, which represent 52%. Positivization of the reaction to soluble antigen corresponded in nearly all cases to the positivization of reactivity at 48 hours and 30 days to Mitsuda-type antigen. In some instances, however, we observed a positive 48-hour reaction to Mitsuda antigen and a negative reaction to soluble antigen and vice versa. These differences could be due to antigenic differences in the two preparations, since cell-wall antigens may be of more importance in Mitsuda-type preparations and cytoplasmic antigens in soluble antigen.

The fourth stage of our studies has been concerned with the possible use of the mixture of killed *M. leprae* and live BCG in the immunoprophylaxis of leprosy. The arguments to support the use of this mixture in preventive vaccination are as follows: (1) The evident immunotherapeutic effect in LL, BL and persistently Mitsuda-negative indeterminate leprosy, characterized by the induction of important immunological reactivity toward *M. leprae* in these patients. (2) The conversion of persistently Mitsuda-negative contacts to strong reactors, after a single vaccination in the majority of cases. (3) The immunological changes induced by vaccination with the mixture of *M. leprae* and BCG are stable; our observations include a small group of patients and contacts in which these changes have persisted for ten years.

From an epidemiological point of view, the use of a vaccine against leprosy in endemic areas is of particular interest in those groups who have an elevated risk of infection; that is to say, in contacts. In addition, it is of particular interest to identify that subgroup which is susceptible to the development of progressive forms of the disease among contacts, since that group is largely responsible for the maintenance of the endemic.

A series of studies was carried out in order to broaden the universe of contacts and to try to detect the susceptible individuals within this universe. The group of contacts was extended to include not only those living in the same household, but also non-household contacts, including relatives, friends, frequent visitors and frequently-visited households, school companions, co-workers, etc. In the

epidemiological study of contacts in endemic areas of Venezuela, an average of 50 contacts were identified for each leprosy patient; five were household and 45 non-household contacts. This type of systematic study of both types of contacts has been referred to as epidemiological screening.

The identification of the susceptible subgroup of contacts was studied subsequent to the development of a soluble antigenic extract for use in 48-hour skin tests, prepared from *M. leprae* purified by the Draper 1979 protocol from the tissues of experimentally infected armadillos. The rupture of *M. leprae* is brought about by eight passages of the bacillary suspension through a French pressure cell at 10,000 lbs/in^2; subsequent ultrafiltration gives the fraction with a molecular weight of less than 30,000 which is used.

The intra dermal 48-hour skin reaction produced by this soluble antigenic extract has been determined in 700 patients with BL and LL leprosy and is negative in more than 99%. The soluble antigen has been used in 2634 household and non-household contacts, 12 years of age or older, in the areas where immunoprophylactic studies are being carried out in Venezuela (Apure and Táchira states).

The results of this study are shown in Table 3. The proportion of negative reactions shown in the last column of this Table (21.8%) is of particular importance in our program of immunoprophylaxis, which will include some 70,000 persons from the endemic area, since the protocol is based upon the selection of negative reactors to soluble antigen for vaccination and control [3].

TABLE 3. — *Reaction to SA in contacts of leprosy patients in relation to Age.*

Age group	n. ex.	Reactions to SA	
		Avg. induration (mm)	% "negatives" 0–9 mm
12–19 years	927	13.1	29.2
20–39 years	969	17.6	13.8
40 and more	738	14.1	23.2
Total	2,634	15.05 mm	21.8%

The capacity of this antigen to identify non-reactors among patients also applies to persistently Mitsuda-negative contacts. In these contacts, we have observed discordance between the reaction to PPD, which may be strongly positive, and the negative reactions to soluble antigen. When the positive reactions to soluble antigen were studied in contacts, there was correlation to PPD reactivity in those contacts who had a BCG vaccination scar, demonstrating that the soluble antigen detects cross reactivity to BCG. In non-reactors (LL, BL and Mitsuda-negative indeterminate leprosy, Mitsuda-negative contacts), strong positivity to tuberculin PPD is frequently associated with soluble antigen negativity. It is clear that both the specific and cross-reacting antigens of *M. leprae* are involved in the absence of reactivity in non-reactors.

Another aspect of interest from the epidemiological point of view is the study of antibodies to the glycolipid isolated by Brennan as well as soluble antigen in the sera of the group of non-reactors to soluble antigen. In preliminary studies using an ELISA test to measure antibodies to phenolic glycolipid I in 300 contacts who did not react to soluble antigen in skin tests, about 3% had exceptionally high titers. This suggests the presence of a significant bacterial population of *M. leprae*, and would correspond to an incidence of about 3 per thousand in the total population studied.

Another aspect of this study which may be of importance is the bacteriological examination of skin smears in that group of persons who give negative skin tests to soluble antigen and have high levels of antibody to glycolipid. This examination might permit the early diagnosis of LL or BL clinical disease at a stage when clinical manifestations are not yet apparent.

In the preliminary study of 2634 contacts, the 570 non-reactors to soluble antigen were divided into two groups; 360 were vaccinated with the *M. leprae*-BCG mixture and 210 received BCG alone.

The responses to soluble antigen at 60 days, 8 months and 14 months after vaccination in these two groups are shown in Table 4. A statistically significant difference is observed between the percentage of negative reactors persisting after BCG vaccination (7.8%) and after vaccination with the mixture (1.9%) at 60 days. This difference increases at six months (49.2 and 13.7%, respectively) and remains relatively stable at 14 months (42 and 19.4%). Not only were there differences in the percentage of reactors observed, but the average size of positive reactions was significantly greater in the *M. leprae*-BCG

TABLE 4. — *Response to SA induced by vaccination with the mixture* M. leprae + *BCG or BCG in contacts initially "negative" (comparative evaluation).* Táchira and Apure States 1981–1982

Stages and Groups	n	mm. Induration		% Reactions (mm.)		
		Average	Std. Dev.	0–9	10–14	15 y +
Group BCG						
Initial reaction	210	5.0	3.0	100.0	0.0	0.0
60 day control	180	15.0	4.8	7.8	40.6	15.6
8 month control	118	8.9	5.7	49.2	35.6	15.2
14 month control	69	10.8	9.1	42.0	20.3	37.7
Group vaccinated M. leprae + BCG						
Initial reaction	360	5.0	3.1	100.0	0.0	0.0
60 day control	308	21.2	6.9	1.9	10.7	87.4
8 month control	204	16.3	7.2	13.7	22.1	64.2
14 month control	93	17.5	9.5	19.4	10.8	69.8

group. The significant number of reactions of 15 mm or greater at 6, 8 and 14 months suggests an important persistence of *M. leprae*-specific reactivity in the group vaccinated with the mixture. The results demonstrate that the responses to BCG were much weaker and less persistent than the response to the *M. leprae*-BCG mixture.

These preliminary results, showing a significant response to *M. leprare*-BCG vaccination in a population of persons who appear to be at particularly high risk of developing progressive disease by epidemiologic and immunologic criteria, form the basis for an immunoprophylaxis trial in more than 60,000 contacts in Venezuela, which may provide the foundation for the addition of a new and powerful element to the control of leprosy.

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VACCINE STRATEGIES FOR THE ERADICATION OF LEPROSY

BARRY R. BLOOM

Chairman, Department of Microbiology and Immunology
Albert Einstein College of Medicine
Bronx, New York 10461

Chairman, IMMLEP Steering Committee,
Special Programme for Research and Training
in Tropical Diseases
World Health Organization, Geneva

From ancient times, in virtually every culture, leprosy has evoked singular images of horror and fascination. There is no other disease whose sufferers were historically cast out of society, buried alive, or burned at the stake. There is no other disease whose very name, in some cultures, is taboo and cannot be written or uttered. Leprosy is thus a disease of the mind as well as of the body, and one of the peculiar aims of the scientific approaches to this disease is to deal with the unique fear and stigma associated with it. To this day leprosy remains an enormous problem and challenge:

i) The etiologic agent, *Mycobacterium leprae*, remains one of the very few pathogens of man that cannot be grown in culture;

ii) There is a long latency, perhaps 5 years, between presumed infection and manifestation of disease, and as a consequence the mode of transmission remains unknown;

iii) While 13 million people are estimated to have leprosy around the world, the disease has a relatively low prevalence, seldom exceeding 1-5/1000 in endemic areas;

iv) The reasons why leprosy disappeared from Europe at the end of the last century, yet is currently increasing in some developing countries, remain unclear;

v) At least one contributory factor is the recent emergence of both primary and secondary drug-resistant organisms. This has necessitated the recommendation for combined chemotherapy, a regimen a great deal more expensive than the standard dapsone monotherapy used for 20 years. What makes the study of leprosy most appealing from an immunological point of view is the fact that there is a well established immunologic basis for the manifestations of the disease and that there is no evidence supporting the view that the disease is ordinarily transmitted from animals to man, suggesting that it may be possible to design a vaccine that would be capable of eradicating this historic scourge of man from the face of the earth.

To accomplish this task will require enormous effort and commitment. It has been possible, largely through the auspices of WHO, to interest and engage scientists from all over the world who possess special expertise relevant to the common goal, and to create a network, a "laboratory without walls" to permit the exchange of ideas, information and scarce reagents. As will become evident, many of the newest techniques of immunology and molecular biology, as well as sophisticated epidemiology, are being brought to bear on the problem. While funds for the research effort have been limited, much has been learned and much already accomplished. A greater level of resources will be required to carry out field studies on large numbers of people to adequately test the effectiveness of any candidate vaccines. At another level, for any vaccine to be effective, there will have to be a major change in attitudes of the people in leprosy endemic countries about the disease, so that rather than shunning it and waiting until it is advanced before seeking treatment, they will want to be protected before they have the disease, or treated and cured at the earliest signs of disease. This will require the understanding, participation, and support of governments, health workers, community leaders and religious groups, without which the scientific efforts may prove fruitless.

The premise upon which the IMMLEP program was founded is that it would be possible to develop a vaccine which provided protection against clinical leprosy. That premise was based on an additional assumption that much of immunology, microbial biochemistry, mechanisms of bacterial killing and resistance to intracellular parasites, identification, purification and production of appropriate antigens of *M. leprae* or related microorganisms would

emerge from an intensive global research effort by many investigators. Optimism was derived as well from the availability of *M. leprae* grown in the armadillo. An enormous amount that has been learned in recent years about the complexities and interactions of cells of immune systems, networks, suppression, and inflammatory and cytocidal mechanisms, which, rather than definitively answering the basic questions, have opened new avenues and raised new questions. What has emerged from the acquisition of knowledge in recent years is clearly that there is not a single rationale for a single vaccine, but several rationales for several different types of vaccines which must be considered and explored in model systems and small scale trials, in order to make the wisest decision about what is likely to be most useful or effective in the field.

I. Premises

A. *Induction of Cell Mediated Immunity Will Confer Protection Against Infection.* The basic assumption of any vaccine is that induction of a state of immunologic reactivity to *M. leprae* antigens will lead to protection against it. Perhaps the key observation which established a relationship between immunity and protection derived from the study of the different courses of disease of patients across the spectrum of leprosy. Leprosy is a spectral disease: at one pole of the spectrum, the tuberculoid form of the disease, patients develop high levels of cell-mediated immunity and kill the bacilli in the tissues, albeit often with concomitant damage to the nerves around which the bacilli grow. At the lepromatous pole, patients are less able or unable to restrict the growth of the organism and lack cell-mediated immunity. In contrast, there appears to be a negative correlation between the level of circulating antibodies in patients and ability to restrict the growth of *M. leprae*, higher titers generally being found in lepromatous than in tuberculoid patients. The basic premise, then, is supported by a strong correlation between cell-mediated immunity and ability of patients to kill or restrict the growth of *M. leprae*. That is simply a correlation, however, not a proof or a guarantee that a person exhibiting cell-mediated immunity to leprosy bacilli cannot develop clinical leprosy. Obviously, patients with tuberculoid leprosy have some organisms which were able to grow, and do have a clinical disease. Of particular interest are the old findings of Chatterjee and Dharmendra that lepromin-positive subjects who contract leprosy develop only tuberculoid and not lepromatous leprosy.

The question remains how strong this correlation is. In order to provide protection against an intracellular bacterium, it is necessary to develop an immune response which produces three consequences: killing of the microorganism, degradation of the bacillus and clearance of antigen and ultimately of immune complexes. That is what is required to generate a disease-free state. At the present time the molecular mechanisms for intracellular killing of mycobacteria, particularly in macrophages, remain unclear, although there is recent evidence which indicates that oxidative cytocidal mechanisms involving the superoxide anion (O_2^-), hydrogen peroxide, (H_2O_2), hydroxyl radical ($OH^\cdot$) and hypohalide may be involved. Non-specifically or immunologically activated macrophages, under the influence of signals from T lymphocytes, have a greatly augmented ability to produce these oxygen radicals and metabolites which may be responsible for the killing event. What is important to emphasize, however, is that from many experimental studies performed in simpler organisms, the killing effects are quantitative rather than qualitative. The ability of a single activated macrophage to produce H_2O_2, for example, is limited. When that cell is infected with one or two microorganisms, the level of H_2O_2 produced may be sufficient to kill both organisms. When that cell is infected with five organisms, the level may still be sufficient to kill two, which means that three microorganisms will not be killed and may grow. It is probably for this reason that it has never been possible to show an absolute quantitative correlation between the diameter of skin test reactivity and the degree of resistance of animals to infection with micro-organisms.

A great deal more is known about the degradative enzymes within macrophages, which include a large list of proteases, nucleases, glycosidases, and lipases capable of destroying most normal biological materials. Yet mycobacteria have unique cell wall and lipid structure which render them much more resistant to degradation than almost any other organism, and it is for this reason that antigens persist for such long periods of time. Nevertheless, the correlation between cell-mediated immunity and resistance to growth of the organism in tuberculoid patients, the correlation between cell-mediated immunity macrophage activation and increased cytocidal oxygen metabolites and in degradative enzymes suggests that induction of immunity should lead to increased resistance, although that resistance cannot be conceived of as being absolute.

B. *Specific Cell-Mediated Immunity Can Be Induced by Immunization with Killed* M. leprae *or Other Mycobacteria.* The second specific experimental premise is that *Mycobacterium leprae* or other cultivable mycobacteria can produce cell-mediated immunity to antigens of the leprosy bacillus. Probably the first line of evidence to support that view is a modern reinterpretation of the Mitsuda test. The Mitsuda test would appear to be unique among all tests for cell-mediated immunity in that it is read not at 24-48 hours, but at 28 days. Since in almost all other systems it is possible to detect preexisting immunity by skin tests that are read at 48 hours, another simple interpretation of the Matsuda test is that it is not only a skin test which measures preexisting cell-mediated immunity, but is, in fact, a weak vaccine. As such, it has been designed to discriminate between individuals who are unresponsive to antigens of leprosy bacillus, either because they have lepromatous disease or because they have been unexposed to the bacillus or cross-reactive antigens, and those who have already been infected, clinically or subclinically, and for whom the Mitsuda test is a booster shot which augments weak prior existing sensitization, or in fact simply is able in 28 days to sensitize them. The fact that a significant percentage of normal individuals in leprosy nonendemic countries or areas become Matsuda positive suggests either that it is a weak vaccine, or that some individuals have been primed against cross reactive antigens.

A second line of evidence indicating that *M. leprae* is immunogenic derives from the studies on purified *M. leprae* carried out in mouse, guinea pigs and armadillos which indicate that in the absence even of oil adjuvants purified and killed *M. leprae* are capable of engendering delayed-type hypersensitivity. In the mouse there is convincing evidence that in addition to cell mediated immunity, high levels of protection against infection by viable *M. leprae* can be engendered. On the other hand the specificity remains unclear. At the moment there are very few unique antigens which distinguish *M. leprae* from all other mycobacteria. It is clear that vaccination of mice with BCG will protect against growth and dissemination of live *M. leprae*, and there is clear evidence that sensitization with *M. leprae* will lead to cross-reactions to a variety of other mycobacterial antigens. It is thus very difficult to establish what the unique and specific antigens of the lepra bacillus are, whether some must be included in the vaccine to induce protection, and whether other mycobacteria share these key antigens. The dilemma in interpreting cross reactive immunization is

compounded by the results of two large scale BCG vaccination trials in which the degree of protection against leprosy varied from 80% in Uganda to 20% in Burma. The reasons for the difference in these results remain unknown, although they suggest that BCG may provide some but not full protection against leprosy.

II. Vaccine strategies

There are at present two rationales for vaccination against leprosy. One is immunoprophylaxis, which is designed to protect a population at risk against developing clinical leprosy. The second is immunotherapy, which is designed to convert anergic lepromatous patients to a state of cell-mediated immunity, in the hope that they will then cure their infection, and ultimately their disease.

A. *A killed* M. leprae *vaccine.* Such a vaccine would be designed exclusively for immunoprophylaxis, since a vast amount of evidence indicates that lepromatous patients are immunologically unresponsive to the leprosy bacilli that they are harboring and to *M. leprae* antigens introduced in skin tests. The premise would be that a naive population would be primed to positive immune reactivity to specific antigens of the leprosy bacillus. When they became infected at some later time, the infecting organisms would serve to boost their already existing levels of cell-mediated immunity, and the patients would develop either subclinical leprosy and eliminate the organisms, or, at worst, develop a tuberculoid type of self-healing disease.

Such a vaccine has the potential for providing information on one of the key problems in leprosy, namely the identification of patients at high risk for lepromatous leprosy. If killed *M. leprae* were found to have a high conversion rate in the leprosy non-endemic population, and there were individuals in the leprosy endemic area who failed to convert to the vaccine, even upon revaccination, it might be argued that their unresponsiveness was due to the fact that they were incubating lepromatous leprosy and already anergic prior to the onset of detectable clinical symptoms of lepromatous leprosy. Thus nonresponders to the vaccine could, in principle, be considered at high risk, identified and then treated with chemotherapy, although this is expensive and logistically difficult.

B. *Killed or Live mycobacterial vaccines to provide crossreactive immunity against* M. leprae. As mentioned above, the first experimental tests of

this strategy were those using BCG vaccination to protect against leprosy, where the results in different parts of the world yielded vastly different rates of protection. There are studies of small numbers of patients with borderline and polar lepromatous leprosy who were vaccinated with BCG, in which clinical improvement was reported, although many of the patients developed reversal reactional symptoms. As a prophylactic vaccine against leprosy, BCG has provided some protection in Uganda, Burma and India, but except in Uganda, never above 25%, which is inadequate protection from a public health point of view.

Two cultivable mycobacterial strains have been reported in India to be effective, after being killed, at inducing cell-mediated immunity in lepromatous patients, and one must await with interest further scientific characterization of the strains and further data on their effectiveness. There are two difficulties with the use of such vaccines. The first is that in the absence of identifiable *M. leprae*-specific antigens, it is very difficult to know which mycobacteria have appropriate specific antigens cross-reactive with antigens required for protection against *M. leprae*. One hopes that as the biochemical purification of mycobacterial protein, glycoprotein and lipid antigens progresses, and monoclonal antibodies are developed, such specific antigens may be identified and cultivatable organisms screened for expression of those antigens. The second concern is that even if unique specific or cross-reactive antigens are found, how can one be sure that they will not engender immunological unresponsiveness or suppression, rather than priming for immunity to the key antigens? Another concern is the possible use of living microorganisms in populations some of whose recipients may have some immunodeficiency, or immunological unresponsiveness against mycobacterial antigens. The immunotherapy of cancer patients with live BCG vaccines and the unexpectedly high incidence of disseminated BCGosis serve to emphasize that concern. One of the appealing aspects of this strategy, however, is the ability to produce very large amounts of such a live cross-reactive vaccine very inexpensively, and they are likely to be effective longer than killed vaccines.

C. *A vaccine of killed* M. leprae *plus living BCG*. The basis for this vaccine derived from Convit's observations that when killed *M. leprae* were injected into the skin of lepromatous patients together with BCG, there was degradation and clearance of the *M. leprae* which was not seen when leprosy bacilli were inoculated alone. Based on these

observations Convit has demonstrated that such a vaccine of killed *M. leprae* plus BCG has strong immunotherapeutic effectiveness in patients with indeterminate, borderline, and, most recently, even in polar lepromatous patients, leading to skin test conversion, degradation of organisms in the skin and marked clinical improvement. The immunological rationale for this mixed vaccine is not fully clear, although it has fundamental implications for understanding the basic mechanisms of immune regulation in man. It may well be that BCG causes activation of T cells specific for its antigens, which then produce lymphokines which: i) have the ability to convert ordinary macrophages into antigen presenting cells, which then augment the ability of lepra antigens to be appropriately presented; and ii) expand small numbers of clones of T cells capable of recognizing specific *M. leprae* antigens. In any case, the data that you will hear provide evidence that this vaccine has therapeutic activity in patients who are otherwise anergic, and should have immunoprophylactic potential in the normal population. One major advantage of this vaccine would be that if there were contacts at high risk for lepromatous leprosy and harboring leprosy bacilli, this vaccine should force them to immunoconversion and serve therapeutically to cure their infection while it is still subclinical.

III. Problems Inherent in Vaccines against Leprosy

A. *Epidemiologic.* The only way that any of these vaccine strategies can be tested meaningfully is first by induction of resistance in appropriate animal models and then by field trials in man. Relatively small scale field trials can be set up to ask the question whether these antigen preparations are capable of inducing cell mediated immunity to antigens of the leprosy bacillus. It becomes a much greater problem to ascertain whether induction of cell-mediated immunity confers with it resistance to infection by *M. leprae*. For therapeutic trials, which in this case become the most feasible, one has simply to test relatively small numbers of patients with well defined stages of disease and look for therapeutic benefit as well as immunoconversion. With respect to protection of normal population, field trials become very complex. Leprosy bacilli are very slow growing organisms, the prevalence rate may be as low as 0.5 per 1000 population, and assuming that four out of five cases of leprosy are likely to be of the tuberculoid variety, this

means that one may have to vaccinate 1000 people to see a diminution in one detectable case of lepromatous disease over a decade. The third population for vaccination which is appealing is that of household contacts of patients with lepromatous leprosy, who are known to have a higher incidence of leprosy, yet the logistics of identifying those individuals and monitoring them with the vaccine are probably more cumbersome than larger scale mass vaccination in field trial areas in many countries.

Finally there is the question of the effectiveness of a vaccine in protecting individuals with subclinical infection. There is basically no precedent for using a vaccine against a disease of such long duration and low prevalence, and one must assume the study would have to be continued for 10-15 years before results could be evaluated.

B. "*The vaccine causes leprosy*". One prediction in vaccinating a large population in a leprosy endemic area is a likelihood that patients who are harboring indeterminate or borderline disease without having manifested clinical symptoms, after vaccination and the induction of relatively high levels of cell-mediated immunity, will begin to show the signs of tuberculoid leprosy. There are two consequences. The first that one can almost certainly expect is the cry from the public health and administrative authorities that the vaccine is causing harm and causing disease, and it will take a long process of education and preparation as well as careful monitoring and availability of appropriate treatment to minimize this problem. The more serious consequence is that some patients who are harboring the leprosy bacillus around the nerves, as they develop rapid cell-mediated immunity may be expected to develop nerve damage, and this must be anticipated and appropriate and rapid treatment provided. In this regard, the studies of Convit on the BCG plus *M. leprae* vaccine in patients with leprosy have been very encouraging in that only a low incidence of neurological symptoms have appeared at no greater prevalence than with chemotherapy alone, and these have been minor.

C. *The duration of sensitization.* Because of the low incidence of disease, and the long latent period before diseases are manifest, in order to provide protection over a long period of time it is necessary that such a vaccine have enduring sensitization. At the moment it is unclear how long a single vaccination confers cell-mediated immunity. In the guinea pig, a single high vaccine dose of killed *M. leprae* is capable of sensitizing animals to positive reactivity to first skin test one year later.

The duration of sensitization in man remains to be established, and if it is not able to confer high levels of sensitization over a ten-year period, then revaccination or booster vaccination of the population may have to be considered in any vaccine protocol.

D. *Unknown variables.* While a great deal of information is available, there remain a large number of scientific variables which will not be known at the time of vaccination trials. The mode of transmission of the disease is unknown. What factors determine the form of disease and whether one develops a positive or suppressed immune response to the specific antigens of the leprosy bacillus, what the role of the genetic constitution of the populations is, and what role environmental mycobacteria have in enhancing or suppressing responsiveness to the vaccine in different populations all remain unknown; yet each could play a significant role in determining the outcome in an individual and in a population.

IV. Future Directions

A. *Seroepidemiology.* The increasing availability of specific monoclonal antibodies should make it possible to identify new *M. leprae* specific antigens which should permit worldwide accurate and inexpensive epidemiological testing: (i) for infection by *M. leprae*; (ii) for studying the mode of transmission; (iii) for characterizing the latent period; and (iv) for identifying individuals at high risk for developing leprosy, hopefully predicting the form of disease to which they are prone. In addition, with such reagents it should be possible to engineer clones of *E. coli* or other microbial hosts expressing *M. leprae* specific epitopes, which could then be used as antigens for standardized epidemiologic testing. If using either *M. leprae*-specific antigens or monoclonal antibodies in immunoassays permits the identification of people in a population who have recently been infected with *M. leprae*, it would permit targeting any of the vaccines to the most susceptible group, thereby reducing the number of people required to be immunized and hopefully decreasing the cost of an eradication program.

B. *Recombinant DNA produced antigens for vaccines.* It is possible that some of these specific antigenic determinants may be important for developing protective immunity. Because of the limitations on vaccine

production in the armadillo, one hopes that it may be possible to produce effective vaccines by recombinant DNA technology in future. The difficulty, however, is that polypeptide antigens alone are unlikely to be as effective as mycobacteria in inducing cell-mediated immunity, as they would lack the extraordinary adjuvant activity possessed by the mycobacteria. Further development of effective adjuvants for inducing cell-mediated immunity in man is urgently required.

C. *Genetically engineered mycobacterial vaccines.* It is not totally unrealistic to conceive of the transfer of genetic information for leprosy-specific protective antigens into cultivable, non-pathogenic mycobacteria, such as BCG vaccine strains, that could provide an ideal vaccine, i.e., one that contains specific protective antigens, lacks tolerogenic determinants and possesses a potent adjuvant for cell-mediated immunity. Were such a vaccine strain to be developed and engineered with genes for protective antigens against other infectious agents, it could have enormous usefulness for immunizing against many diseases for which cell-mediated immunity is critical to resistance.

V. Conclusion

The present methods of control of leprosy are inadequate. The concept of treating patients who already have the disease, and may have been infectious and transmitting *M. leprae* for years before a diagnosis was made, is inadequate. Detection of patients by the traditional "case-finding" methods, more often than not passive rather than active, is clearly inefficient. Problems of the cost of combined chemotherapy, of persisting organisms even after chemotherapy, and the emergence of drug resistant organisms all argue that another strategy, based on preventing rather than treating leprosy, is needed.

Recent scientific developments indicate that at least one vaccine, and possibly others, are capable of providing specific immunity to the leprosy bacillus in man. New tools are being developed for the early diagnosis of infection and disease, and from the scientific point of view one awaits the results of field studies to confirm the feasibility of protecting the people exposed to infection against leprosy by vaccination.

Even if these scientific expectations and hopes are fulfilled, how are we to deal with the stigma and social problems associated with

leprosy? It is too late, in my judgment, to call the disease Hansen's Disease and fool the patients, their families or the community almost anywhere in the world. It is too late for social science questionnaires on people's attitudes toward leprosy. Everyone knows what an appropriate or acceptable answer is supposed to be, and it is unlikely that such surveys will uncover the real fear and prejudice associated with the disease. Clearly, education in a public health context is important, yet help from the sociologists will be crucial in specific contexts, e.g., in cultures where the use of the word "leprosy" is taboo. In my judgment, the most important thing that can be done to change attitudes is to have something tangible and substantial to provide the patients and their communities. This means new scientific tests to identify people with subclinical disease, and appropriate drugs or vaccines to prevent any clinical disease. Ideally, if there were an effective prophylactic vaccine, it should be possible to convince people of leprosy endemic countries that leprosy is a disease which, after centuries of producing destruction of bodies and minds, can be prevented and cured.

With the best available science and with understanding and support from national, community and religious leaders, in my judgment an effective vaccine has the potential to eradicate leprosy from the face of the earth in one generation or less. That makes the vaccine strategy for the eradication of leprosy a compelling one.

EPIDEMIOLOGICAL ASPECTS OF LEPROSY IN BRAZIL

LYGIA M. CEZAR DE ANDRADE
Fundação Oswaldo Cruz, Deptº de Medicina Tropical, Laboratório de Hanseníase, Av. Brasil, 4365,
Manguinhos 21.040, Brazil.

Brazil, a federal republic occupying 47% of the South American continent, has an area of 8,511,965 square kilometers. Most of its territory lies between the Equator and the Tropic of Capricorn. Brazil's territorial limits are the parallels 5°16′19″ North and 33°45′09″ South and the meridians 34°45′54″ and 73°59′32″ West of Greenwich.

This situation produces the great variety of geographical features and climates observed in this beautiful country.

Brazil is divided into 27 political subdivisions:

— AC (Acre), AM (Amazonas), RR (Roraima), PA (Pará), AP (Amapá), MA (Maranhão), PI (Piauí), CE (Ceará), RN (Rio Grande do Norte), PB (Paraíba), PE (Pernambuco), FN (Fernando de Noronha), AL (Alagoas), SE (Sergipe), BA (Bahïa), MG (Minas Gerais), ES (Espírito Santo), RJ (Rio de Janeiro), SP (São Paulo), PR (Paraná), SC (Santa Catarina), RS (Rio Grande do Sul), RO (Rondônia), MT (Mato Grosso), MS (Mato Grosso do Sul), GO (Goiás), DF (Distrito Federal). For many purposes the territory of Fernando de Noronha is considered in the State of Pernambuco.

Leprosy was introduced into Brazil after its discovery by the Portuguese and disseminated by the African slaves. The first cases, following the colonization pathways, appeared along the Atlantic coast from Rio de Janeiro to Pernambuco.

According to Fernando Terra, quoted by Agricola & Risi (2) the first cases were reported around the year 1600 and by the end of that century the extension of the disease already required prophylactic measures.

Neverthless until 1921 almost nothing had been done against the disease (3). In that year the first surveys were undertaken, notwithstanding the great difficulties due to the extensive territory and scarce technical and financial resources.

In 1924, the total cases registered were 7,224 with two principal foci recognised, one in the northern states of Pará and Maranhão and one in the southern states of São Paulo and Minas Gerais.

One year later the registered cases numbered 9,003, and in 1936 the prevalence of leprosy for the country was 0.7 per thousand inhabitants, with 31,920 registered cases.

In 1937 there were 35,308 known patients (1). From these 11,902 were segregated in specialized institutions (33.71%).

From 1938 onwards a more detailed study was undertaken in this sense, culminating in 1941 in the foundation of the National Leprosy Service and the undertaking of more accurate epidemiological surveys.

According to Agricola and Risi (2), in the early stages of the sulphone era, in 1946, the epidemiological situation of leprosy in Brazil is shown in table I and figure 1.

In their work the authors came to the following conclusions:

a — There was compared with the composition of the general population.

- a. 1 — Higher prevalence of the disease in males than in females;
- a. 2 — Higher prevalence in foreigners than in the natives;
- a. 3 — Equal distribution of the disease according to the skin colour (White, black, brown and yellow);
- a. 4 — High frequency of the disease in the population aged less than 15 years in the northern region, in comparison with the other regions, reaching almost twice that of the southern region.

b — The stage of socio-cultural and economic development differed from place to place;

c — The internal migrations influenced the expansion of the endemicity;

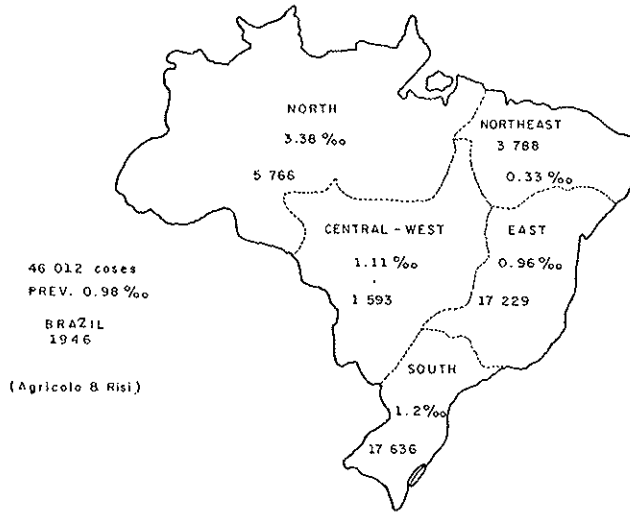
d — The proportion of the composition of the rural and urban population influenced the prevalence of the disease.

TABLE I — *Leprosy Frequency in the Federal Units and Rates per Thousand Inhabitants.* — Brazil 1946.

NATURAL REGIONS AND F. U.	REGISTERED CASES	RATE
NORTH	5 766	3.38
RO	42	1.72
AC	277	3.00
RR	16	1.14
AP	43	1.65
AM	1 816	3.71
PA	3 572	3.37
NORTHEAST	3 788	0.33
MA	1 214	0.86
PI	260	0.28
CE	1 282	0.54
RN	243	0.28
PB	199	0.12
PE	498	0.16
AL	92	0.08
EAST	17 229	0.96
SE	117	0.19
BA	157	0.04
MG	11 546	1.50
ES	1 253	1.45
RJ	1 283	0.61
FD	2 873	1.42
SOUTH	17 636	1.19
SP	14 135	1.72
PR	1 750	1.23
SC	678	0.51
RS	1 073	0.28
C. WEST	1 593	1.1
MT	533	1.11
GO	1 060	1.12

BRAZIL – 1946

LEPROSY NATURAL REGIONS: PREVALENCE RATE PER 1,000 INHABITANTS



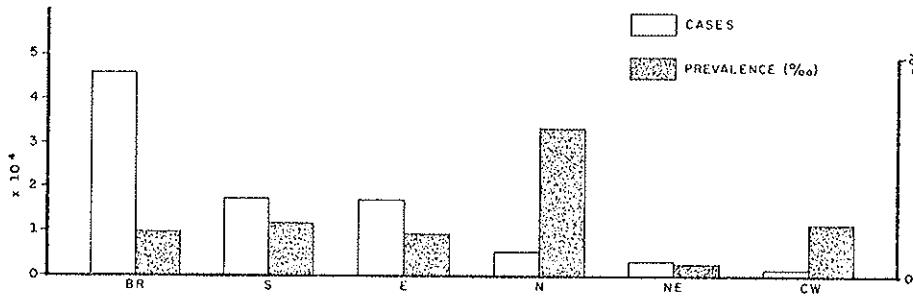


FIG. 1

In truth, these data do not represent the reality of the problem, as can be illustrated by the example of what happened in the district of Candeias, state of Minas Gerais, where an intensive survey took place conducted by del Favero (4).

Before the extensive survey, this district presented a prevalence rate of 0.45 patients per thousand inhabitants and 0.008 patient per km^2. These numbers increased to 3.52/1000 and 0.071, respectively, as the result of an extensive survey conducted there, and up to 9.64 patients per thousand inhabitants and 0.187 patients per km^2 after the intensive survey took place. This shows the necessity of conducting good surveys for a correct appraisal of epidemiological conditions.

Table II and figure 2 show Agricola & Risi's data adjusted to Brazil's now current territory division adopted for Public Health purposes in five "Coordenadorias de Saúde".

As in other regions of the world, the distribution of the disease follows a patchy pattern.

The Amazon Region, with huge forests, hot and super-humid climate and the heaviest rainfalls, showed the highest prevalence rate: 2.24/1,000. In contrast, the northeastern region, with a hotter climate, record of recurring droughts, scrubby thorn woodland (*catinga*) and a moisture deficiency, showed the lowest prevalence rate: 0.19/1,000. This region is also an old focus of leprosy.

Great diversity between prevalence rates is observed also among the several federal units, varying from 3.71/1,000 in the Amazon state to 0.04/1,000 in Bahia.

Factors that could contribute to this diversity are:

a — Climate acting upon the physiology and life habits of the host, and on the viability of the pathogen through different humidity, temperature and solar light levels;

b — Stage of socio-cultural and economic development, differing from place to place;

c — Migrations influencing the expansion of the endemicity;

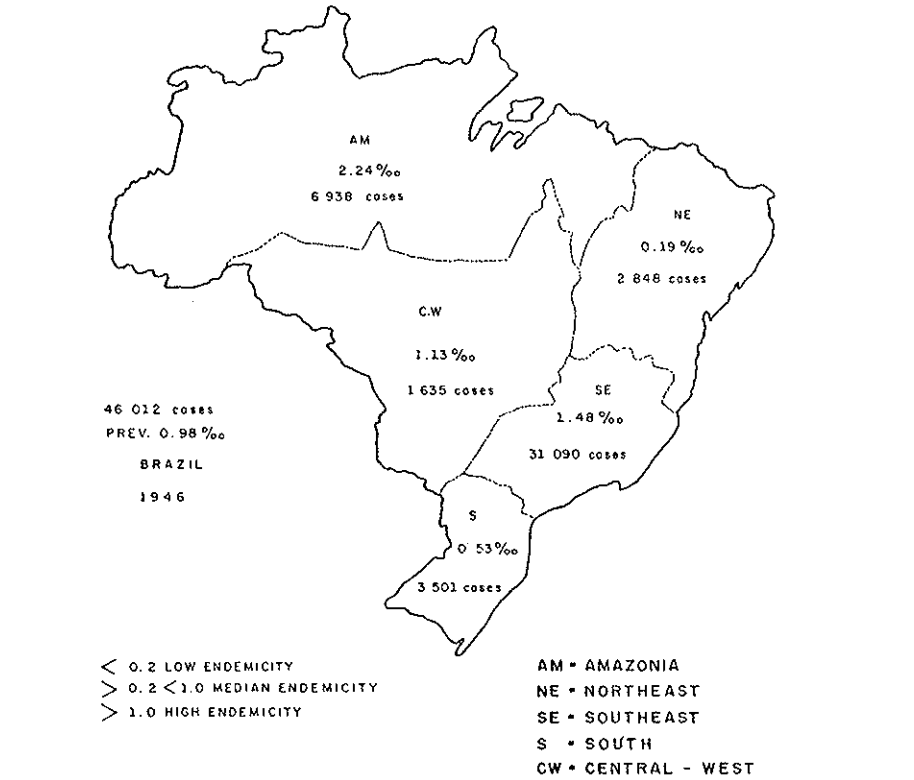
d — Variations in proportions of the rural and urban populations.

The more recent data available regarding the situation of the leprotic endemicity in Brazil refer to December 31, 1982, and were reported by Prof. Aguinaldo Gonçalves, Director of the National Division of Sanitary Dermatology, Ministry of Health (5).

TABLE II — *Leprosy Frequency and Prevalence Rate per Thousand Inhabitants.* – Brazil 1946.

	TOTAL	RATE
BRAZIL	46 012	0.98
AMAZONIA	6 938	2.24
AC	277	3.00
RR	16	1.14
AP	43	1.65
AM	1 816	3.71
PA	3 572	3.37
MA	1 214	8.86
NORTHEAST	2 848	0.19
PI	260	0.28
CE	1 282	0.54
RN	243	0.28
PB	199	0.12
PE	498	0.16
AL	92	0.08
SE	117	0.19
BA	157	0.04
SOUTHEAST	31 090	1.48
MG	11 546	1.50
ES	1 253	1.45
RJ	1 283	0.61
DF	2 873	1.42
SP	14 135	1.72
SOUTH	3 501	0.53
PR	1 750	1.23
SC	678	0.56
RS	1 073	0.28
WEST-CENTRAL	1 635	1.13
RO	42	1.72
MT	533	1.11
GO	1 060	1.12

LEPROSY MORBIDITY – SANITARY REGIONS BRAZIL – 1946



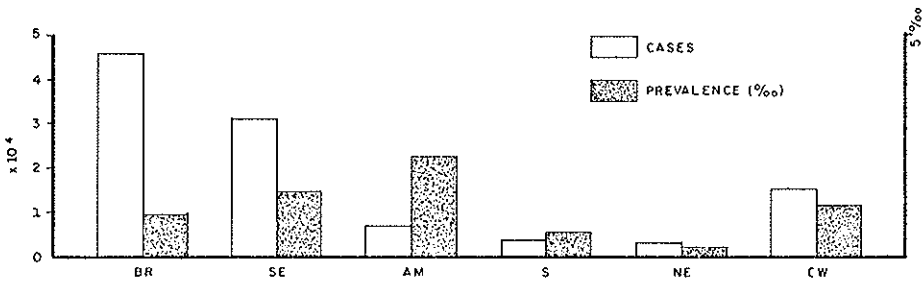


FIG. 2

In that year the total number of registered cases was 198,700, corresponding to a prevalence rate of 1.57 per thousand inhabitants. These values place the country, according to WHO criteria, in the range of high endemicity.

Gonçalves (5), quoting Motta, states that the Brazilian cases represent 80% of all the registered cases in the Americas.

Still according to WHO criteria (6), due to sub-registration caused by different factors these numbers are not representative of the actual situation, and must be multiplied by 1.75. So doing, the number of cases quoted here increases to a total of 347,725 and the prevalence rate to 2.74/1,000 inhabitants.

Table III shows the prevalence and incidence rates, number of registered cases, patients under control and new cases detected during the year, according to the "Coordenadorias Regionais de Saúde" and federal administrative units (Fig. 3 and 4).

Hanseniasis for leprosy and Virchowian (V) for lepromatous are here employed in accordance with the official nomenclature adopted by Brazil's Ministry of Health.

All the regions constitute high endemicity areas, with one exception: the Northeast region, considered an area of median endemicity. Of the federal units, 16 (AC, AM, RR, PA, AP, MA, MG, ES, RJ, SP, PR, RO, MT, MS, GO and DF) are high grade areas of endemicity with prevalence rates varying from 10.84 in Acre to 1.06 in the Federal capital. Eight (PI, CE, PB, PE, SE, BA, SC, RS) are areas of median endemicity, with prevalence rates varying from 0.97 in Piauí to 0.24 in Paraíba, and two (RR and AL) are low endemicity areas, presenting prevalence rates of 0.13 in Rio Grande do Norte and 0.11 in Alagoas (F. U. stands for federal unit).

Analysing the prevalence and incidence rates, the sanitary regions can be placed in the following decreasing order: Amazonia, Central West, Southeast, South and Northeast, varying from 3.95/1,000 and 35.29 per 100,000 inhabitants to 0.47/1,000 and 5.52/100,000, respectively.

In this case, there was a correspondence between both rates, which was not observed in the federal units, the state of Acre presenting the highest prevalence rate in the country: 10.84/1,000, and the state of Amazon the highest incidence rate: 99.74/100,000 inhabitants, while Alagoas figures with the lowest prevalence rate: 0.11/1,000, and Rio Grande do Norte the lowest incidence rate reported for the country: 1.14/100,000 inhabitants. Now if we refer to

TABLE III — *Hanseniasis - Morbidity and Patient Control by Region and Federal Unit.* – Brazil 31/12/1982.

REGIONS AND F	REGISTERED CASES					UNDER CONTROL						NEW CASES REGISTERED 1982	
	RATE per [illegible] INHAB.	TOTAL	CLINICAL FORMS			TOTAL	OUT-PATIENTS				HOSPITALIZED		
			V + D	I	T		TOTAL	V + D	I	T		Nº	RATE P/ 100 000 INHAB.
BRAZIL	1.57	198 700	105 404	47 122	46 174	123 109	114 147	58 949	26 286	28 912	8 964	16 994	13.40
AMAZÔNIA	3.95	40 553	18 492	10 278	11 783	27 314	26 215	11 558	6 224	8 433	1 101	3 632	35.29
AC	10.84	3 556	1 315	1 369	872	1 417	1 280	348	636	296	137	193	58.84
AM	10.43	16 374	7 301	3 934	5 139	10 605	10 495	4 491	2 056	3 948	110	1 565	99.74
RR	1.45	132	51	18	63	115	115	49	12	54	2	25	27.47
PA	2.91	11 002	4 991	2 660	3 351	9 994	9 191	3 955	2 373	2 863	753	916	24.23
AP	4.38	850	459	225	166	459	459	284	104	71	—	118	60.82
MA	2.01	8 639	4 375	2 072	2 192	4 774	4 675	2 431	1 043	1 201	99	815	18.95
NORTHEAST	0.47	15 315	7 410	3 543	4 362	10 800	10 064	4 979	2 060	3 025	736	1 798	5.52
PI	0.97	2 201	1 024	566	611	1 024	956	511	211	234	68	251	11.03
CE	0.72	4 033	2 399	809	825	2 692	2 403	1 396	403	604	289	438	7.85
RN	0.13	260	170	31	59	207	137	81	17	39	70	23	1.14
PB	0.24	684	306	215	163	650	609	266	199	144	41	78	2.70
PE	0.58	3 733	1 461	842	1 430	2 891	2 750	1 117	575	1 058	141	486	7.54
AL	0.11	233	109	51	73	131	131	63	29	39	.....	31	1.47
SE	0.69	830	312	213	305	515	491	183	124	184	24	85	7.04
BA	0.33	3 341	1 629	816	896	2 690	2 587	1 362	502	723	103	406	4.03
SOUTHEAST	1.75	96 630	53 957	22 377	20 296	50 668	44 886	23 663	10 296	10 927	5 782	7 023	12.70
MG	2.47	34 469	18 510	8 311	7 648	6 536	4 538	1 556	753	2 229	1 998	1 991	10.77
ES	3.29	7 072	2 937	2 792	1 343	5 465	5 178	2 226	1 980	972	287	560	26.11
RJ	1.38	16 616	8 500	3 310	4 806	12 691	11 258	5 566	2 333	3 359	1 433	1 577	13.15
SP	1.41	38 473	24 010	7 964	6 499	25 976	23 912	14 315	5 230	4 367	2 064	2 895	10.64
SOUTH	1.37	27 095	15 136	6 679	5 280	23 197	22 525	13 025	5 498	4 002	672	2 053	10.37
PR	2.72	21 344	11 009	6 008	4 327	18 778	18 418	10 005	5 040	3 373	360	1 663	21.22
SC	0.59	2 290	1 476	371	443	1 564	1 439	947	242	250	125	152	3.95
RS	0.42	3 461	2 651	300	510	2 855	2 668	2 073	216	379	187	238	2.93
CENTRAL-WEST	2.15	19 107	10 409	4 245	4 453	11 130	10 457	5 724	2 208	2 525	673	2 488	28.00
RO	2.66	1 604	765	256	583	1 227	1 146	547	182	417	81	132	21.89
MT	2.35	3 060	1 568	752	740	2 804	2 680	1 327	692	661	124	635	48.88
MS	1.70	2 517	1 585	313	619	276	210	210	—	—	66	340	23.00
GO	2.53	10 478	5 726	2 651	2 101	5 542	5 140	2 951	1 098	1 091	402	1 093	26.39
DF	1.06	1 448	765	273	410	1 281	1 281	689	236	356	—	288	21.11

HANSENIASIS–PREVALENCE

ABSOLUTE NUMBERS AND RATE PER 1,000 INHABITANTS ACCORDING TO REGIONS – BRAZIL – 1982

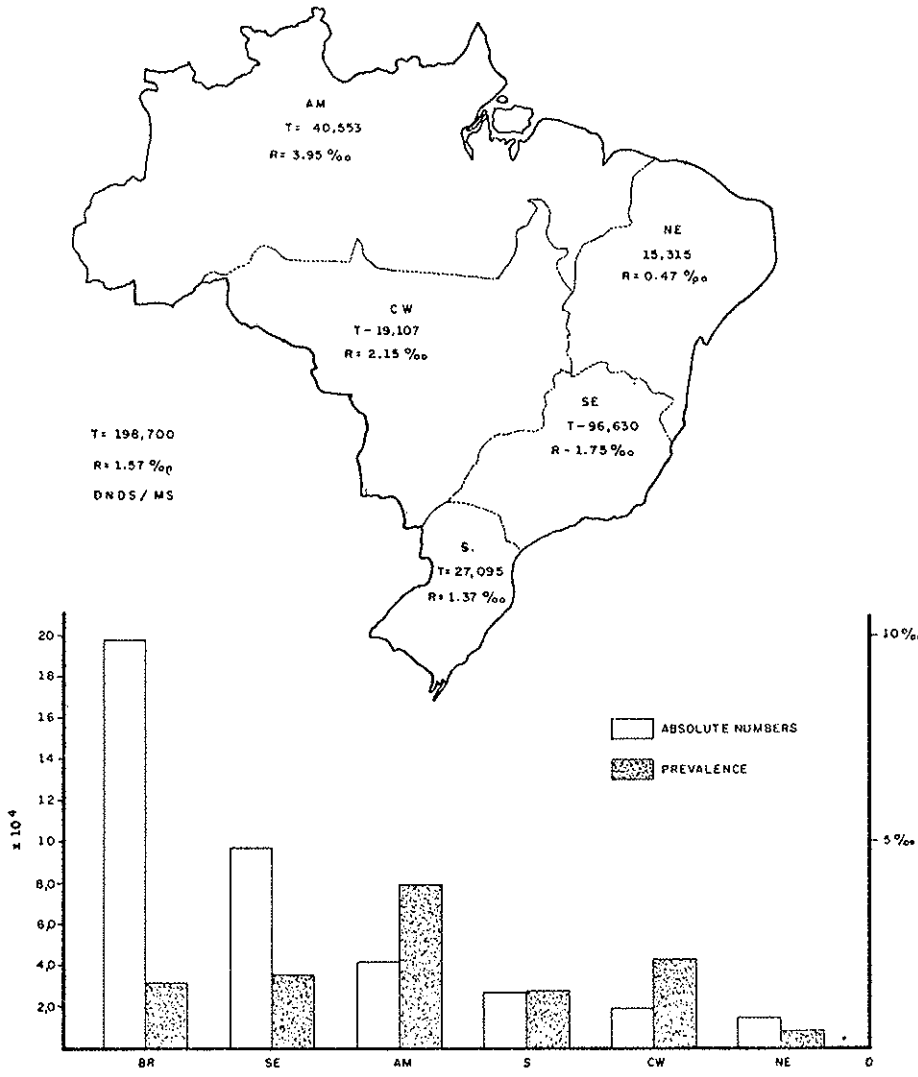


FIG. 3

HANSENIASIS–PREVALENCE

PERCENTAGE OF REGISTERED CASES AND OF V + D FORMS ACCORDING TO REGIONS – BRAZIL – 1982

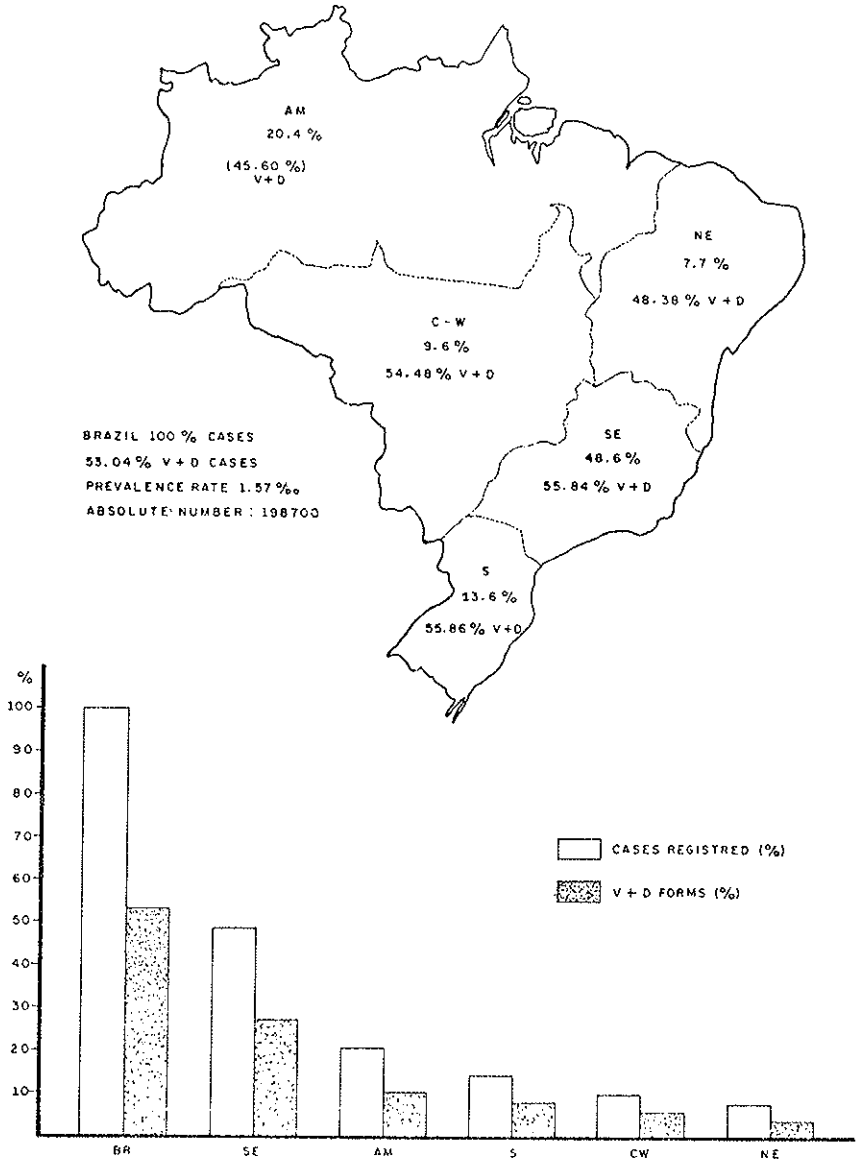


FIG. 4

the absolute numbers of cases recorded, the regions according to the decreasing order will be placed as follows:

First, the Southeastern region with the highest numbers: 96,630 registered cases or 48.6% of the sick population of the country and 7,023 new cases or 41.4% of all new cases detected in Brazil in 1982. This region, Brazil's most developed and industrialized one, comprises 10.86% of the area of the country and 43.6% of the general population, presenting the highest demographic density: 59.78 inhabitants per square kilometer.

Next comes the Amazonia region presenting 40,553 known cases, less than half the Southeast region's cases or 20.4% of the sick population, and 3,632 new cases or 21.4% of all new cases detected during the year. This region comprises 43.07% of the nation's area and 8.1% of its population with 2.80 inhabitants per square kilometer.

In the third place stands the Southern region, with 27,095 registered cases or 13.6% of the country's reported cases and 2,053 new cases detected or 12.0% of all new cases reported. Next to the Southeastern region in socio-cultural and economic development, the Southern region comprises 6.79% of the nation's area and holds 15.6% of its population and supports 34.27 inhabitants per km^2.

The Central region comes next with 19,107 registered cases (9.6%) and 2,488 (14.6%) new cases detected, and contains 24.94% of the nation's area, 7.0% of its population and 4.18 inhabitants per km^2.

The last position is assigned to the Northeastern region with 15,315 registered cases or 7.7% of all known cases, and 1,798 new cases reported, equalling 10.6% of all new cases detected in the period. This region's area equals 14.38% of the nation's area, participates with 25.7% of the general population and contains 26.69 inhabitants per km^2 (See table XVIII and XIX).

Outstanding is the great difference existing between fractions of the sick and general population in these regions, particularly in the Amazon region, where the fraction of the sick population is 20.4% and that of the general population is only 8.1%, and in the Southeastern region where the sick population's fraction is 48.6% and the general population's is 43.6%.

In table III are displayed the clinical forms and their distribution in absolute numbers. In table IV-V which shows the percent coefficient of the same, the sharp predominance can be noted of the "Polar" forms all over the country: 78.28%. Although not a "Polar" form, the

Dimorphous form had to be included in this group due to the Brazilian system of epidemiological records that register the infectious forms together (See table V).

Such high percentages of "Polar" forms as 91.33 (RS), 88.08 (RN), 87.56 (MS), 86.37 (RR), 84.04 (RO), 83.94 (CE), 83.79 (SC), 81.14 (DF), 80.07 (RJ) and 79.29 (SP) were registered in the federal units.

The V + D group predominated in all the federal units with one exception: Roraima, but with very few cases registered.

The V + D rate varied from 76.60% in Rio Grande do Sul to 36.98% in Acre, the Southeastern, Southern and Central-Western regions presenting the highest coefficients in general. The Amazonia and Northeastern regions presenting lower rates of V + D and higher rates of T forms.

In table VI case control rates for Brazil in general are 61.96% for all forms and 62.62% for V + D forms. These numbers are below the 75% rate recommended by WHO.

The Southern region is unique in presenting a good control of cases: 85.61% of all cases and 89.79% of V + D cases.

The Northeastern region, although not reaching the recommended percentage for all cases, presents a good control of the V + D cases: 74.98%.

The Southeastern region, despite being the best developed region, shows the lowest rate of case control of all forms, with the aggravating circumstance that it shelters the largest contingent of the sick population.

Only 13 of the federal units presented a case control rate above 75% for all forms.

Table VII shows the distribution, in absolute numbers and in percentage, of the patients under control, considering the clinical forms, regions and federal units.

Considering that *greater attention* should be paid to the control of infectious cases, it is salient to point out that the case control rate of T form in Brazil, in the Amazonia and in the Southeastern region is higher than that of the V + D forms. The same happened in five of the federal units, perhaps because the T cases, being less numerous and subjected to fewer periodical revisions, are easier to control.

The good performance of case control achieved by the states of Pará, Mato Grosso and Paraíba reaching very high rates of control in all forms of Hanseniasis is noteworthy.

TABLE IV — *Hanseniasis* – Registered Cases 1982.

REGIONS AND F. U.	RATE P/1 000	TOTAL	CLINICAL FORMS					
			V + D		I		T	
			TOTAL	%	TOTAL	%	TOTAL	%
BRAZIL	1.57	198 700	105 404	53.04	47 122	23.71	16 174	23.24
AMAZONIA	3.95	40 553	18 492	45.60	10 278	25.34	11 783	29.05
AC	10.84	3 556	1 315	36.98	1 369	38.50	872	24.52
AM	10.43	16 374	7 301	44.59	3 934	24.02	5 139	31.38
RR	1.45	132	51	38.64	18	13.64	63	47.73
PA	2.91	11 002	4 991	45.36	2 660	24.18	3 351	30.46
AP	4.38	850	459	54.00	225	26.47	166	19.53
MA	2.01	8 639	4 375	50.64	2 072	23.98	2 192	25.37
NORTHEAST	0.47	15 315	7 410	48.38	3 543	23.13	4 362	28.48
PI	0.97	2 201	1 024	46.52	566	25.71	611	27.76
CE	0.72	4 033	2 399	59.48	809	20.06	825	24.46
RN	0.13	260	170	65.38	31	11.92	59	22.70
PB	0.24	684	306	44.74	215	31.43	163	23.83
PE	0.58	3 733	1 461	39.14	842	22.55	1 430	38.31
AL	0.11	233	109	46.78	51	21.89	73	31.33
SE	0.69	830	312	37.59	213	25.66	305	36.75
BA	0.33	3 341	1 629	48.76	816	24.42	896	26.82
SOUTHEAST	1.75	96 630	53 957	55.84	22 377	23.16	20 296	21.00
MG	2.47	34 469	18 510	53.70	8 311	24.11	7 648	22.19
ES	3.29	7 072	2 937	41.53	2 792	39.48	1 343	18.99
RJ	1.38	16 616	8 500	51.15	3 310	19.92	4 806	28.92
SP	1.41	38 473	24 010	62.40	7 964	20.70	6 499	16.89
SOUTH	1.37	27 095	15 136	55.86	6 679	24.65	5 280	19.49
PR	2.72	21 344	11 009	51.58	6 008	28.15	4 327	20.27
SC	0.59	2 290	1 476	64.45	371	16.20	443	19.34
RS	0.42	3 461	2 651	76.60	300	8.67	510	14.73
CENTRAL-WEST	2.15	19 107	10 409	54.48	4 245	22.22	4 453	23.30
RO	2.66	1 604	765	47.69	256	15.96	583	36.35
MT	2.35	3 060	1 568	51.24	752	24.57	740	24.18
MS	1.70	2 517	1 585	62.97	313	12.43	619	24.59
GO	2.53	10 478	5 726	54.65	2 651	25.30	2 101	20.05
DF	1.06	1 448	765	52.83	273	18.85	410	28.31

Good performances in this aspect, if not with as high coefficients, have been achieved also by the states of Paraná, Pernambuco and Rondônia.

The importance of all forms in case control should be stressed: the V + D due to their infectiousness, the T due to the incapacities engendered and the I as source of infectious and T forms.

TABLE V — *Hanseniasis Prevalence.* – Brazil 1982.

REGIONS AND F. U.	RATE P/1 000	CLINICAL FORMS			
		P* %	V + D %	I %	T %
BRAZIL	1.57	78.28	53.04	23.71	23.24
AMAZONIA	3.95	74.65	45.60	25.34	29.05
AC	10.84	61.50	36.98	38.50	24.52
AM	10.43	75.97	44.59	24.02	31.38
RR	1.45	86.37	38.64	13.64	47.73
PA	2.91	75.82	45.36	24.18	30.46
AP	4.38	73.53	54.00	26.47	19.53
MA	2.01	76.01	50.64	23.98	25.37
NORTHEAST	0.47	76.86	48.38	23.13	28.48
PI	0.97	73.78	46.52	25.71	27.76
CE	0.72	83.94	59.48	20.06	24.46
RN	0.13	88.08	65.38	11.92	22.70
PB	0.24	68.57	44.74	31.43	23.83
PE	0.58	77.45	39.14	22.55	38.31
AL	0.11	78.11	46.78	21.89	31.33
SE	0.69	74.34	37.59	25.66	36.75
BA	0.33	75.58	48.76	24.42	26.82
SOUTHEAST	1.75	76.84	55.84	23.16	21.00
MG	2.47	75.89	53.70	24.11	22.19
ES	3.29	60.52	41.53	39.48	18.99
RJ	1.38	80.07	51.15	19.92	28.92
SP	1.41	79.29	62.40	20.70	16.89
SOUTH	1.37	75.34	55.86	24.65	19.49
PR	2.72	71.85	51.58	28.15	20.27
SC	0.59	83.79	64.45	16.20	19.34
RS	0.42	91.33	76.60	8.67	14.73
C. WEST	2.15	77.78	54.48	22.22	23.30
RO	2.66	84.04	47.69	15.96	36.35
MT	2.35	75.42	51.24	24.57	24.18
MS	1.70	87.56	62.97	12.43	24.59
GO	2.53	74.70	54.65	25.30	20.05
DF	1.06	81.14	52.83	18.85	28.31

* Including Dimorphous cases, although not polar.

TABLE VI — *Hanseniasis — Registered Cases 1982.*

REGIONS AND F. U.	PREV. P/1 000	TOTAL		UNDER CONTROL			NEW CASES		
				TOTAL		V + D %	TOTAL		INC. P P/100
		Nº	%	Nº	%		Nº	%	
BRAZIL	1.57	198 700	100	123 109	61.96	62.62	16 994	100	13.4
AMAZONIA	3.95	40 553	20.41	27 314	67.35	67.20	3 632	21.4	35.2
AC	10.84	3 556		1 417	39.85	36.42	193		58.8
AM	10.43	16 374		10 605	64.77	62.58	1 595		99.7
RR	1.45	132		115	87.12	96.07	25		27.4
PA	2.91	11 002		9 994	90.38	91.00	916		24.2
AP	4.38	850		459	54.00	61.87	118		60.8
MA	2.01	8 639		4 774	55.26	57.21	815		18.9
NORTHEAST	0.47	15 315	7.71	10 800	70.52	74.98	1 798	10.6	5.5
PI	0.97	2 201		1 024	46.52	55.08	251		11.0
CE	0.72	4 033		2 692	66.75	68.86	438		7.8
RN	0.13	260		207	79.61	78.23	23		1.1
PB	0.24	684		650	95.03	95.42	78		2.7
PE	0.58	3 733		2 891	77.44	82.34	486		7.5
AL	0.11	233		131	56.22	57.80	31		1.4
SE	0.69	830		515	62.05	65.38	85		7.0
BA	0.33	3 341		2 690	80.51	88.70	406		4.0
SOUTHEAST	1.75	96 630	48.63	50 668	52.43	52.21	7 023	41.4	12.7
MG	2.47	34 469		6 536	18.96	15.90	1 991		10.7
ES	3.29	7 072		5 465	77.27	82.53	560		26.1
RJ	1.38	16 616		12 691	76.38	79.14	1 577		13.1
SP	1.41	38 473		25 976	67.52	66.95	2 895		10.6
SOUTH	1.37	27 095	13.64	23 197	85.61	89.79	2 053	12.0	10.3
PR	2.72	21 344		18 778	87.98	93.65	1 663		21.2
SC	0.59	2 290		1 564	68.29	71.27	152		3.9
RS	0.42	3 461		2 855	82.49	84.08	238		2.9
CENTRAL-WEST	2.15	19 107	9.62	11 130	58.25	60.16	2 488	14.6	28.0
RO	2.66	1 604		1 227	76.49	75.03	132		21.8
MT	2.35	3 060		2 804	91.63	91.51	635		48.8
MS	1.70	2 517		276	10.96	16.97	340		23.0
GO	2.53	10 478		5 542	52.89	57.56	1 093		26.3
DF	1.06	1 448		1 281	88.46	90.06	288		21.1

TABLE VII — *Hanseniasis - Distribution of Patients Under Control According to Clinical Forms, Region and Federal Unit.* – Brazil 1982.

Regions and F. U.	Clinical Forms								
	V + D			I			T		
	Registered Cases	Under Control	% of Control	Registered Cases	Under Control	% of Control	Registered Cases	Under Control	% of Control
BRAZIL	105 404	66 006	62.62	47 122	27 235	57.80	46 174	29 868	64.68
Amazônia	18 492	12 426	67.20	10 278	6 286	61.16	11 783	8 602	73.00
AC	1 315	479	36.42	1 369	636	46.45	872	302	34.63
AM	7 301	4 569	62.58	3 934	2 056	52.26	5 139	3 980	77.44
RR	51	49	96.07	18	12	66.66	63	54	85.71
PA	4 991	4 542	91.00	2 660	2 420	90.97	3 351	2 982	88.98
AP	459	284	61.87	225	104	46.22	166	71	42.77
MA	4 375	2 503	57.21	2 072	1 058	51.06	2 192	1 213	55.33
Northeast	7 410	5 556	74.98	3 543	2 136	60.29	4 362	3 108	71.25
PI	1 024	564	55.08	566	211	37.28	611	249	40.75
CE	2 399	1 652	68.86	809	414	51.17	825	626	75.87
RN	170	133	78.23	31	26	83.87	59	48	81.35
PB	306	292	95.42	215	204	94.88	163	154	94.47
PE	1 461	1 203	82.34	842	616	73.15	1 430	1 072	74.96
AL	109	63	57.80	51	29	56.86	73	39	53.42
SE	312	204	65.38	213	124	58.21	305	187	61.31
BA	1 629	1 445	88.70	816	512	62.74	896	733	81.80
Southeast	53 957	28 169	52.21	22 377	11 004	49.17	20 296	11 495	56.64
MG	18 510	2 944	15.90	8 311	1 089	13.10	7 648	2 503	32.72
ES	2 937	2 424	82.53	2 792	2 030	72.70	1 343	1 011	75.27
RJ	8 500	6 727	79.14	3 310	2 476	74.80	4 806	3 488	72.57
SP	24 010	16 074	66.95	7 964	5 409	67.92	6 499	4 493	69.13
South	15 136	13 592	89.79	6 679	5 547	83.05	5 280	4 058	76.85
PR	11 009	10 311	93.65	6 008	5 066	84.32	4 327	3 401	78.59
SC	1 476	1 052	71.27	371	248	66.84	443	264	59.59
RS	2 651	2 229	84.08	300	233	77.66	510	393	77.05
Central-West	10 409	6 263	60.16	4 245	2 262	53.28	4 453	2 605	58.49
RO	765	574	75.03	256	194	75.78	583	459	78.73
MT	1 568	1 435	91.51	752	694	92.28	740	675	91.21
MS	1 585	269	16.97	313	02	0.63	619	05	0.80

In table VIII we can appreciate the control data concerning household contacts of V + D patients.

There are 310,198 household contacts of V or D patients corresponding to 105,404 V or D patients, a ratio of 2.94 V or D patient contacts for each V or D patient. But, considering the contacts and cases under control, there are 118,329 contacts for 86,006 V or D patients originating a new ratio of 1.79 V or D patient contacts for one V or D case.

The situation of contact surveillance in Brazil is very poor as only 38.14% of the country's household contacts of V or D patients are controlled. Rates above 75% appear only in five states, while rates under 50% appear in 11 states. Piauí has no control at all, and no information is available about Goias.

In the following table the new cases detected during 1982 according to clinical form and to region and federal unit are shown (Table IX, figures 5 and 6).

The total number of detected new cases in Brazil, that year, was 16,994 with a general incidence rate of 13.40 cases per 100,000 inhabitants.

Of these cases, 74% were Polar forms (the Dimorphous form, which although not Polar, is included here due to the notification system adopted in Brazil), V + D forms (45%) prevailing over T forms (28%): one V or D case to 0.64 T case (Table X, figure 7).

The Amazon region, although presenting the highest incidence rate, 35.29 new cases per 100,000 inhabitants, remained in second place when considering the absolute number of detected new cases: 3,639 or 21.37% of all new cases detected during the year. The proportion of "Polar" forms was 76.91%, the V + D forms (39.71%) almost equalling the T forms (37.20%), the ratio being 1 V or D case to 0.94 T case.

The Northeastern region, presenting the lowest incidence rate (5.52/100,000), registered only 1,798 new cases or 10.59% of all cases, but recorded the highest coefficient in the country for Polar forms 77.42%, the T form (39.71%) slightly above the V + D forms (37.71%) the proportion being 1 V or D case to 1.05 T case.

These two regions, although in contrasting positions with regard to the incidence and prevalence rates, present a very similar picture, considering some features of the disease, such as type and age-group distribution.

The Southeastern region, presenting an incidence rate of 12.70 detected new cases per 100,000 inhabitants, registered the largest number of new cases: 7,023 corresponding to 41.33% of all the nation's

TABLE VIII. — *Hanseniasis - Distribution of Registered Patients and of Household Con*
Under Control. – Brazil 1982.

REGIONS	PATIENTS			HOUSEHOLD CONTACTS OF V + D		
	REGISTERED CASES	CONTROLLED	% OF CONTROL	REGISTERED CASES	CONTROLLED	% CON
BRAZIL	198 700	123 109	61.96	310 198	118 329	38
AMAZÓNIA	40 553	27 314	67.35	91 734	45 784	49
AC	3 556	1 417	39.85	6 641	1 338	20
AM	16 374	10 605	64.77	50 000	27 332	54
RR	132	115	87.12	278	126	45
PA	11 002	9 944	90.38	18 168	13 807	75
AP	850	459	54.00	1 589	906	57
MA	8 639	4 774	55.26	15 058	2 275	15
NORTHEAST	15 315	10 800	70.52	11 187	7 468	66
PI	2 201	1 024	46.52	.....	.....	...
CE	4 033	2 692	66.75	3 451	3 279	95
RN	260	207	79.61	749	440	58
PB	684	650	95.03	1 409	710	50
PE	3 733	2 891	77.44	2 793	1 063	38
AL	215	131	56.22	435	54	12
SE	830	515	62.05	300	270	90
BA	3 341	2 690	80.51	2 050	1 652	80
SOUTHEAST	96 630	50 668	52.43	101 911	39 405	38
MG	34 469	6 536	18.96	46 363	5 433	11
ES	7 072	5 465	77.27	8 385	4 935	58
RJ	16 616	12 691	76.38	11 850	6 256	52
SP	38 473	25 976	67.52	35 313	22 781	64
SOUTH	27 095	23 197	85.61	94 687	18 704	19
PR	21 344	18 778	87.98	84 718	15 129	17
SC	2 290	1 564	68.29	4 482	2 234	49
RS	3 461	2 855	82.49	5 487	1 341	24
CENTRAL-WEST	19 107	11 130	58.25	10 679	6 968	65
RO	1 604	1 227	76.49	...	...	...
MT	3 060	2 804	91.63	4 361	3 386	77
MS	2 517	276	10.96	294	86	29
GO	10 478	5 542	52.89	3 121	2 052	65
OF	1 448	1 281	88.46	2 903	1 444	49

Source: SES/DNDS/SNPES

TABLE IX — *Distribution of new Cases of Hanseniasis, According to Clinical Forms, by Region and Federal Unit.* – Brazil 1982.

Regions and F. U.	Clinical Forms						Total	Rate */100 000
	V + D		I		T			
	Total	%	Total	%	Total	%		
BRAZIL	7 630	44.90	4 418	26.00	4 939	29.06	16 994	13.40
Amazônia	1 435	39.51	846	23.29	1 351	37.20	3 632	35.29
AC	73	37.83	40	20.72	80	41.45	193	58.84
AM	601	38.40	302	19.29	662	42.31	1 565	99.74
RR	10	40.00	01	4.00	14	56.00	25	27.47
PA	371	40.50	234	25.54	311	33.96	916	24.23
AP	42	35.59	49	41.53	27	22.88	118	60.82
MA	338	41.47	220	26.99	257	31.54	815	18.95
Northeast	678	37.71	399	22.19	714	39.71	1 798	5.52
PI	100	39.85	75	29.88	76	30.27	251	11.03
CE	195	44.52	93	21.24	150	34.24	438	7.85
RN	10	43.48	05	21.74	08	34.78	23	1.14
PB	29	37.18	29	37.18	20	25.64	78	2.70
PE	133	27.37	97	19.96	256	52.67	486	7.54
AL	13	41.94	09	29.03	09	29.03	31	1.47
SE	24	28.24	17	20.00	44	51.76	85	7.04
BA *	174	42.86	74	18.23	151	37.19	406	4.03
Southeast	3 201	45.58	1 965	27.98	1 857	26.44	7 023	12.70
MG	955	48.34	568	28.25	468	23.41	1 991	10.77
ES	240	42.85	218	38.93	102	18.22	560	26.11
RJ	666	42.23	348	22.06	563	35.71	1 577	13.15
SP	1 340	46.29	831	28.70	724	25.01	2 895	10.64
South	1 137	55.38	522	25.42	394	19.20	2 053	10.37
PR	890	53.52	465	27.96	308	18.52	1 663	21.22
SC	95	62.50	31	20.39	26	17.11	152	3.95
RS	152	63.86	26	10.93	60	25.21	238	2.93
Central-West	1 179	47.39	686	27.57	623	25.04	2 488	28.00
RO	54	40.91	32	24.24	46	34.85	132	21.89
MT	278	43.78	195	30.71	162	25.51	635	48.88
MS	228	67.06	43	12.65	69	20.29	340	23.00
GO	520	47.57	284	25.99	289	26.44	1 093	26.39
DF	99	34.37	132	45.83	57	19.80	288	21.11

Source: SES/DNDS/SNPES

* The Clinical form of 7 patients was not assigned.

HANSENIASIS – INCIDENCE

ABSOLUTE NUMBERS AND RATE PER 100,000 INHABITANTS ACCORDING TO REGIONS – BRAZIL – 1982

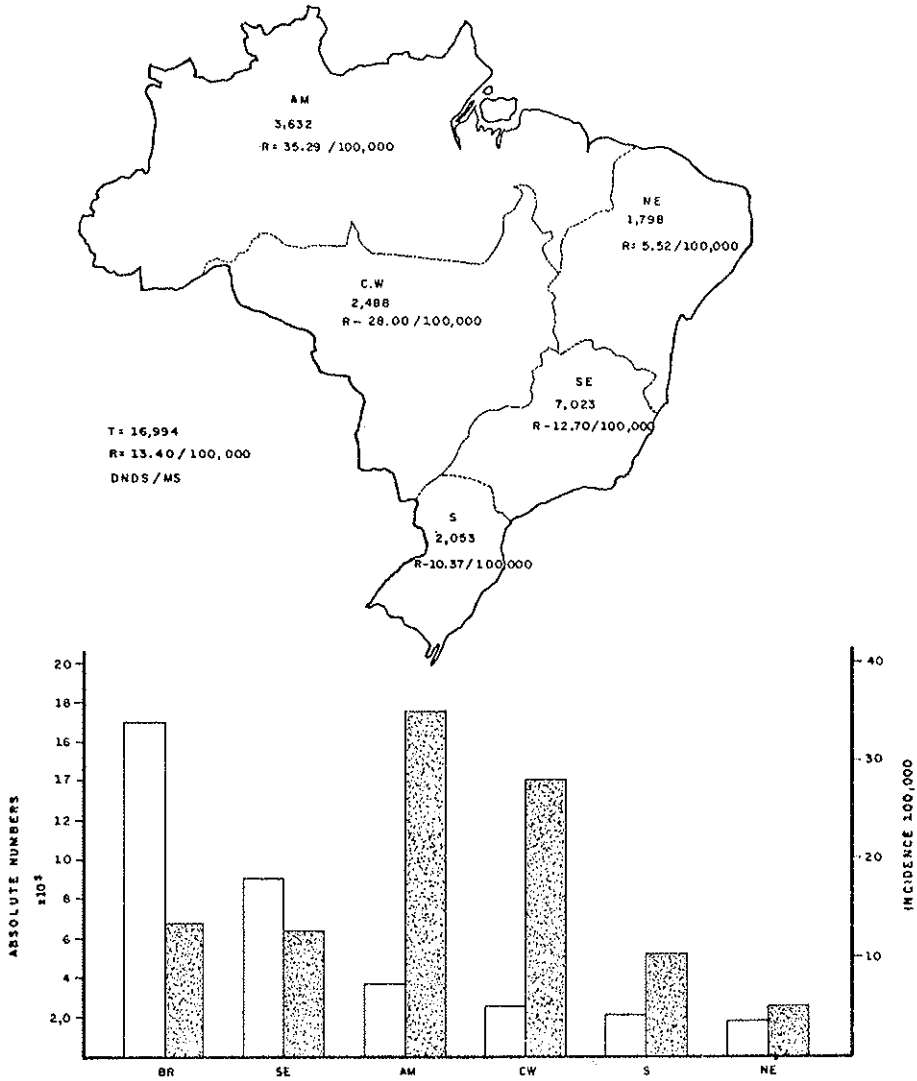


FIG. 5

HANSENIASIS – INCIDENCE

ABSOLUTE NUMBERS AND RATE PER 100,000 INHABITANTS ACCORDING TO FEDERAL UNIT

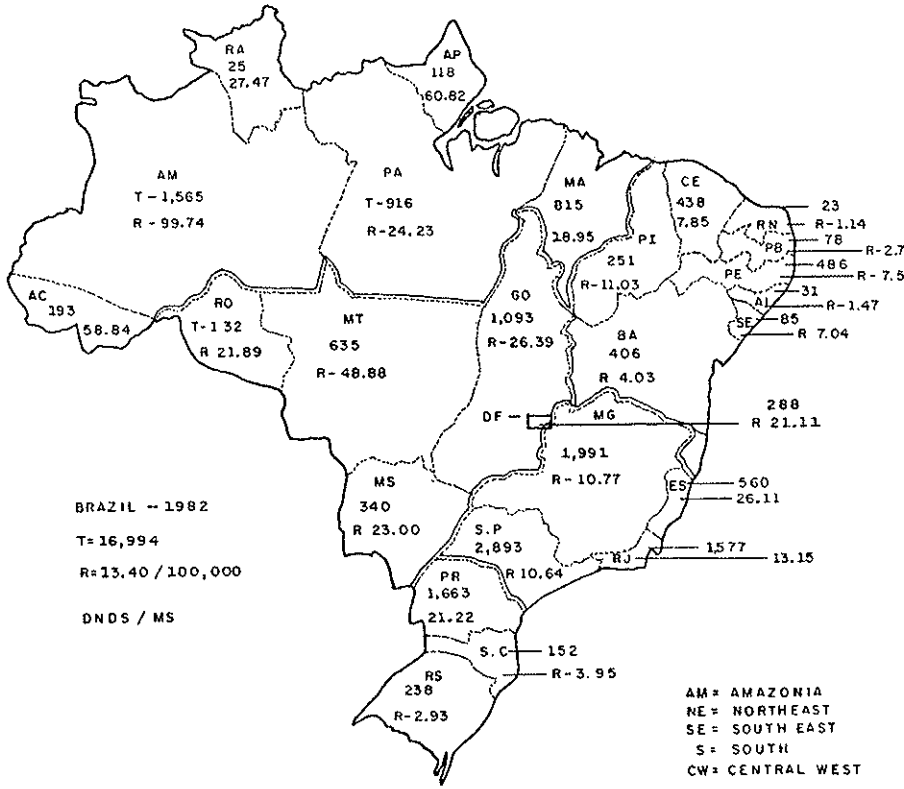


FIG. 6

TABLE X — *Hanseniasis – Incidence Rates According to Clinical Forms and Regions* – Brazil 1982.

REGION	DETECTED CASES	INC. 100 000	POLAR %	V + D %	I %	T %	NI %
BRAZIL *	16 994	13.40	74.00	45.00	26.00	29.00	55.00
AMAZÔNIA	3 632	35.29	76.71	39.51	23.29	37.20	60.49
NORTHEAST	1 798	5.52	77.42	37.71	22.16	39.71	61.87
SOUTHEAST	7 023	12.70	72.02	45.58	27.98	26.44	54.42
SOUTH	2 053	10.37	74.58	55.38	25.42	19.20	44.62
C. WEST	2 488	28.00	72.43	47.39	25.57	25.04	50.61

* Coefficients in round numbers.

detected new cases. The proportion of "Polar" forms was 72.02%, the lowest in the country, but the V + D cases (46.58%) prevailed over the T cases (26.44%) in the proportion of one V or D case to 0.58 T case.

This region, in comparison with the others, has recorded the highest coefficient of I forms: 27.98%.

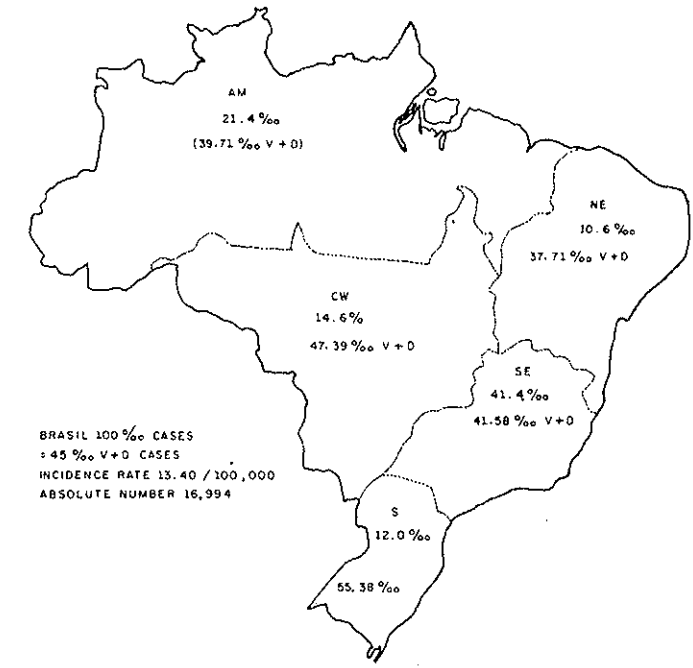
The Southern region, with an incidence rate of 12.08/100,000 inhabitants, presented 2,053 new cases and 74.58% of "Polar" forms showing the highest coefficient of V + D forms of all regions: 55.38%, against 19.20% of T cases. The proportion is of one V or D case to 0.35 T case.

Finally the Central-Western region, with an incidence rate of 14.64 new cases per 100,000 inhabitants, shows a total of 2,448 detected new cases. The coefficient of "Polar" forms attained 72.43%, the V + D cases (47.39%) prevailing over the T cases (25.04%) in the proportion of 1 V or D case to 0.53 T forms.

Comparing the situation in the federal units, one can see that in the Southeastern, Southern and Central-Western regions, the component states followed the pattern of their region, (Table IX) the V + D forms prevailing in all of them with one exception: the Federal District, which presented a predominance of I cases.

HANSENIASIS – INCIDENCE

PERCENTAGE OF DETECTED NEW CASES AND V + D FORMS ACCORDING TO REGIONS – BRAZIL – 1982



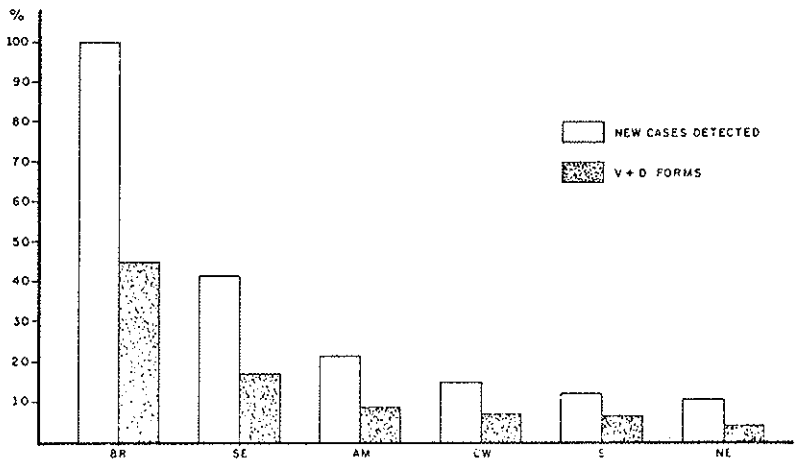


FIG. 7

In the Amazon region, with a slightly higher proportion of V + D cases (39.51%) over T cases (37.20%), V and D cases prevailed in only two federal units: Pará and Maranhão, T cases prevailed in three units and I cases in one unit.

In the Northeast, the only region with a predominance of T forms (although small: 39.71% of T against 37.71% of V + D cases), five of the eight states there included presented prevailing V + D forms, while only two of them registered a predominance of T forms, and in one the V + D and I coefficient was the same: 37.18%.

Of the detected new cases, the non-infectious ones (T + I) predominated in general and in all the regions, except in the Southern region, where infectious new cases predominated as shown in table X.

Now if the incidence according to the age-groups is examined (table XI), a sharp difference is noted between the number of detected new cases in the age-groups 0-14 years and in the 15 years and over age-group (table XII).

The total new cases detected in the country amounted to 16,994, giving an incidence rate of 13.40 per 100,000 inhabitants. Of these, only 1,407 or 8.28% fell on the 0-14 years age-group, and were so divided among the regions:

1 — Amazon region – 644 detected new cases or 17.73% of all the region's new cases;

2 — Northeastern region – 199 detected new cases or 11.07% of all the region's new cases;

3 — Southeastern region – 328 detected new cases or 4.67% of all the region's new cases;

4 — Southern region – 77 detected new cases or 3.75% of all the region's new cases;

5 — Central-Western region – 159 detected new cases or 6.39% of all the region's new cases.

These results are similar to those described by Agricola & Risi (2), in 1946.

Considering the federal units, the portion of detected new cases in the 0-14 years group presented a great diversity as is shown in table XIII.

TABLE XI — *Hanseniasis - Distribution, by Region and Federal Unit, of Registered New Cases According to Clinical Form and Age-Groups* – Brazil 1982.

REGIONS AND F. U.	CLINICAL FORMS								TOTAL
	V + D		I		T		TOTAL		
	0–14 years	15 and over	0–14 years	15 and over	0–14 years	15 and over	0–14 years	15 and over	
BRAZIL	354	7 264	523	3 892	530	4 404	1 407	15 567	16 994
AMAZÔNIA	163	1 272	203	643	278	1 073	644	2 988	3 632
AC	02	71	03	37	04	76	09	184	193
AM	90	511	94	208	188	474	372	1 193	1 565
RR	—	10	—	01	—	14	—	25	25
PA	43	328	54	180	54	257	151	765	916
AP	03	39	23	26	03	24	29	89	118
MA	25	313	29	191	29	228	83	732	815
NORTHEAST	42	631	60	339	97	615	199	1 592	1 798
PI	08	92	03	72	08	68	19	232	251
CE	13	182	09	84	04	146	26	412	438
RN	—	10	—	05	—	08	—	23	23
PB	—	29	03	26	07	13	10	68	78
PE	12	121	24	73	55	201	91	395	486
AL	02	11	06	03	—	09	08	23	31
SE	02	22	03	14	01	43	06	79	85
BA *	05	164	12	62	22	127	39	360	406
SOUTHEAST	70	3 124	164	1 798	94	1 760	328	6 682	7 023
MG **	21	927	67	498	18	447	106	1 872	1 991
ES	06	234	05	213	02	100	13	547	560
RJ	25	641	32	316	52	511	109	1 468	1 577
SP	18	1 322	60	771	22	702	100	2 795	2 895
SOUTH	25	1 112	41	481	11	383	77	1 976	2 053
PR	22	868	40	425	09	299	71	1 592	1 663
SC	01	94	01	30	01	25	03	149	152
RS	02	150	—	26	01	59	03	235	238
CENTRAL-WEST	54	1 125	55	631	50	573	159	2 329	2 488
RO	13	41	02	30	07	39	22	110	132
MT	10	268	16	179	12	150	38	597	635
MS	16	212	04	39	06	63	26	314	340
GO	14	506	25	259	18	271	57	1 036	1 093
DF	01	98	08	124	07	50	16	272	288

TABLE XII — *Distribution of New Cases of Hanseniasis According to Age-Groups, Region and Federal Unit* – Brazil 1982.

REGIONS AND F. U.	AGE-GROUPS				TOTAL
	0 to 14 years		15 years and more		
	TOTAL	%	TOTAL	%	
BRAZIL	1 407	8.28	15 567	91.60	16 994
AMAZÔNIA	644	17.73	2 988	82.27	3 632
AC	09	4.66	184	95.34	193
AM	372	23.76	1 193	76.24	1 565
RR	.....	.....	25	100.00	25
PA	151	16.48	765	83.52	916
AP	29	24.58	89	75.42	118
MA	83	10.18	732	89.82	815
NORTHEAST	199	11.07	1 592	88.54	1 798
PI	19	7.56	232	92.44	251
CE	26	5.93	412	94.07	438
RN	.....	.....	23	100.00	23
PB	10	12.82	68	87.18	78
PE	91	18.72	395	81.28	486
AL	08	25.80	23	74.20	31
SE	06	7.05	79	92.95	85
BA	39	9.61	360	88.67	406 *
SOUTHEAST	328	4.67	6 682	95.14	7 023
MG	106	5.32	1 872	94.02	1 991 **
ES	13	2.32	547	97.68	560
RJ	109	6.91	1 468	93.09	1 577
SP	100	3.45	2 795	96.54	2 895
SOUTH	77	3.75	1 976	96.25	2 053
PR	71	4.26	1 592	95.74	1 663
SC	03	1.97	149	98.03	152
RS	03	1.26	235	98.74	238
CENTRAL-WEST	159	6.39	2 329	93.61	2 488
RO	22	16.66	110	83.34	132
MT	38	5.98	597	94.02	635
MS	26	7.64	314	92.36	340
GO	57	5.21	1 036	94.79	1 093
DF	16	5.55	272	94.45	288

Source: SES/DNDS/SNPES.

* Unknown age for 07 cases included.
** Unknown age for 13 cases included.

TABLE XIII — *Hanseniasis Absolute Numbers and Proportion of New Cases in Patients Under 15 Years of Age According to Clinical Form and to Region and Federal Unit* – Brazil 1982.

Region and F. U.	V + D		I		T		Total
	Number of Cases	%	Number of Cases	%	Number of Cases	%	
BRAZIL	354	25.16	523	37.17	530	37.67	1 407
Amazônia	163	25.31	203	31.52	278	43.17	644
AC	02	22.22	03	33.33	04	44.45	09
AM	90	24.19	94	25.27	188	50.54	372
RR	...	...	...	...	...	...	...
PA	43	28.48	54	35.76	54	35.76	151
AP	03	10.34	23	79.32	03	10.34	29
MA	25	30.12	29	34.94	29	34.94	83
Northeast	42	21.11	60	30.15	97	48.74	199
PI	08	42.11	03	15.78	08	42.11	19
CE	13	50.00	09	34.62	04	15.38	26
RN	...	...	...	...	...	...	...
PB	...	...	03	30.00	07	70.00	10
PE	12	13.19	24	26.37	55	60.44	91
AL	02	25.00	06	75.00	—	...	08
SE	02	33.33	03	50.00	01	16.67	06
BA	05	12.82	12	30.77	22	56.41	39
Southeast	70	21.34	164	50.00	94	28.66	328
MG	21	19.81	67	63.21	18	16.98	106
ES	06	46.15	05	38.46	02	15.39	13
RJ	25	22.93	32	29.36	52	47.71	109
SP	18	18.00	60	60.00	22	22.00	100
South	25	32.47	41	53.25	11	14.28	77
PR	22	30.98	40	56.34	09	12.68	71
SC	01	33.33	01	33.33	01	33.33	03
RS	02	66.67	...	...	01	33.33	03
Central-West	54	33.96	55	34.59	50	31.45	159
RO	13	59.09	02	9.09	07	31.82	22
MT	10	26.31	16	42.11	12	31.58	38
MS	16	61.54	04	15.38	06	23.08	26
GO	14	24.56	25	43.86	18	31.58	57
DF	01	6.25	08	50.00	07	43.75	16

Source: *Health Services of the Federal Unit.*
MS/SNPES/DNDS-SE.

The following facts stand out:

1º — In the Amazon region (17.73% of all cases), the very low coefficient 4.66% in the state of Acre and no new cases detected in this age-group in Roraima; (few patients);

2º — The extreme variation among the age-group coefficients of detected cases within the states of the Northeastern region (11.07%), where they varied from 25.80% in Alagoas to 5.93% in Ceará and no new cases recorded in Rio Grande do Norte;

3º — The position of Rondônia, with 16.66% of the state's detected cases for this age-group, and the other four units of the Central-Western region (6.39%) with coefficients only varying between 7.64% and 5.21%.

Referring to the clinical forms in this age-group (Table XIII) and considering the whole country, we will see that the T form (37.67%) prevailed over the V + D (25.16%) and almost equalled the I form (37.17%).

Very high coefficients of T forms are found in the Northeastern (48.74%) and Amazonia regions (43.17%).

In the other three regions the Indeterminate form prevailed, with outstanding coefficients such as 53.25% and 50% in the Southern and Southeastern regions, respectively. The Central-Western region showed only 34.59% of I forms, a coefficient still slightly higher than those of the other two clinical forms.

The data concerning the federal units show that:

a — in five of them the V + D form prevailed over the two others, and with very high coefficients in some units such as 66.67% in Rio Grande do Sul;

b — in nine the Indeterminate form prevailed, with very high coefficients in several of them, like Amapá – 79.32%, Alagoas – 75%, Minas Gerais – 63.21%, São Paulo – 60%, Paraná – 56.43% and Brasília, the federal capital, with 50% of I forms;

c — the T form prevailed only in six states, two in the Amazon region, three in the Northeast, and one in the Southeastern region;

d — the T equalled the I form in Pará and Maranhão states;

e — the T form equalled the V + D in Piauí state;

f — in Santa Catarina the three forms were in equilibrium;

g — no new cases in this age-group were recorded in Roraima;

h — no information about this item was reported by Rio Grande do Norte.

Examining the 15 years and over age-group, we verify that in Brazil, as expected, the V + D form predominates with 46.66% of the detected new cases, and the same occurs in 21 of the federal units. In four of them located in the Northeastern and Amazonia region, the I form prevails, as occurs also in the Federal District, with 45.59% of I cases (table XIV).

Comparing both age-groups in the general and sick population, we verify that in the 0-14 and 15 and over age-groups, coefficients of participation in the general population are 37% to 63% (1:1.70) and in the sick population 8.28 to 91.72% (1:11.08), respectively.

The corresponding incidence rates are: 2.99 and 19.5 per thousand inhabitants, a low rate in the first group.

Referring to the general population, the indexes are: 1.11 per thousand in the first age-group and 12.29 in the 15 and over age-group. Here we must bear in mind three factors: exposition (time and index case), incubation period and lack of early diagnosis.

The attack rate in household contacts of V or D patients under surveillance that contracted Hanseniasis is shown in table XV.

In general this rate is low: 2.09% for the country.

For the regions the rates are: Amazonia: 1.39% – Northeast: 2.11%; Southeast: 2.92%; South: 1.40% and Central-West: 5.39%.

Considering the federal units, higher attack rates are found in: Minas Gerais (8.57%), Pernambuco (6.49%), Maranhão (6.46%) and Goiás (5.26%).

The lowest rates are found in Amazonas (0.88%), Rio Grande do Norte (0.68%), Paraíba (0.56%), Acre (0.44%) and Bahia (0.24%).

In Sergipe no household contacts of V or D patients contracting Hanseniasis are shown. Rondônia and Mato Grosso present no information about this subject and no contact surveillance is carried out in Piauí.

Outstanding is the very singular position of Mato Grosso do Sul, which figures with the amazing attack rate among household contacts of 74.41%.

In table XVI the absolute numbers are shown of: registered household contacts of V or D patients, those under surveillance and those who contracted the disease, according to clinical form and to region and federal unit.

TABLE XIV — *Hanseniasis Absolute Numbers and Proportion of New Cases in Patients Aged 15 Years or More According to Clinical Form and to Region and Federal Unit* – Brazil 1982.

Region and F. U.	V + D		I		T		Total
	Number of Cases	%	Number of Cases	%	Number of Cases	%	
BRAZIL	7 264	46.66	3 892	25.00	4 404	28.29	15 567
Amazônia	1 272	42.57	643	21.52	1 073	35.91	2 988
AC	71	38.59	37	20.11	76	41.30	184
AM	511	42.83	208	17.44	474	39.73	1 193
RR	10	40.00	01	4.00	14	56.00	25
PA	328	42.88	180	23.53	257	33.59	765
AP	39	43.82	26	29.21	24	26.97	89
MA	313	42.76	191	26.09	228	31.15	732
Northeast	631	39.64	339	21.29	615	38.63	1 592
PI	92	39.65	72	31.03	68	29.32	232
CE	182	44.17	84	20.39	146	35.44	412
RN	10	43.48	05	21.74	08	34.78	23
PB	29	42.65	26	38.23	13	19.12	68
PE	121	30.63	73	18.48	201	50.89	395
AL	11	47.83	03	13.04	09	39.13	23
SE	22	27.85	14	17.72	43	54.43	79
BA	164	45.56	62	17.22	127	35.28	360 *
Southeast	3 124	46.75	1 798	26.91	1 760	26.34	6 682
MG	927	49.52	498	26.60	447	23.88	1 872
ES	234	42.78	213	38.94	100	18.28	547
RJ	641	43.66	316	21.53	511	34.81	1 468
SP	1 322	47.30	771	27.58	702	25.12	2 795
South	1 112	56.28	481	24.34	383	19.38	1 976
PR	868	54.52	425	26.70	299	18.78	1 592
SC	94	63.09	30	20.13	25	16.78	149
RS	150	63.83	26	11.06	59	25.11	235
Central-West	1 125	48.31	631	27.09	573	24,60	2 329
RO	41	37.27	30	27.27	39	35.46	110
MT	268	44.89	179	29.98	150	25.13	597
MS	212	67.52	39	12.42	63	20.06	314
GO	506	48.84	259	25.00	271	26.16	1 036
DF	98	36.03	124	45.59	50	18.38	272

Source: *Health Services of the Federal Unit.*

* Unknown age for 07 cases included.

MS/SNPES/DNDS-SE.

TABLE XV — *Hanseniasis - Distribution, According to Region and Federal Unit, Ho*
Contacts of V + D *Patients that Became Sick During the Period* – Brazil 1982.

REGIONS AND F. U.	REGISTERED CONTACTS OF V + D PATIENTS	V + D PATIENTS CONTACTS UNDER CONTROL	V + D PATIENTS CONTACTS THAT BECAME SICK	% OF CONTACTS THAT BECAME SICK	INCIDENCE 100 000 C UNDER C
BRAZIL	310 198	118 329	2 403	2.09	2 09
AMAZÔNIA	91 734	45 784	638	1.39	1 39
AC	6 641	1 338	06	0.44	44
AM	50 000	27 332	243	0.88	88
RR	278	126	03	2.38	2 38
PA	18 168	13 807	203	1.47	1 47
AP	1 589	906	36	3.97	3 37
MA	15 058	2 275	147	6.46	6 46
NORTHEAST	11 187	7 468	158	2.11	2 11
PI	.....	.....	.....	.....	
CE	3 451	3 279	76	2.31	2 31
RN	749	440	03	0.68	68
PB	1 409	710	04	0.56	56
PE	2 793	1 063	69	6.49	6 49
AL	435	54	02	3.70	3 70
SE	300	270	.....	.....	
BA	2 050	1 652	04	0.24	24
SOUTHEAST	101 911	39 405	1 152	2.92	2 92
MG	46 363	5 433	466	8.57	8 57
ES	8 385	4 935	77	1.56	1 56
RS	11 850	6 256	109	1.74	1 74
SP	35 313	22 781	500	2.19	2 19
SOUTH	94 687	18 704	262	1.40	1 40
PR	84 718	15 129	197	1.30	1 30
SC	4 482	2 234	26	1.16	1 16
RS	5 487	1 341	39	2.90	2 90
CENTRAL-WEST	10 679	6 968	193	5.39	5 38
RO	...	...	...	...	..
MT	4 361	3 386	...	...	..
MS	294	86	64	74.41	74 41
GO	3 121	2 052	108	5.26	5 26
DF	2 903	1 444	21	1.45	1 45

Source: SES — SE-DNDS/MS

TABLE XVI — *Distribution of Virchowians and Dimorphous Patients Household Contacts That Contracted Hanseniasis in the Period, According to Clinical Form and to Region and Federal Unit* – Brazil 1982.

Region and F. U.	Registered Contacts	Under Surveill.	Contracted Hanseniasis			
			Total	V + D	I	T
BRAZIL	310 198	118 329	2 403	912	937	548
Amazônia	91 734	45 784	638	247	198	187
AC	6 641	1 338	06	...	...	...
AM	50 000	27 332	243	119	49	75
RR	278	126	03	01	----	02
PA	18 168	13 807	203	72	67	64
AP	1 589	906	36	06	22	08
MA	15 058	2 275	147	49	60	38
Northeast	11 187	7 468	158	51	58	49
PI	----	----	----	----	----	----
CE	3 451	3 279	76	31	24	21
RN	749	440	03	03	----	----
PB	1 409	710	04	01	02	01
PE	2 793	1 063	69	11	32	26
AL	435	54	02	02	----	----
SE	300	270	----	----	----	----
BA	2 050	1 652	04	03	----	01
Southeast	101 911	39 405	1 152	413	514	225
MG	46 363	5 433	466	197	183	86
ES	8 385	4 935	77	29	33	15
RJ	11 850	6 256	109	27	47	35
SP	35 313	22 781	500	160	251	89
South	94 687	18 704	262	119	100	43
PR	84 718	15 129	197	83	80	34
SC	4 482	2 234	26	13	10	03
RS	5 487	1 341	39	23	10	06
Central-West	10 679	6 968	193	82	67	44
RO	...	...	...	...	...	...
MT	4 361	3 386	...	...	...	...
MS	294	86	64	28	17	19
GO	3 121	2 052	108	42	45	21
DF	2 903	1 444	21	12	05	04

Source: SES
SE-DNDS/MS

In general more contacts contracted I forms than other forms (I = 38.99%, L = 37.95% and T = 22.80%).

Considering the regions, in Amazonia (39%), Southern (45%) and Central-Western regions (42%) V + D forms have predominated in the detected new cases in contacts.

A predominance of I forms is observed among new cases detected in contacts that occur in the Southeastern (45%) and Northeastern regions (37%).

Currently due to the new orientation adopted by the Public Health authorities, there are very few patients still kept in seclusion, practically all because of social reasons.

In table XVII the absolute numbers, proportion of in patients and ratio of in-patients to number of total registered cases are shown. As expected, the great majority of in-patients are V or D cases, as much in the country in general as in all regions, exception being made for the state of Rondônia, where 51.85% of the in-patients are tuberculoid cases.

Table XX shows the historical series of new cases detected in Brazil in the period comprising the years 1946 to 1982. In this series we can observe that the incidence rate increased steadily from 1946 to 1959, then it decreased, attaining the lowest incidence rate recorded in the nation: 5.76/100,000 inhabitants, in 1966.

From this point onwards it increased again, reaching the highest coefficients in the last four years recorded in table XX.

The corresponding curves and linear regression calculated for the incidence rate, supplied by my colleague, Sergio Moreira Viana, are shown in figures 8, 9 and 10.

According to Gonçalves (5) the endemicity is spreading in Brazil with a relative incrementation of the T forms.

Many factors can be influencing those data, such as internal migrations, increasing rate of urbanization and above all the better or worse action of the Health Services.

According to these data also, it seems that almost 40 years of sulphone therapy have not had much effect on the disease control.

TABLE XVII — *Hanseniasis - Absolute Numbers and Proportion of Hospitalized Patients, According to Clinical Form and to Region and Federal Unit* – Brazil 1982.

Region and F. U.	V + D		I		T		Total	% Ratio to Nº of Reg. Pat.
	Nº	%	Nº	%	Nº	%		
BRAZIL	7 059	78.75	949	10.59	956	10.66	8 964	4.51
Amazônia	870	79.02	62	5.63	169	15.35	1 101	2.71
AC	131	95.62	—	—	06	4.38	137	3.85
AM	78	70.91	—	—	32	29.09	110	0.67
RR	02	100.00	—	—	—	—	02	1.51
PA	587	77.96	47	6.24	119	15.80	753	6.84
AP	—	—	—	—	—	—	—	—
MA	72	72.73	15	15.15	12	12.12	99	1.14
Northeast	577	78.40	76	10.32	83	11.28	736	4.81
PI	53	77.94	—	—	15	22.06	68	3.09
CE	256	88.58	11	3.81	22	7.61	289	7.18
RN	52	74.28	09	12.86	09	12.86	70	26.92
PB	26	63.41	05	12.20	10	24.39	41	5.99
PE	86	60.99	41	29.08	14	9.93	141	3.77
AL	—	—	—	—	—	—	—	—
SE	21	87.50	—	—	03	12.50	24	2.89
BA	83	80.58	10	9.71	10	9.71	103	3.08
Southeast	4 506	77.93	708	12.25	568	9.82	5 782	5.98
MG	1 388	69.47	336	16.82	274	13.71	1 998	5.79
ES	198	68.99	50	17.42	39	13.59	287	4.06
RJ	1 161	81.02	143	9.98	129	9.00	1 433	8.62
SP	1 759	85.22	179	8.67	126	6.11	2 064	5.36
South	567	84.38	49	7.29	56	8.33	672	2.48
PR	306	85.00	26	7.22	28	7.78	360	1.68
SC	105	84.00	06	4.80	14	11.20	125	5.45
RS	156	83.42	17	9.09	14	7.49	187	5.40
Central-West	539	80.09	54	8.02	80	11.89	673	3.52
RO	27	33.33	12	14.82	42	51.85	81	5.04
MT	108	87.10	02	1.61	14	11.29	124	4.05
MS	59	89.39	02	3.03	05	7.58	66	2.62
GO	345	85.82	38	9.45	19	4.73	402	3.83
DF	—	—	—	—	—	—	—	—

Source: MS/SNABS/DNDS/SE

TABLE XVIII — *Hanseniasis - Prevalence* – Brazil 1982.

	AREA	% AREA	G. POP.*	% POP.	INHAB. km²	SICK POP.	% S. P.**	PATIENT km²
BRAZIL	8 511 965	100.00	126 806 000	100.00	14.90	198 700	100.0	14.90
AMAZÓNIA	3 666 799	43.07	10 264 000	8.1	2.80	40 553	20.4	0.01
NORTHEAST	1 219 983	14.34	32 566 000	25.7	26.69	15 315	7.7	0.01
SOUTHEAST	924 935	10.86	55 294 000	43.6	59.78	96 630	48.7	0.10
SOUTH	577 723	6.79	19 797 000	15.6	37.27	27 095	13.6	0.05
CENTRAL WEST	2 122 499	24.94	8 885 000	7.0	4.18	19 107	9.6	0.01

* General population.
** Sick population.

TABLE XIX — Brazil 1982.

REGION	BRAZIL	AMAZÓNIA	NORTHEAST	SOUTHEAST	SOUTH	C. WEST
Area Total	8 511 965	3 666 799	1 219 983	924 935	577 723	2 122 499
Area %	100.00	43.07	14.34	10.66	6.79	24.94
Pop. Total	126 806 000	10 264 000	32 566 000	55 294 000	17 797 000	8 885 000
Pop. %	100.00	8.10	25.70	43.60	15.60	7.00
Inhabit/Km²	14.90	2.80	26.69	59.78	37.27	4.18
* Migration		305 713	– 5 464 696	2 890 946	7 683	2 260 354

Source: IBGE

* Data referring to 1980.

TABLE XX — *Hanseniasis - Historical Series of New Cases Detected in Brazil 1946/1982.*

YEAR	CLINICAL FORMS						NUMBER OF DETECTED NEW CASES	RATE PER 100 000 INHABITANTS
	V + D		I		T			
	Nº	%	Nº	%	Nº	%		
1946	2 376	62.31	789	20.69	648	17.00	3 813	8.01
1947	2 553	62.33	813	19.85	730	17.82	4 096	8.42
1948	2 775	61.53	925	20.51	810	17.96	4 510	9.07
1949	3 111	63.55	1 041	21.27	743	15.18	4 895	9.63
1950	3 008	63.74	925	19.60	786	16.66	4 719	9.08
1951	3 116	61.72	997	19.75	936	18.53	5 049	9.40
1952	3 067	59.40	1 081	20.94	1 015	19.66	5 163	9.27
1953	3 176	58.88	1 130	20.95	1 088	20.17	5 394	9.37
1954	3 121	58.68	1 079	20.29	1 119	21.03	5 319	8.94
1955	3 269	56.75	1 164	20.21	1 327	23.04	5 760	9.39
1956	3 431	55.43	1 367	22.08	1 392	22.49	6 190	9.79
1957	3 640	51.43	1 810	25.58	1 627	22.99	7 077	10.87
1958	3 441	48.27	1 845	25.88	1 843	25.85	7 129	10.64
1959	3 720	49.81	2 005	26.85	1 743	23.34	7 468	10.90
1960	3 257	48.17	1 963	29.03	1 542	22.80	6 762	9.61
1961	2 868	46.54	1 833	29.74	1 462	23.72	6 163	8.51
1962	2 748	49.58	1 621	29.25	1 173	21.17	5 542	7.43
1963	2 721	47.37	1 684	29.32	1 339	23.31	5 744	7.49
1964	2 778	49.54	1 457	25.98	1 353	24.48	5 588	7.08
1965	3 034	51.61	1 453	24.72	1 392	23.67	5 879	7.25
1966	2 472	51.49	1 246	25.95	1 083	22.56	4 801	5.76
1967	2 788	51.26	1 479	27.19	1 172	21.55	5 439	6.35
1968	2 773	49.80	1 499	26.92	1 296	23.28	5 568	6.33
1969	2 771	49.32	1 489	26.50	1 358	24.18	5 618	6.22
1970	2 811	51.39	1 456	26.62	1 203	22.99	5 470	5.88
1971	3 037	51.04	1 406	23.63	1 507	25.33	5 950	6.22
1972	3 285	51.24	1 652	25.77	1 474	22.99	6 411	6.52
1973	3 374	49.39	1 776	26.00	1 681	24.61	6 831	6.75
1974	3 991	48.68	2 288	27.91	1 920	23.41	8 199	7.87
1975	4 532	48.73	2 419	26.01	2 349	25.26	9 300	8.68
1976	4 439	46.02	2 552	26.45	2 656	27.53	9 647	8.94
1977	4 448	46.62	2 362	24.77	2 729	28.61	9 539	8.62
1978	5 390	44.95	3 419	28.51	3 184	26.54	11 993	10.58
1979	6 798	47.29	3 553	24.72	4 024	27.99	14 375	12.37
1980	6 354	43.78	3 708	25.54	4 453	30.68	14 515	12.19
1981	7 597	44.79	4 321	25.48	5 040	29.72	16 959	13.67
1982	7 630	44.90	4 418	26.00	4 939	29.06	16 994	13.40
TOTAL	135.700	50,28	68.025	25,20	66.136	24,50	269.861	

HANSENIASIS

RATE OF NEW CASES DETECTED PER 100,000 INHABITANTS
BRAZIL 1946-1982

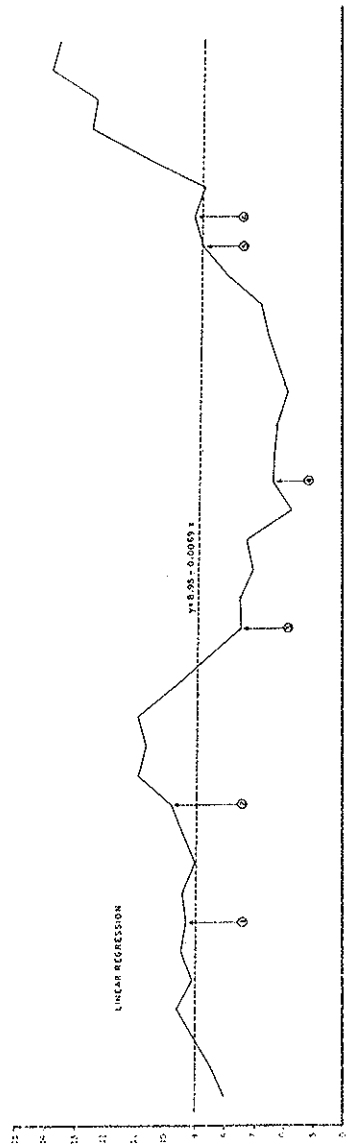


FIG. 8

HANSENIASIS

NEW CASES DETECTED: RATE PER 100,000 INHABITANTS
BRAZIL

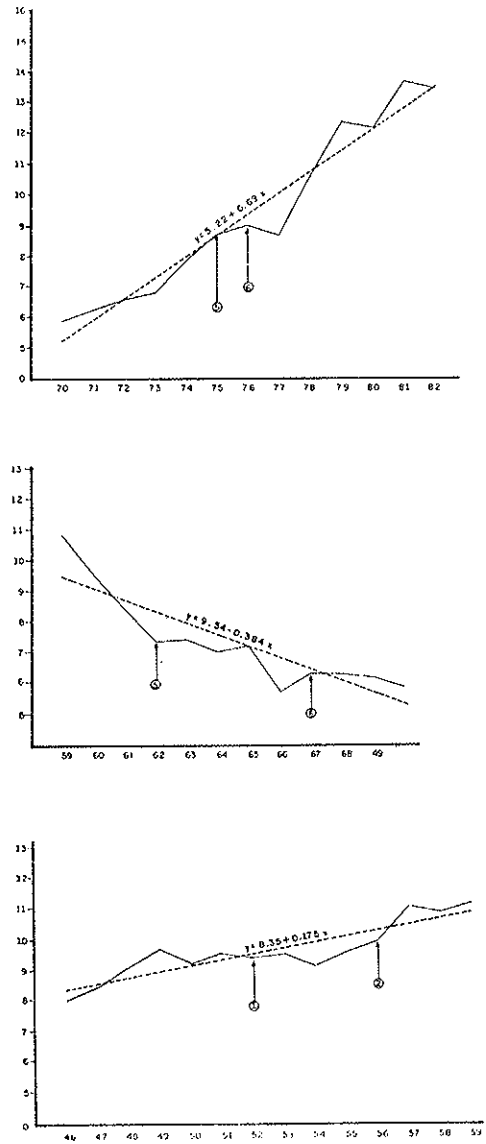


FIG. 9

HANSENIASIS

NEW CASES DETECTED: RATE PER 100,000 INHABITANTS
BRAZIL

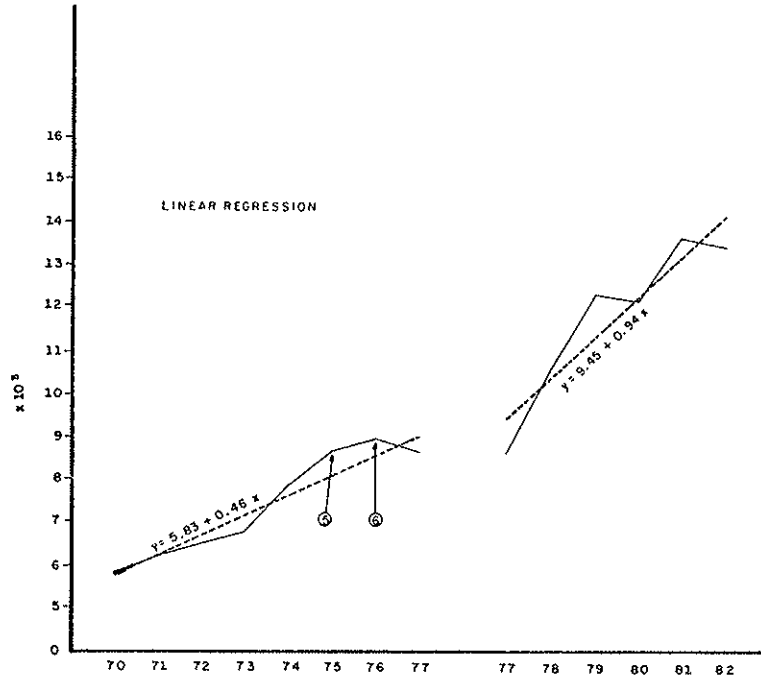


FIG. 10

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SOCIAL ASPECTS OF LEPROSY IN BRAZIL

LYGIA M. CEZAR DE ANDRADE
Oswaldo Cruz Foundation
Fiocruz - Rio de Janeiro - Brazil

Hanseniasis is a very serious social problem in Brazil because of its aspects of neurological disease with a great potential of deformation and physical incapacity. According to the most optimistic statistics, this physical incapacity reaches more than 40% of the patients.

Manaus, in the State of Amazonas, registers approximately 2,000 retirements per year due to the disease. This number includes the city and rural zone. This fact, of course, requires a lot of money from the Government, because of the high percentage of the patients' physical incapacity nowadays (Gonçalves, 1979).

Brazil has 80% of all leprosy cases registered in Latin America. According to the latest statistics, there were almost 200,000 cases registered in 1982 (Gonçalves, 1983), causing a very serious social problem to the country.

The physical incapacity of the leprosy patients brings psychic, professional, family and social consequences, as leprosy is one of most incapacitating diseases of medical pathology.

Almost half a century of sulphone therapy did not change the Brazilian social problem at all. Deformations continue to be the most important of the incapacities because of the psychological and social aspects involved.

People face the disease in just the same way they did in the past centuries before the clinical cure of the disease was achieved, causing the patient's segregation — segregation that is promoted by himself, his family and chiefly by the community in which he lives.

The reason for this segregation is connected as much with the word "leprosy" as with the leprosy patient, that is, as much with the cultural as with the social categories.

Categories are defined by cultural images, which are mental representations based on sensorial experiences. Leprosy as a cultural category is defined by cultural images which make that whole called leprosy. In general, this image presents similarities and discrepancies when cultural and scientific categories of the disease leprosy are compared.

In society, each person is socialized to adjust himself to the leprosy phenomenon, based on his cultural categories and not through scientific knowledge, which is restricted to a few specialists.

So, cultural images of leprosy that define it as a category represent the answer of culture to society's necessity to face this reality.

Domingos S. Gandra Jr. in his thesis: "Leprosy — An Introduction to the Study of the Social Phenomenon of Stigmatization", presents a number of interviews with 43 patients, 16 doctors and 640 common people held in 43 cities of Minas Gerais State. The interviews were carried on by the author and collaborating people trained for this purpose.

The group interviewed was composed of 351 women (57.6%) and 258 men (25%), a total of 609 persons.

Considering age, the majority of persons (35.8%) belonged to the 21-30 years age-group, and referring to school grade the complete secondary course prevailed (25.3%).

Using this thesis, we will try to focalize two main social aspects: the way healthy people act and think under their taboos; and how the leprosy community thinks about their cure, and also how they live with their taboos.

By analysing these interviews, we could see that there are many points of contact between both communities: healthy and patients, such as the idea of supernatural causes (resulting from the action of supernatural beings, through their own will or through human motivations like sorcery) and natural causes (or the various agents of Nature directly or indirectly appointed as causers of the disease). Heredity is one of the natural causes mentioned as provoking the disease.

Very important is the idea of *transmission* because it is related to *contamination*. Among the interviewed persons 24.8% think that leprosy is easily contagious.

Contamination is a belief based on an emotional inclination to think that the contact of the patients with their belongings or someone else's belongings can transmit the disease. This fact causes an automatic and unthoughtful reaction.

Leprologists are an example of this fact. Society and even other doctors look at them as if they were leprosy patients. All the difficulties these doctors must face are well known.

Pressed by other doctors and by the community, they cannot keep a private clinic. This prejudice is a hindrance to the new Brazilian sanitary policy of Hanseniasis integration into the general Health Services.

The interviews show that objects and even places utilized by the patients can contaminate healthy people (13.3%); it is a general belief that even the place where a patient has sat is capable of transmitting the disease.

The idea that the disease is incurable is very common (36.8%), but little by little things are changing, for 19.8% of the people interviewed think that leprosy has a cure and 12.3% answered that they didn't know if it is curable or not.

Concerning treatment the more persistent image is that of isolation. The images collected in the interviews about leprosy treatment are scarce. There are patients who believe that if they could transmit the disease to somebody else they would be cured.

As the social category of "lepers" is formed by individuals that present certain characteristics that lead society to identify them as having the disease classified in the cultural category of "leprosy", and as the images of the patients are fundamental to acknowledge the references society adopts for this classification, we have to know which are these images and how they are produced.

The production of these images happens independently of the contact with a leprosy patient. They are transmitted by a socializing process, formal or not formal, that influences society's behaviour and attitudes in the presence of the patient.

The informal socializing process has a great influence on the production of these images and on the way people will act. Literature, newspapers, cinema, radio, television and folk-tales condition not only the social category of "lepers" but also other images connected with other categories.

These associations of thought are very important for understanding the community behaviour toward leprosy patients. Patients' moral and physical characteristics are linked with psychological association. The same happens to emotional association.

By analysing global physical images of the patient, we can notice that the majority talks about some aspects in words such as: disgusting (11.8%), horrible (7.4%), with a bad smell (5.1%).

Even if the reality about the patient has been modified by the introduction of sulphone-therapy, cultural images remain almost the same.

There is still a big difference between leprosy patients' reality and cultural images about it, because these cultural images are based on old stories told in books, films, folk tales and other socializing processes, and have not yet been adjusted according to the present day scientific reality.

People generally keep in mind only certain aspects of these stories and myths. Time and place are forgotten but not the physical, psychological and even moral descriptions of the patients. They act as base and reinforcement of the conditioned "leper" images.

The most important aspects about cultural images of lepers are the deformities. Some parts of the human body when they are deformed are regarded as a characteristic of the social category called "leper" and have a greater meaning when we analyse the social process of someone's identification in the social category of leper.

According to the interviews, more deformities are memorized regarding some parts of the body: ear (6.2%), nose (13.5%), eyebrows (7.7%) and fingers (22.3%). We can observe that the descriptions of the patients found in books, magazines and personal talks are very similar to these here presented.

This shows that there are similarities between the update images and the reality of old descriptions.

The images of organic and functional alterations that call communities' attention are ulcers or "wounded body" (55.3%), *macules* or "spotted body", independent of their color (3.7%), insensibility (18.1%) and edemas or swelling in any part of the body (12.3%).

These data show that there is a stigma connected with the cultural category "leprosy" and the social category "leper". But in this social category will be included only patients that present characteristics agreeing with the images society has produced for this category, whether or not they are leprosy patients.

An interesting experiment was made with 100 people in Bambuí, in Minas Gerais State. Three photographs were shown: one of a tuberculoid leprosy patient, another of a lepromatous patient and the third of someone with American cutaneous leishmaniasis. When asked, most of the people pointed to the leishmaniasis patient as a leper.

Scientific and non-scientific literature is full of stories and facts that prove that leprosy produces similar emotional reactions in the majority of the cultures, whether occidental or oriental.

During the interviews many types of reactions were seen: from crying paroxysms to the violent dismissal of the interviewer, when the word "leprosy" or "leper" was mentioned.

The interviewers even reported that many nights during more than one month they dreamed about the disease, and in their dreams they saw themselves involved with leprosy patients in the different situations. This shows the strong connection of the stimulus with cultural images of the disease and its patients.

Even a better knowledge of the subject does not exclude emotional reactions against the disease or the patient. The best proof of this statement is the emotional reactions of doctors, even leprologists, against the disease. "Leprophobia" is still very common among them, notwithstanding the great progress achieved in the knowledge of Hanseniasis.

It is proved that even having rational information one can have emotional answers. We also know that the emotion produced by leprosy and leper categories generally does not depend upon people's will. Thus, even being rationally convinced, people can be led, by circumstances that cause psychological emotion, to act against their thoughts and desires. That is why some families hesitate to accept the return of a leprosy patient, even when paroled by the hospital and his doctor. Perhaps some sanitary campaigns are not successful because of these psychological emotions.

In general, the members of society cannot accept the fact of this disease occurring in their lives, because society considers leprosy an emotionally undesirable disease. So the diagnosis of the disease is received as an unexpected occurrence. They face the diagnosis as a confirmation of a disease the probability of which they have never thought about during their lives.

When asked: "Which disease are you most afraid of contracting?" 42.2% of the persons interviewed answered "Cancer", 24.8% answered "Leprosy", and 11.8% "Tuberculosis". But when questioned: "Between this disease (the one they mentioned) and leprosy, which one would you rather contract?", they generally changed their opinion and chose the one first rejected (75.3%). Only 20.3% preferred to have leprosy.

This fact shows the great fear the majority of people have of contracting the disease. They do not mention it from the beginning because they consider such eventuality a non-existent probability for them. When they hear the diagnosis, the trauma engendered is so great that it leads the patient to the desire to commit suicide as a first

behavior alternative. This happened in 18.7% of the interviews. But the number of suicides among leprosy patients is very small.

Emotional reactions can be an immediate search for isolation. Leprosy and leper categories produce an emotion that makes people change their contact situation by diminishing their proximity to other people, and even provoking their rejection. The intensity of the isolation can differ from person to person, but it always ends with solidarity patterns whether voluntary or institutional.

Seclusion attitudes vary according to the degree of certainty about the identification in the categories of "leprosy" or "leper".

Discrimination is an attitude through which society draws away from the patient or from any person it includes in the leper category. Unfortunately, discrimination processes, even with time variation, do not follow the scientific progress in the control of the disease. Society has always treated people included in the leper category differently, due to great fear, that is very far from the real dangers created by the disease. So, these discriminatory processes are something more than protection measures, they are part of what we call *segregation.* This segregation creates certain physical limits, that cause a spatial isolation for the group or person included in this category.

Even when society does not impose a formal isolation, as is now happening in Brazil, in view of the transformation of the Leprosaria, the majority of communities continue to impose space limits not only on the Hanseniasis patient, but on their contacts as well, particularly the most intimate ones.

In spite of scientific evolution and the legal measures taken, social behavior was not enough modified, notwithstanding the tendency against segregation on the part of doctors and the associations involved with patients.

While non-stigmatizing diseases promote or strengthen solidarity patterns, stigmatizing diseases like leprosy reinforce the rupture of such patterns.

For a social group to develop an emotional process as an adjustment mechanism to a certain category, it is necessary for the category to have a very special significance for this group: it must represent some *danger* or a deep *depreciation.*

To explain the emotional process related to leprosy and leper categories, the meaning of "danger" would not suffice, because there are other diseases involving much more danger that do not provoke such an emotional reaction.

Leprosy is a phenomenon common to the majority of human societies for many years, and it has awakened similar emotional reactions in all societies, regardless of their cultural differences.

If leprosy and leper categories are just the contrary of a basic or preponderant cultural factor, we must conclude that this factor must appear in all cultures. It must be a universal concept to human societies and also be fundamental to all of them.

The interviews have shown that physical deformation is very much feared. Society is afraid of contamination because of its results. So the basis of people's reaction is the effect and not the act of contamination.

Many diseases are more infectious than leprosy but they do not provoke the same reaction patterns as leprosy. So, infectiousness by itself does not explain these reactions, but the effects — the deformities — can be explained, because they are the fundamental content.

We must then observe how far cultural considerations regarding the human body can establish the basis of a valorization common to several cultures, to the point of establishing prevailing and basic values. The body is the concrete part of the human being and therefore all cultures have patterns of physical beauty that can differ from one culture to another, but are present in all of them. This demonstrates that the body is an object of aesthetic appreciation in all cultures, presupposing physical integrity at any time and in any human society.

The absence of this integrity makes the individual unadapted to the cultural models and forces him to look for a particular way of adapting himself to them.

In all cultures, we have beauty concepts and ways to make the body more beautiful. This proves that in all human societies, we have an appreciation of human appearance represented by the body. Leprosy deformities, as well as functional alterations, mainly the lack of sensibility, are deeply related to fundamental factors of the human being.

Based on these facts, it is understandable how leprosy and leper categories deny the human body integrity. If one's corporal image interacts with other people's images, we can conclude that such images, when representing a denial of the human formal or valorized appearance, produce reactions of unpleasantness, as even against one's will they are deeply connected to one's image.

Therefore we believe that the stigma which is connected with the leper and leprosy categories of all the cultures we know, could only be explained by the negation of physical integrity not only functional but

mainly in what concerns human aspects, that are fundamental factors in any cultural system.

It is based on these factors that people identify the members of a certain society. That is why leprosy is stigmatizing until we are able to develop a treatment capable of avoiding deformities and mutilations.

Before becoming sick the leprosy patient was a healthy person with the same points of view and taboos of the healthy community. So he is overcome by a very deep emotion when he hears the diagnosis of leprosy. This emotion is much more intense and permanent because the patient is at the same time the receiver and the promoter of the stimulus.

As a member of society, and participating in its culture, he has learned how to react and face the disease and the carrier of the disease. When he contracts leprosy, he knows beforehand how other people will react against him. So he begins to develop a psychological mechanism of negation in order to be protected from others.

In a Workshop on Control of Hanseniasis, Francisco A. Vieira Nunes, an ex-leprosy patient who is active in a movement for the reintegration of Hansenians, called MOHAN (Movimento de Reintegração do Hanseniano), reported on the Hansenian point of view regarding difficulties and ways of his reintegration.

The first difficulty concerned limitations, physical discomforts and deformities, which, besides turning daily routine into difficult tasks to be achieved, are the reason for the patient's isolation from society, that causes psychological traumas arising from the patient's defense mechanisms. This led the patient to change his name in order to protect himself and his family.

Next, referring to deformities, Francisco quotes *esthetics*. The loss of esthetics in the hands, feet, and especially in the face, besides causing psychological traumas in the patient, is always a reason for indiscreet questions frequently asked by the healthy community, and throughout the patient's life. After a certain time this situation becomes completely intolerable for the majority of the patients.

The financial question is also a very important problem. Lepers are generally poor and have great difficulties in providing money for their families. These problems become even worse because of their physical discomforts and limitations. Pensions and retirement pay given by the Social Welfare Ministry are not sufficient. Since poverty is very common among leprosy patients, they generally feel like marginals.

People's fear and prejudice against leprosy patients have a strong influence on the patients' isolation from society and on their fear to

have any kind of relationship with other people. They feel ashamed of going to a party or to a social meeting; especially they feel ashamed in their place of work because they feel insecure and afraid of the community's reaction. This fact causes a psychological trauma almost without solution.

The fear demonstrated by doctors and other health professionals makes patients much more insecure. They feel ashamed as if they have a *terrible* disease. If these professionals have this kind of reaction, what about ordinary people? When the health professional accepts the patient, his example makes things easier for the patient's acceptance by his family and community.

The hasty closing or transformation of the leprosaria to other purposes, without previous programming, causes a serious social problem, mainly for those patients that had lived there for a long time, many of them for almost all their lives, having completely lost all links with the outside world and having even been rejected by their families. Without a place to go to or means to survive, they hide in the so-called "vilas" that are an extension of the leprosaria but without any substructure, organization or governament support.

However, good results could be obtained with good planning and some financial resources, as happened in an experiment conducted in the city of St. Louis, Maranhão State, after the closing of its leprosarium, and related by Jorge de Oliveira Macedo in his lecture on "Concrete cases of Colonies Closing" dealing with the recuperation of "Vila Nova" that was transformed into a suburb of St. Louis City. This splendid experiment, carried out with CERPHA's (Comissão Evangélica de Reabilitação de Pacientes de Hanseniasis) precious moral, social and financial support, shows that a well planned and a well conducted work can produce excellent results such as the fair interplay between the healthy and the sick community, there achieved without commotion.

Through well conducted Health Education, the patients became so conscious of the indispensable necessity of taking the prescribed medicine with permanent continuity that no new leprosy case was detected in a population of 2,500 persons.

Such experiments should be repeated in others of the many proliferating "Vilas" in Brazil if we could also count on the help of other philanthropic entities like CERPHA.

This would be a great step towards the solution of the social question created by leprosy prejudice and towards the control of the disease in our country.

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IMMUNOLOGICAL AND EPIDEMIOLOGICAL SPECULATIONS ON LEPROSY

O. G. BIER
São Paulo, Brazil

The infection of man by *Mycobacterium leprae* (ML) leads to a chronic granulomatous infection with a wide spectrum of clinical manifestations, from lepromatous to tuberculoid leprosy.

Refined histopathologic studies combined with bacterioscopy and with the lepromin test led to the amplification of Rabello's classical polar concept of leprosy (LL and TT), by recognizing three intermediates in the borderline group (BL, BB, and BT), thus providing objective criteria for comparing the evolution of the disease in patients subject to different treatments [1].

As an obligate intracellular parasite, *M. leprae* cannot be cultivated *in vitro*, but this was somewhat circumvented by Storrs and Kirchheimer's discovery of the high susceptibility of the nine-band armadillo of the South of the United States (*Dasypus novemcinctus*), a "quantum jump" in the study of leprosy, because it provided a means for obtaining large amounts of bacilli for the preparation of antigens [2]. Up to 10^{10} ML/g of infected tissue can be obtained from infected armadillos and as much as 12.5 kg of infected tissues were held by the IMMLEP tissue bank in May 1981 [3].

As in other diseases caused by intracellular parasites, immunity in leprosy is mainly, if not exclusively, cell mediated (CMI) and involves two kinds of effector cells: macrophages and T lymphocytes. Humoral antibodies may be important in pathogenesis (as in *erythema nodosum leprosum*, ENL), but do not seem to play any direct role in the mechanism of immunity. As a matter of fact, there is a striking contrast between the deficiency of CMI and the high antibody response in the most susceptible multibacillary forms of leprosy (LL and BL). On the contrary, in the paucubacillary forms (TT and BT), antibody formation is poor and CMI is normal.

As a basic immunologist who is not working in the field, I am afraid I cannot contribute much to the critical evaluation of specific data, but I hope to bring some contribution in discussing mechanisms by which immunity in leprosy is established, by focusing especially on the key role of macrophages.

Macrophages act in two different ways: (a) by presenting the antigen at its surface in close proximity of, or complexed to, class II molecules (Ia in the mouse, HLA-D in man) as a modified-self; (b) by destroying intracellular bacteria which in the non-immune host are able not only to survive, but also to multiply inside the phagocyte.

As to T lymphocytes, at least three sets are presently identified: TH (Helper), TC (Cytotoxic), and TS (Suppressor). Monoclonal antibodies are available to distinguish TH (phenotype Lyl+2–) from sets TC and TS of antithetical phenotype (Lyl—2+).

The T-unresponsiveness to ML antigen(s) [4], early attributed to a blocking effect of antibodies or to a deletion of specific clones, is now better interpreted by the antagonistic action of TS, i.e., by a decreased TH/TS ratio, as found in lepromatous patients, except in cases of recent ENL [5].

Macrophage capacity to digest intracellular M. leprae. Some twenty years ago, Beiguelman and Barbieri [6] reported *in vitro* experiments showing that peripheral blood monocytes (PBM) from lepromatous subjects, in contrast with those of tuberculoid cases, were unable to lyse autoclaved ML. It was then hypothesized that the capacity to be "Lyser" was codified by gene(s) phenotypically expressed at the macrophage level by the presence of effective lysosomal enzymes, under the influence of environmental factors, particularly of antigenic stimuli from ML or from cross-reacting mycobacteria. Only a small percentage of the population lacked the gene(s) and remained "Non-Lyser" throughout their life.

Beiguelman's view was supported by Skinsnes [7], who showed that macrophages from lepromatous cases were deficient in β-glucuronidase, whereas those of tuberculoid subjects had a normal content of the enzyme. These findings were, however, contradicted by Avila & Convit [8]. Furthermore, the studies of Drutz *et al.* [9], among others, failed to show any difference in the ability of macrophages from tuberculoid and lepromatous patients to lyse heat-killed ML.

Undoubtedly, as shown by Convit *et al.* [10] in Mitsuda-positive subjects, macrophages accumulated at skin sites injected with concentrated lepromin behave like lysers and transform themselves into

epithelioid cells, but obviously in this case a local activation by lymphokines cannot be excluded. The same applies to the experimental conditions of Beiguelman *in vitro*.

It has been postulated that lepromatous macrophages would not be "activable" by lymphokines, but this possibility was ruled out by Convit *et al.* [11] by elimination of ML subsequent to local *in vivo* activation of lepromatous macrophages by BCG in BCG-sensitive patients.

The body of evidence suggests that the failure of lepromatous macrophages to digest intracellular ML lies in a defective T cell function, albeit an intrinsic defect of the macrophage is probably the primary cause for the incapacity of Mitsuda-negative subjects to mount an effective CMI. It may be postulated that a defect in the presentation and processing of the antigen accounts for a deficient proliferation of TH in favor of TS. In fact, the increased antibody responsiveness in LL patients could imply that the presentation and processing of the antigen must be different, as suggested in [12].

Leprosy and Biozzi mice. In the context of the primary role of the macrophage in the mechanism of immunity in leprosy, it is interesting to compare the immunological behavior of LL and TT patients with that of the two lines of mice obtained by Biozzi *et al.* [14, 15] by selective breeding for the amplitude of antibody response in an outbred population.

The investigation of the genes controlling the immune response has been approached from two different angles. McDevitt and Benacerraf [13] studied the antibody production in relation to specificity, by using inbred animals responders or non-responders to antigens of restricted specificity. This was found to be controlled by one single gene located in the I region of the major histocompatibility complex (MHC) – the Immune Response Gene, Ir.

Biozzi's approach was radically different and consisted in selective breeding for the amplitude of antibody response to polyepitopic antigens, such as sheep erythrocytes or salmonella antigens. The selective experiments led to the development of two lines of mice: High(H) and Low(L) Responders. Five selective breedings have been carried out so far in France and in Brazil. In the most studied Selection I, the selection limit was attained after 16 generations and the interline difference corresponded to 220-fold. Variance analysis of the distribution of responsiveness in interstrain F1 and F2 hybrids and their back-crosses (the homozygous parentals being represented by

animals after the 16th generation) indicated that the difference in antibody response was under the control of 8-10 genes (polygenic regulation).

The phenotypic expression of the genes controlling the amplitude of antibody responsiveness involves a difference in macrophage function, as well as in the differentiation and multiplication of B lymphocytes.

As shown by Weiner & Bandieri [16], splenic macrophages of L mice degrade the antigen more readily than H macrophages. The greater ability of L macrophages to reduce the immunogenicity of the antigen accounts for low antibody production, as well as for increased resistance to infection, and correlates with better capacity to be protected by vaccination (Tables I and II).

TABLE I — *Immunity functions in H and L mice.*

Line	Antibody response	Macrophage function			
		Antigen uptake	Lysosomal enzymes	Intracellular degradation	Surface presentation
H	+ + +	+	+	+	+ + +
L	+	+ + +	+ + +	+ + +	+

TABLE II — *Natural resistance and protective effect of vaccination against* S. typhimurium *in H and L mice.*

Treatment	H Line		L Line	
	Mortality %	MST	Mortality %	MST*
None	100	5.4	100	8.7
Vaccinated	100	8.6	10	

* Mean survival time, days.

As to B lymphocytes, their involvement in the interline difference is indicated by: (a) better antibody response in radiosuppressed recipients when restored with H line than with L line lymphocytes; (b) stronger antibody response in H than in L mice to T-independent antigens like pneumococcus polysaccharide SIII. The possible regulatory role of TH and TS in the two lines of mice is still open to investigation.

At first sight, H mice (high antibody response, hypoactive macrophages) are comparable to lepromatous patients and L mice (low antibody response, hyperactive macrophages) to tuberculoid subjects. However, this statement needs to be qualified: the comparison is only valid for the activated macrophages, after CMI has been established.

Experimental data show that the natural bactericidal activity of lepromatous macrophages is higher than that of tuberculoid cases.

1) By infecting mice with BSG, Lagrange *et al.* [17] found, by viable counting of the mycobacteria in spleen and liver, that there were more bacteria in H mice on days 2 and 21, but in later stages of the infectious process (on day 35) the situation was reversed and countings were higher in the L mice. Similar results were found in the experimental infection of mice with *M. lepraemurium*, in comparative studies with BCG-resistant and sensitive strains of mice (C^3H vs C57BL/6) [18].

It would appear that in the case of replicate antigens the presence of adequate amounts of viable organisms is a prerequisite for the elaboration of CMI. Initial inhibition of intramacrophagic multiplication would then result in a weak cell mediated response, so that in late stages of the infection the macrophage activity remains low, as compared to the case in which the initially lower bactericidal activity of the macrophage is highly intensified by appropriate lymphokine stimulation.

2) Another line of evidence is provided by recent studies [19, 20] on the interaction BCG-macrophage in congenic strains of mice, by using a radiometric test with ^3H-Uracil, an RNA precursor readily incorporated by multiplying mycobacteria but not by macrophages.

Non-stimulated resident peritoneal macrophages from BCG-resistant mice (DBA/2, A/J) are more able to inhibit the growth of BCG than those derived from sensitive mice strains (C57BL/6, BALB/c). On the other hand, PBM cultures, free of T lymphocytes, from lepromatous patients, exhibited a higher natural bactericidal activity as compared to those of tuberculoid patients. This finding

suggests that genes analogous to Bcg^r/Bcg^- control the evolution of leprosy in man towards the lepromatous and tuberculoid forms, respectively.

Mechanisms of T-unresponsiveness in lepromatous leprosy. The immunodeficiency of Mitsuda-negative LL and BL patients lies in a defect in antigen(s) recognition on the level of T lymphocytes.

Three main hypotheses are offered for discussion in relation to this defect:

1) Lepromatous macrophages produce a particular type of immunogen that is appropriate, by interacting with TH and B cells, to elicit antibody formation, but is inappropriate for mounting an effective cell mediated response.

2) T-unresponsiveness in LL and BL subjects is a consequence of the natural bactericidal activity of their macrophages, as explained in the preceding section. The reason why the intensity of CMI varies as a function of the bacterial load of the macrophage is unknown.

3) The lack of T response in lepromatous subjects is due to the antagonistic effect of TS. In this context it is pertinent to consider that the restoration of T-responsiveness by Transfer Factor (TF) may be ascribed to a shift in the balance of TS and TH in favor of the latter. The same may be said in relation to other lymphokines such as α--Interferon and Interleukin 2, whose effectiveness as immunotherapic agents in leprosy is presently under investigation.

An epidemiological speculation. If the degree of macrophage activity and its inversely related antibody responsiveness are polygenic regulated, the individual phenotypic variability in a genetically heterogeneous population may follow a normal distribution curve (Fig. 1)

The bulk of the population is distributed around the median and comprises the individuals that under mild endemic conditions are not subject to infection, whilst the tails of the curve correspond to extreme phenotypes subject to high risk, according to the nature of the infection (macrophage or antibody dependent).

A theory has been proposed by Biozzi *et al.* that postulates that under mild endemic conditions only the individuals situated in the sensitive tails are affected, determining by the continuous loss of one of the two extreme phenotypes the stabilization of the genetic

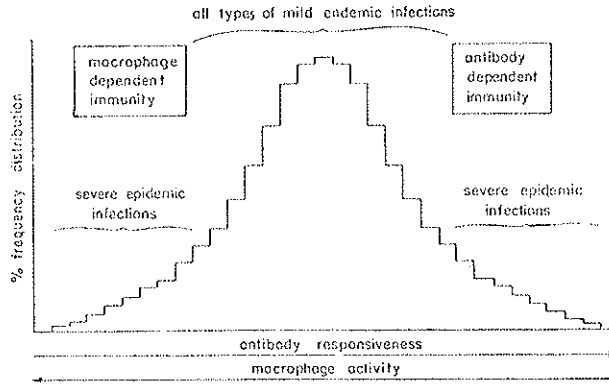

FIG. 1. Hypothetical regulation of genetic heterogeneity to infection according to Biozzi *et al.* (cf. ref. 15).

heterogeneity of the population. As a counterpart, during severe epidemics the individuals situated in one or the other distribution tails would be apt to resist and would ensure the survival of the population.

One might extend Biozzi's epidemiological hypothesis to leprosy, by substituting in Figure 1 the capacity of mounting CMI for macrophage activity, as indicated by the vector pointing to the left. A tail at the extreme right of the curve representing, say 10% of the population, would correspond to the individuals at risk of contracting lepromatous leprosy, whereas a contiguous area of another 10% would comprise those at risk of contracting the tuberculoid form of the disease. The remaining area under the curve would represent 80% of the population that ignores the infection. The percentages given may of course vary under the influence of genetical and environmental factors.

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QUANTITATION OF THE SOLUBLE RECEPTOR OF HUMAN T LYMPHOCYTES FOR SHEEP ERYTHROCYTES BY ELECTROIMMUNODIFFUSION IN THE SERUM OF PATIENTS WITH LEPROMATOUS AND TUBERCULOID LEPROSY

NELSON F. MENDES*, IEDA MARIA LONGO*, NAYLA C. MOURA*, WALTER BELDA**, DILTOR OPROMOLLA***

ABSTRACT

Human T lymphocytes carry a membrane receptor for sheep erythrocytes (E) which is present in a soluble form in normal serum and that may play an immunoregulatory role. We have quantitated the soluble E-receptor by *rocket electrophoresis* in serum semples obtained from 43 normal controls, 32 patients with tuberculoid leprosy and 53 patients with lepromatous leprosy. The means of the *rockets* obtained in these 3 groups were respectively 5.0 mm, 7.5 mm and 10.9 mm. These differences were statistically significant ($p < 0.001$, Kruskal-Wallis test). Increased serum levels of Rs (E-receptor in soluble form) may be one of the mechanisms responsible by depression of cell-mediated immunity in leprosy.

INTRODUCTION

Human T lymphocytes carry in their membrane the so-called E-receptor which is responsible for the well known phenomenon of rosette formation with sheep erythrocytes (Lay *et al.*, 1971, reviewed by Mendes, 1977).

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* Escola Paulista de Medicina, Caixa Postal 20300, Agência Vila Clementino, São Paulo, SP - Brazil.

** Faculdade de Higiene e Saúde Pública da Universidade de São Paulo.

*** Hospital Lauro de Souza Lima, Bauru, São Paulo.

The E-receptor in a soluble form (Rs) is found in normal human serum (Bernd *et al.*, 1983) and can be recovered from the supernatant of heated peripheral lymphocytes (Mendes *et al.*, 1975; Mendes *et al.*, 1982).

Several methods for demonstration and quantitation of Rs have been developed in our laboratory since we have obtained a specific anti-E receptor serum (anti-Rs) by immunizing sheep with autologous erythrocytes (E) coated with Rs. This antiserum is cytotoxic for T cells, inhibits E-rosette formation, agglutinates ERs complexes, identifies T lymphocytes by immunofluorescence and gives a single precipitation line in gel diffusion with preparations containing Rs (Mendes *et al.*, 1982; Bernd *et al.*, 1983).

The most practical method to quantitate Rs in human serum is "Rocket electrophoresis" or electroimmunodiffusion. By this method, we have found abnormally high serum levels of Rs in diseases associated with a depression of cell mediated immunity, such as carcinoma, leukemia, lymphoma, uremia, lepromatous leprosy and bone-marrow aplasia (Moura *et al.*, 1983; Falcão *et al.*, 1984).

The most extensively studied aspect of leprosy immunology has been the failure of lepromatous patients to control the multiplication of *M. leprae*. However, the exact nature of the immunologic deficiency in leprosy remains to be clarified, but there is evidence of a T cell deficiency, a macrophage disfunction and participation of serum factors which lead to a varying degree of nonspecific depression of cell-mediated immunity superimposed on the basic defect (reviewed by Godal, 1981 and Mendes, 1981).

In the present work we have quantitated Rs in the serum of normal individuals and in patients with lepromatous (LL) and tuberculoid leprosy (TT).

Materials and Methods

Serum samples: were obtained from 43 adult normal individuals, 32 adult patients with tuberculoid leprosy and 53 adult patients with lepromatous leprosy, undergoing treatment. The clinical form of the disease has been well characterized by clinical, histopathological and immunological parameters.

Anti-E receptor serum (anti-Rs): was obtained immunizing an adult sheep with autologous E sensitized with Rs. The soluble receptor was obtained from the supernatant of human peripheral lymphocytes

(SHPL) (Mendes *et al.*, 1982). The packed autologous E were incubated with an equal volume of SHPL at 4°C for 18 h under agitation. Sensitized E (ERs) were washed 3 times in cold Hanks' balanced salt solution (HBSS) at pH 7.2. The sheep received a 1 ml sc injection of packed ERs in Freund's complete adjuvant and the dose was repeated twice, 3 weeks apart. Then, weekly ERs injections were given, without adjuvant. Three months after the onset of immunization, the resulting antiserum was capable of blocking E-rosette formation, of agglutinating ERs complexes, it was cytotoxic to T lymphocytes and gave a precipitation line in gel with human serum containing increased amounts of Rs, showing total identity with SHPL.

Quantitation of Rs in serum samples by electroimmunodiffusion "Rocket Electrophoresis": rectangular glass plates (75 × 50 mm) were covered with 7 ml of the following mixture at 56°C: 0.2 ml of anti-Rs, 1.8 ml of saline and 5.0 ml of 1.5% agarose diluted in 3 parts of electrophoresis veronal buffer and 2 parts of distilled water. Seven wells of 3 mm diameter were made at 1 cm from one of the edges of the plate. Each well received 10 μl of serum to be tested and 1 well per plate was filled with 10 μl of control serum. The plates were subjected to 250 V for 3 h in an electrophoresis chamber (Gelman Instruments Company, Ann Arbor, Michigan, USA) containing 1 l of veronal buffer (pH 8.6) and the migration of Rs was from the cathode to the anode. After migration, the plates were washed in saline for 24 h at ambient temperature, then were dried at 37°C and stained with amido black. The resulting "rockets" were measured in mm. The concentration of Rs in the serum samples tested is proportional to the height of the "rockets" obtained.

Results

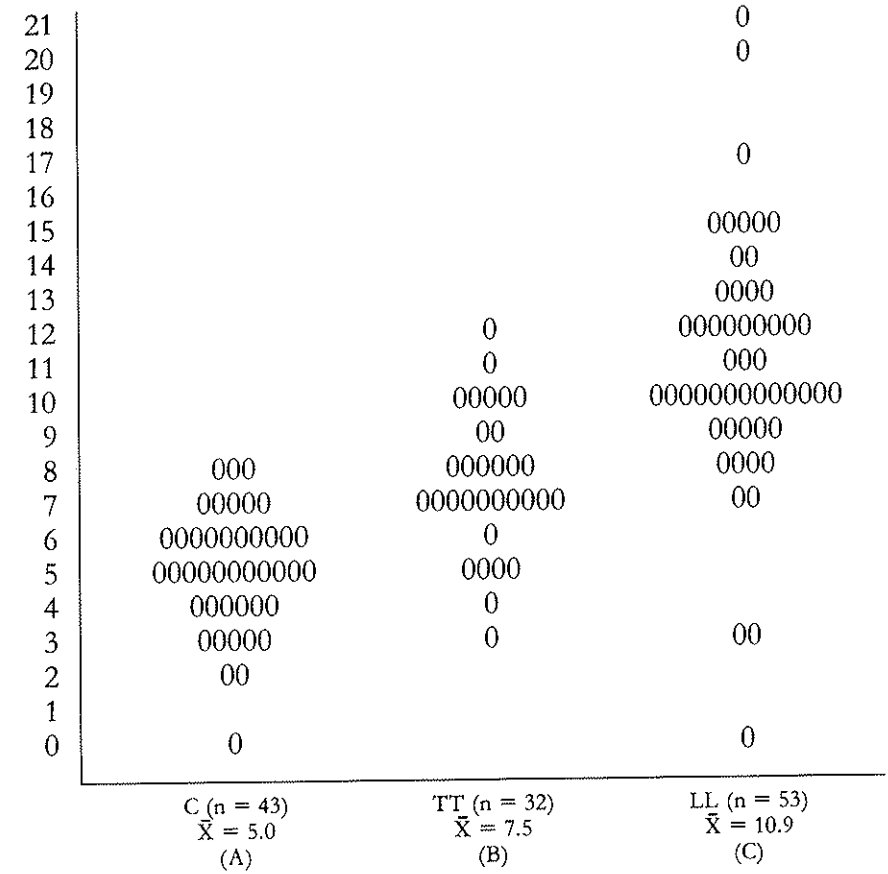
The results are illustrated in Figure 1 and the statistical analysis using the Kruskal-Wallis test showed a significant increase of Rs in the serum of patients with lepromatous and tuberculoid leprosy as compared with normal individuals ($p < 0.001$). Patients with tuberculoid leprosy showed Rs serum levels in an intermediate range, between normal controls and lepromatous leprosy. The means of the "rockets" obtained in each group were as follows: lepromatous leprosy: 10.9 mm; tuberculoid leprosy: 7.5 mm; normal controls: 5.0 mm.

Discussion

Our results have shown increased serum levels of Rs in lepromatous and tuberculoid leprosy patients as compared with normal individuals.

Studies from our institution (Musatti *et al,* 1979; Musatti *et al.,* 1980; Moura *et al.,* 1983) and others (Owen *et al,* 1976; Oh *et al.,* 1981) have indicated that Rs may be a regulatory molecule, released from the surface of T cells, that serves as a negative feedback control of their multiplication and function. Recently, our laboratory has demonstrated that Rs is present in preparations of the so-called immunoregulatory α--globulin (IRA), a substance that suppresses T cell-dependent immune responses and inhibits E rosette formation (Musatti *et al.,* 1983). The increase of Rs serum levels in pathological conditions may be explained by one of the following mechanisms: lymphocyte destruction, increased synthesis, decreased catabolism or diminished elimination. In lepromatous leprosy, the affected lymph nodes show a depletion of T cells as revealed by the adherence to sheep erythrocytes in cryostat tissue sections, probably indicating local lymphocyte destruction (Mendes *et al.,* 1974).

The observation that augmentation of Rs indicates depressed cell-mediated immunity, elucidates our results, with higher Rs values in lepromatous than in tuberculoid patients. This latter group of patients also showed abnormally high levels of Rs as compared with normal individuals, supporting other studies that demonstrated that even in the tuberculoid form there is a relative immunodeficiency (Bullock *et al.,* 1968; Han *et al.,* 1971),



C normal controls
TT tuberculoid leprosy patients
LL lepromatous leprosy patients
$\bar{X}$ mean
n number of individuals

Kruskal-Wallis between A,B,C: H' = 69.62; $p < 0.001$
Multiple comparisons:

Groups	$\lvert\bar{R}_i - \bar{R}_j\rvert$	msd	msl
A × B	30.34	22.47	$\simeq 0.001$
A × C	63.26	20.05	< 0.001
B × C	32.91	21.88	< 0.001

$\lvert\bar{R}_i - \bar{R}_j\rvert$ = difference between means of the ranks in the two groups compared
msd = minimal significant difference
msl = minimal significant level

FIGURE 1. Quantitation of Rs in the serum of patients with lepromatous and tuberculoid leprosy.

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CONCLUSIONS

Introduction

From ancient times, in virtually every culture, leprosy has evoked vivid images of fear and fascination. Sufferers were historically cast out of society, buried alive or burned at the stake. There is no other disease whose very name remains forbidden in some cultures and can be neither written nor uttered. Victims of this infectious disease often suffer physical deformity and crippling, and even today are frequently stigmatized or condemned to social ostracism. In cultures strongly affected by Judeo-Christian influence, the stigmata of leprosy largely result from a misinterpretation of what is termed "leprosy" in translations of the original Hebrew scriptures. For example, most authorities today see no resemblance between the single disease now recognized as leprosy and those conditions referred to as "leprosy" in Leviticus: 13, 14. Many other cultures impose similarly severe measures on sufferers of leprosy to those described in the Old Testament. However, with modern understanding of the disease, and with the availability of curative medicines, there is no justification for the physical segregation and social ostracism of patients with leprosy. In keeping with this concept, the appellation "leper" is obsolete and unacceptable; and the term "leprosy patients" or, where more appropriate, "Hansen's disease patients", should be used. Today leprosy afflicts an estimated 10-12 million people and is a major health problem in many developing countries. Our knowledge of the chemical composition of *M. leprae* and the limited information available on its metabolism have come from studies on organisms obtained from experimentally infected armadillos.

Leprosy has had a global distribution but is becoming more and more confined to the tropical and sub-tropical regions. In the Middle Ages leprosy was highly endemic in Northern Europe but now has nearly disappeared as an endemic disease. The reason for this disappearence is unknown, but it occurred before there was any specific treatment available. There is good reason to believe that the eradication of leprosy in this geographic area resulted from socio-economic advances. If we assume, and there is good reason to do so, that leprosy bacilli are airborne, the improved housing that began

to develop in the Middle Ages reduced contamination of the air by *M. leprae* in living quarters.

The mode of transmission of leprosy is unknown, but most likely the *M. leprae* enter the body via the lining of the upper respiratory passages or through broken skin. In most populations, even after the leprosy bacilli enter the tissues, 90-95% of the individuals do not get leprosy because their natural resistance or specific immune responses kill the invading organisms. Many patients develop early small lesions of leprosy and often neither the patient nor anyone else is aware of the disease. The clinical forms of leprosy vary widely and are outlined in Fig. 1.

The time lapse between the entry of the leprosy bacillus into the human body and the appearance of disease ("incubation period") may be as long as 20 years, but averages 2-3 years. The most common early sign of leprosy is a single small patch anywhere on the skin. In the dark skinned patient the patch is mildly hypopigmented (never white), but in the lighter skinned is slightly reddened. There may be a slight loss of sensation within this spot, but this may be difficult to detect. This form of the disease is called "indeterminate leprosy". A biopsy specimen from such lesions shows only a few lymphocytes and histocytes around neurovascular bundles and rare acid-fast bacilli (*M. leprae*) in nerves. The immune response of the patient determines the course of the disease. There often is complete healing at this stage; however, depending on the immune response, one of several advanced forms of leprosy may develop.

If there is a strong immune response to the leprosy bacillus, known particularly as cell-mediated immunity, the disease is confined to one or a few randomly distributed lesions in the skin, and peripheral nerves in these areas may be damaged, even destroyed. This form is known as "tuberculoid leprosy". Microscopic examination of tuberculoid lesions reveals cellular infiltrations called granulomas around neurovascular bundles and dermal appendages (hair follicles and sweat glands). The granulomas are composed of epitheloid cells and lymphocytes that usually invade and destroy nerves and dermal appendages causing loss of sensation, loss of hair and dryness within the lesion. Acid-fast bacilli are scarce in lesions of tuberculoid leprosy.

If cell-mediated immunity is weaker than in tuberculoid leprosy, a broad range of clinical forms of disease called "borderline (or dimorphous) leprosy" develops. The numbers of lesions in the skin are greater and less sharply defined than in the tuberculoid form. Because

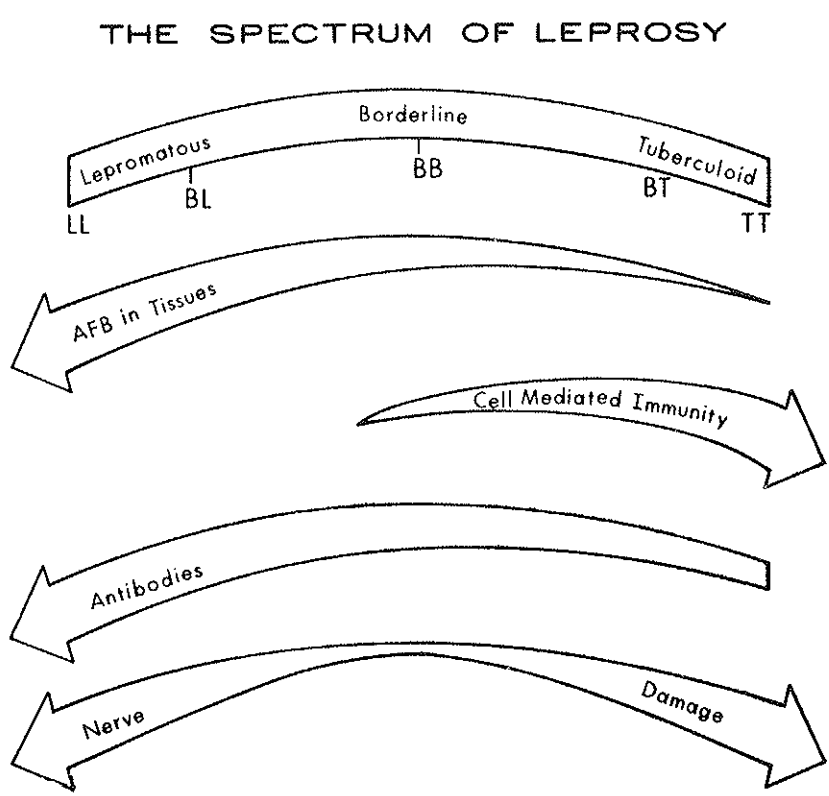

Fig. 1. The clinical and histopathologic types of leprosy vary from the immunologically unresponsive lepromatous (LL) to the high-resistant tuberculoid (TT) forms, with a spectrum of intermediate forms (BL, BB, BT). Numbers of acid-fast bacilli (AFB) in the tissues are greatest in polar LL leprosy and inversely related to the level of cell-mediated immunity. Antimycobacterial antibody levels generally correlate with bacterial load. Nerve damage can occur in all forms of leprosy.

of the wider dissemination of disease in borderline leprosy, nerves are more extensively damaged, with resulting sensory loss and crippling deformities, especially of the hands, feet and eyes.

Loss of sensation and paralysis of muscles render the hands and feet particularly susceptible to damage from trauma, even the minor trauma of walking and ordinary manual activities. If unattended, the destruction of tissues will gradually destroy the hands and feet. Paralysis of the muscles of the face not only disfigures, but, more importantly, may prevent the normal blinking of the eyes. This leads to drying of the cornea and sometimes blindness.

Patients who lack cell-mediated immunity to the bacillus develop a widely disseminated type of disease called "lepromatous leprosy". Virtually the entire skin is infiltrated by the leprosy bacilli and the cellular reaction to these organisms. The skin may be so uniformly involved that it is difficult to detect at first sight, or there may be nodular infiltrations, especially in the cooler parts of the body such as the central portion of the face, ears and extensor surfaces of the forearms and thighs. In males the testes may be destroyed, with resulting impotence and sterility. With far advanced disease the cartilage and bone of the nose are destroyed and the nose is depressed, giving the patient the classic "leonine facies". Skin from the patients reveals nearly complete replacement of the dermis by histiocytes, frequently patched with leprosy bacilli. These patients may shed myriad bacilli in their nasal secretions, or from open ulcers or wounds in the skin. They are contagious, and are the foci from which the disease may spread.

Although a serologic test for the leprosy may soon be available, diagnosis still depends on clinical and/or histopathologic findings. The lepromin test is never diagnostic and can only be used to predict the course of leprosy in a given patient. Patients who have positive lepromin tests are likely to develop tuberculoid or borderline leprosy, while those with a negative lepromin reaction can be expected to ger lepromatous disease.

Once leprosy is diagnosed, specific chemotherapy must be instituted. Of equal importance is the instruction of the patient in caring for insensitive hands, feet and eyes to prevent deformity and blindness.

Epidemiology and Control

Global estimates of the number of leprosy patients are between 10 and 12 millions distributed in all continents, the bulk of the cases occurring in Asia, Africa, and parts of Latin America. Almost one billion people live in areas where the prevalence is at least one per 1000. About one-fifth to one-third of the patients suffer from significant physical disabilities. The disease affects both sexes and all ages. Clustering of disease, particularly family clustering, is well recognized in leprosy. Decline of leprosy, as studied in Norway and recently in some other countries, is known to be associated with specific changes in age-specific incidence and proportions of lepromatous cases.

Airborne spread as the most important mode of transmission in leprosy is increasingly recognized. Although the human case with multibacillary disease is the only recognized source of infection, reports in recent years of leprosy-like disease among feral armadillos and the occurrence of leprosy among a few armadillo handlers have raised the possibility of non-human reservoirs. However, the epidemiological significance of these recent findings needs further evaluation. Subclinical infection in leprosy is known to occur widely in endemic areas, but its study in relation to epidemiological factors has not yet become possible for lack of simple tools with sufficient specificity and sensitivity. Similarly, inadequacy of tools has made it difficult to study possibilities of re-infection in leprosy.

The relationship between infection and disease in leprosy, as in other diseases, does not appear to be a constant one. It is likely that a large number of exposed people get infected, but do not develop the disease. This therefore suggests that the study of the factors which determine the disease is at least as important as the study of those which determine infection. While genetic association has been demonstrated both for tuberculoid and lepromatous leprosy through HLA markers, its importance relative to environmental influences is to be further explored.

The progress in basic research in leprosy in recent years has opened new opportunities, particularly for immuno epidemiological studies, and these opportunities should be fully exploited. Development of tools which can serve as intermediate markers in vaccine and drug trials is also of high priority.

The current approach to leprosy control is through secondary prevention based on chemotherapy, where the major objective is to decrease incidence of the disease to acceptable levels through early detection and mass treatment of patients. This approach also results in cure of the disease and prevention of the deformities among patients, which represents the key to control. As chemotherapy aims to eliminate the agent from the host, in order to be effective it should be bactericidal and capable of preventing occurrence of drug resistance. Dapsone, the drug used for over 35 years, has become relatively ineffective due to the emergence of drug resistance. Primary and secondary dapsone resistance is now known to occur in most endemic countries in alarming frequencies. The answer to this situation is the use of multidrug therapy, which includes at least three drugs for treatment of multibacillary leprosy and two drugs for paucibacillary

leprosy. Rifampicin, the most effective bactericidal drug against leprosy, should form part of any multidrug therapy. The urgent need to implement multidrug therapy in leprosy control programmes has been well recognized (WHO Study Group Report on Chemotherapy of Leprosy in Control Programmes, Geneva 1982, TRS 675), and in order to enable this, WHO has recommended standard multidrug regimens, which are effective, safe and operationally feasible for use in control programmes. These recommendations have been endorsed by the International Leprosy Association and other bodies. Unless the various agencies responsible for leprosy control implement multidrug therapy as quickly and as widely as possible, the leprosy situation in the world can become much more serious.

Other factors of importance in leprosy control are early case detection and case holding. Unless these are effective, chemotherapy by itself cannot produce the desired results in the community.

Currently leprosy control is organized in many countries through specialized services, and in others through primary health care services. Some use a combination of both. Whatever the approaches are, one of the important elements in successful control is participation of the community elicited through health education and literacy programmes including adult education by utilising all relevant media of communication including mass media. Government commitment and community participation are indispensable in leprosy control in view of the social problems associated with leprosy.

The development of health infrastructure varies widely with countries, and the introduction of multidrug therapy in leprosy control has exposed the real need for strengthening of the infrastructure, through training of personnel, establishment of appropriate laboratory services in the field, and the provision of drugs and other supplies. There is also a need to improve the managerial capability at the country level. In this connection an area of research often neglected but of great relevance is health services research, which could identify the best possible approaches within resource constraints.

Leprosy is unique among diseases in attracting support from voluntary organizations, national and international. These organizations have played very important roles in leprosy control programmes in many countries. It is important that new efforts be directed towards implementation of technical policies for leprosy control, and that close cooperation between governments, international agencies such as WHO and non-governmental agencies be encouraged and further strengthened.

Epidemiological research is an essential component of leprosy control, in order to achieve earlier detection and better treatment, which are required to effectively cure the patient and reduce transmission.

While for the foreseeable future leprosy control has to be based on a secondary prevention approach through chemotherapy, it is only a primary prevention approach through an effective vaccine that can bring about a steep fall in disease occurrence. In this connection the research efforts being made by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases and other agencies are of great importance, and need reinforcement, particularly from the point of view of resources.

Leprosy in Animals

A. *Experimental Infection*

Because *M. leprae* has not yet been grown *in vitro*, the need for animal models of the disease is of great importance. The ideal model would be an immunologically intact animal species that could serve as a source of the organism and also manifest the entire spectrum of the clinical form of the disease including the reactional episodes and paralytic deformities commonly encountered in leprosy patients. There is no single animal species that satisfies all these requirements. The models currently available are:

1) *Mice*: Normal mice have been important to detect viable *M. leprae*, to screen drugs for their effect on the multiplication of *M. leprae*, and to screen candidate vaccines for eventual use in field studies. By immunologic manipulation, the susceptibility of the normal mouse can be altered to permit greater multiplication of *M. leprae*, and these animals have been used to detect small numbers of viable *M. leprae* in patients undergoing therapy. Nude (athymic) mice and rats permit the development of disseminated leprosy and have potential as a source of *M. leprae*.

2) *Nine-banded armadillos (Dasypus novemcinctus):* The nine-banded armadillo from the southern United States is highly susceptible to leprosy. More than 80% of inoculated animals develop lepromatous disease, and tissues harvested at necropsy contain up to 10^{10} *M. leprae* per gram of tissue. Additional studies are needed to determine the

susceptibility of nine-banded armadillos from Latin America as well as the susceptibility of seven-banded armadillos (*Dasypus hybridus*) and eight-banded armadillos (*Dasypus sabanicola*) indigenous to Latin America. Studies should be undertaken to determine the suitability of nine-banded armadillos from the southern U.S. as models for experimental chemotherapy.

3) *Primates*: The discovery of naturally acquired leprosy in a mangabey monkey (*Cercocebus atys*) prompted attempts to transmit leprosy to normal mangabey monkeys and to other species of monkeys. Experimental leprosy has been transmitted to normal mangabeys and dose response studies using human *M. leprae* demonstrate that the onset of disease in mangabeys is dose-dependent. The response of normal mangabeys infected by various routes is currently being evaluated. The autopsy and histopathologic evaluation of tissues from infected mangabeys with active disease confirmed disseminated leprosy with extensive involvement of the skin of the face, ears, extremities, tail and scrotum. Only minimal involvement of the liver and spleen was seen. Thus, the disease in mangabeys simulates that seen in humans. The results of transmission studies in rhesus monkeys (*Macaca mulatta*) and African green monkeys (*Cercopithecus aetheops*) demonstrate that these species are also susceptible to leprosy. The ready availability of thesus and African green monkeys enhance their value as primate models for the study of leprosy.

B. *Naturally Acquired Infection*

The discovery of naturally acquired leprosy in three genera of animals demonstrates that leprosy is not a disease confined to humans, and the lepromatous patient can no longer be considered the only possible source of *M. leprae.*

1) *Nine-banded Armadillos*: Naturally acquired leprosy in nine-banded armadillos was first reported in 1975 when the disease was diagnosed in a small number of armadillos captured in southern Louisiana. The identity of the organism isolated from naturally infected armadillos has been confirmed as *M. leprae*, using all of the criteria available for the identification of an organism as the leprosy bacillus. To date 104 armadillos captured in Louisiana have been found with the disease, with rates of infectivity ranging from 40% to 29.6%. In a recently completed survey of 451 armadillos captured in Texas, an overall prevalence of 4.6% was reported with rates of infectivity

ranging from 1% to 15.4%. A recent report has implicated armadillos as the source of infection in 5 patients from Texas, four of whom were from areas in Texas where naturally-infected armadillos have been found. The large number of infected armadillos in the southern U.S. requires that armadillos be considered reservoirs of the disease in these areas. Investigations are needed to determine if naturally acquired leprosy occurs in armadillos in Latin America.

2) *Chimpanzee (Pan troglodytes):* Naturally acquired leprosy in a chimpanzee was reported in 1977. The animal was imported from Sierra Leone where leprosy in humans is highly endemic. The identity of the organism was confirmed as *M. leprae* and histopathologic examination of tissues confirmed disseminated leprosy. The prevalence of naturally acquired leprosy in chimpanzees is not known, but epidemiologists should be aware that this species could be a potential reservoir of the disease.

3) *Mangabey Monkey*: This animal was imported to the U.S. from West Africa in 1975. The first lesions were seen in 1979 and consisted of firm nodules on the face and ears. It was never inoculated with *M. leprae* and was on a cholesterol metabolism study at the time the disease was diagnosed. Microbiologic, histopathologic and immunologic studies have confirmed the identification of the etiologic agent as *M. leprae*. Paralytic deformities developed in this animal. This is the first leprosy-infected animal species in which deformities similar to those that develop in human leprosy have been observed.

The animal responded to treatment with antileprosy drugs (Rifampin and Dapsone). It is likely that this animal contracted the disease as a result of contact with an individual with lepromatous leprosy. However, the results of transmission studies demonstrate that mangabeys are susceptible to leprosy and therefore it is possible that infection occurred as a result of contact with leprosy-infected mangabeys in the wild. The prevalence of leprosy in mangabeys in the wild is unknown, but epidemiologists should be aware that as a species they are susceptible to leprosy and are therefore potential reservoirs of the disease.

CELLULAR IMMUNOLOGY

A. *Status of the Field*

It has recently become clear that host factors play a dominant role in tissue damage and clinical manifestations in leprosy. Among host factors, immune responses to antigens of the leprosy bacillus appear to exert a key role in determining the clinical form of disease that will develop after infection. Moreover, as other infectious diseases, most individuals will combat the leprosy bacillus at such an early stage after infection that immunity will emerge without observable clinical manifestations. This is often referred to as "sub-clinical infection". A precise definition and immunological characterization of sub-clinical infection are of fundamental importance to gain insight into the epidemiology of the disease and how effective immune responses operate against the leprosy bacillus. Such understanding is also required for rational approaches to vaccine development and immunotherapy.

Among the two major effector mechanisms of the immune system, the cell-mediated and the humoral antibody compartments, the former appears to be primarily responsible for the defence against the leprosy bacillus. For example, in those subjects that develop disseminated multibacillary disease, there is a selectively unresponsive T-cell effector mechanism, macrophage disfunction, and participation of serum factors that may depress cell-mediated immunity. These defects are largely selective *vis-à-vis* antigens of the leprosy bacillus and have been a subject of intensive research in recent years. The results of this research suggest that in multibacillary patients, specific T-cells are prevented from growing and executing their function. Emerging evidence suggests a deficiency in the appropriate growth factor for such cells. These findings open new possibilities of restoring immunological competence in lepromatous leprosy and patients with other immunodeficiency syndromes.

Nerve damage plays a major role in the development of deformity in leprosy by causing hypoaesthesia and paralysis. There is considerable evidence pointing to the involvement of T-cells in nerve damage in patients with non-lepromatous forms of the disease. Apparently, leprosy bacilli may remain undetected in the nerves for long periods of time, but when eventually becoming recognized by T-cells, a local inflammatory response is made which leads to nerve damage. The

involvement of T-cells in nerve damage suggests that new modalities of immunosuppressive therapy may be considered for treatment of such patients.

B. *Future Prospects*

Host-parasite interactions in leprosy are complex. Recent advances in cellular immunology have provided considerable insight into the involvement of the T-cell compartment in host defence and tissue damage. However, apart from an apparent role of phenolic glycolipid, a unique antigen of the leprosy bacillus, we are quite ignorant about the antigenic determinants that are engaged in T-cell responses. New technological developments (T-cell clones and hybrids) have now set the stage for intensified research in this area. Although such studies require considerable resources and will be time-consuming, they are likely to lead to the identification of antigens specific for the leprosy bacillus which will form the basis for better skin tests. They will also allow a more detailed examination of the type of responses found in subclinical infection as compared to patients. This may provide insight into antigens related to protective immunity and consequently important for vaccine development.

The production of a rapidly increasing number of regulatory molecules of the immune system (lymphokines, interleukins, interferons) by recombinant DNA technology provides new insights to understand how host cells kill and degrade leprosy bacilli and new approaches to restoring such mechanisms in patients when these are deficient. T-cell growth factor (interleukin-α) and γ-interferon are candidates for such studies.

The Antibody Response in Leprosy

The antibody response has not been as well studied as the cell-mediated immune response in leprosy, in part because the protective immunity to infection by *M. leprae* is not directly related to the presence of circulating antibodies. While immune complexes clearly appear to play a role in the pathogenesis of hypersensitivity reactions such as erythema nodosum leprosum, these reactions are usually managed at the clinical level. The reagents available for the study of antigen-antibody reactions until very recently were not adequate to permit the development of specific serological tests. Such tests, if

available, would be important for the diagnosis of subclinical or clinical types of infection, evaluation of therapy and detection of relapse, seroepidemiological studies of infection and transmission and study of the regulation of the cell-mediated immune response to *M. leprae* by antibodies, among others. Several recent developments in the study of *M. leprae*, as well as general immunology, provide the basis for the development of sensitive, specific serological tests in leprosy. Perhaps one of the most important of these developments has been the isolation, purification and demonstration of specific serological activity of phenolic glycolipid I, a complex molecule which comprises an important part of the cell wall of *M. leprae*, and has not been identified in any other natural source. The hybridoma technique for the production of specific monoclonal antibodies allows the identification of specific antigenic determinants even when they represent a small portion of large, complex molecules containing several determinants, some of which may demonstrate cross reactivity. By this technique additional antigenic determinants unique for *M. leprae* have been demonstrated. A test employing specific antigen, patient sera and an antibody to immunoglobulin bearing an enzyme marker (ELISA test) provides a highly sensitive system for measuring the antigen-antibody combination. This system is easily adapted to the study of a large number of small serum samples and is particularly suitable for use in developing countries with limited resources.

Several studies have demonstrated that antibody levels are highest in multibacillary leprosy and decrease across the clinical spectrum of disease, occurring in low levels in tuberculoid leprosy; they decrease after treatment and may show an increase prior to relapse. In the study of clinical disease, measurements of antibody levels may be a useful tool in evaluating treatment, in detecting the presence of persisting viable bacteria which are not killed because of inadequate treatment or drug resistance, and in the early detection of relapse. Determination of the particular class of antibody involved in these reactions may be important, as well as the specificity; it remains to be determined if antibodies of a particular specificity are associated with the specific clinical type of disease. The principal response to phenolic glycolipid I is an antibody of the IgM class, which must be borne in mind in serological testing.

The use of serological tests may be of even greater interest and potential importance in aspects of leprosy control related to early detection of disease, detection of subclinical infection seroepidemiological studies of infection rates and transmission.

Multibacillary forms of leprosy with an average incubation period of several years may be the source of new infections in the community during the long period prior to clinical evidence of disease; a specific serological test for detecting the presence of *M. leprae* may offer the only possibility for detecting this type of subclinical infection, since cell-mediated reactivity to *M. leprae* is absent. Recent studies have shown the subsequent development of clinical disease in a small number of contacts of leprosy patients who had specific antibodies to *M. leprae* in their sera at a time when the disease was not yet apparent.

If vaccination of general populations against leprosy should prove too expensive to carry out, the measurement of specific antibodies to *M. leprae*, together with tests of cell-mediated immunity, could allow the detection of particularly susceptible groups and individuals within the population, perhaps recently infected by *M. leprae*, who would be important subjects for selective vaccination. In leprosy research, the availability of monoclonal antibodies to the specific antigens of *M. leprae* may permit the detection of those antigens in tissues and in other micro-organisms, evaluation of immunopathologic and regulatory mechanisms and development of detection systems for use in advanced biotechnology and isolation of such antigens.

Molecular Biology

New advances in recombinant DNA technology have provided powerful tools for basic and applied research in human health problems. Three general components of vaccine research can benefit significantly from current recombinant DNA technology:

1) the establishment of toxonomic similarities and differences in the etiologic agent at the DNA level;

2) the identification and isolation of genes which specify antigens potentially relevant to immunity, and

3) the large scale production of the antigen in relatively pure form.

For example, sensitive DNA hybridization techniques can be used to determine whether different pathogen isolates contain identical genomic DNA sequences. Genes that encode antigens of interest can be isolated by using antibodies to identify the products of individual

foreign genes in *E. coli* host cells. Thus, genes which specify parasite antigens can be simultaneously identified and isolated by using antibodies from patients afflicted with the parasite. The isolated genes of interest can be expressed in procaryotic or eucaryotic hosts to produce large amounts of antigens, which can be used for research, diagnostic or vaccine purposes.

Recombinant DNA libraries have been constructed with DNA from *Mycobacterium leprae* to facilitate the isolation of genes whose products may be useful for the diagnosis or prophylaxis of leprosy. These DNA libraries are being surveyed with antibodies that recognize protein epitopes of the *M. leprae* bacillus. Clonally isolated peptide epitopes, rather than whole protein antigens, may be particularly useful for specific serodiagnosis. Development of techniques that permit efficient surveys for recognition of recombinant peptides by T-cells will provide a measure of the relevance of these clonal gene products to components of the cell-mediated immune system. Ultimately, recombinant DNA techniques could conceivably be used to introduce particular genes encoding *M. leprae* antigens into cultivable bacteria for vaccine purposes.

VACCINATION

A series of events has occurred in the last two decades which have justified the priority given to research on the development of a preventive vaccine against leprosy. These include the following:

1) The evidence that in general worldwide terms, the endemic situation of leprosy has not improved since the introduction of treatment with sulfones in 1942.

2) The development of drug-resistant strains of *M. leprae* has acquired unquestionable importance in Asia and Africa. The appearance of isolates resistant to Rifampicin, in the relatively short period that this drug has been in use, suggests that the problem of drug resistance could expand with incalculable consequences.

3) Internal migration in developing countries, from rural areas to the cities, is motivated by a search for better living conditions. This poses the possibility of the creation of new urban foci of infection which could require new methods of control. Preventive vaccination, if effective and available, would clearly be a first option.

The conventional methods of control, including early diagnosis, treatment and public health education, must be applied for decades in order to be effective; they are frequently abandoned before their objectives can be fulfilled. Epidemiometric models demonstrate that development of a highly effective prreventive vaccine could have a significant impact on the incidence of leprosy within a decade. The evidence that cell-mediated immunity is associated with protective responses to *M. leprae* and the fact that animal reservoirs do not appear to play an important role in transmission are additional factors which help in defining a vaccine strategy.

Schematically, three approaches to vaccination have been proposed:

a) killed *M. leprae*

b) use of a living avirulent mycobacterium which shares common antigens effective in inducing protection

c) use of a mixture of killed *M. leprae* together with a living non-pathogenic mycobacterium such as BCG.

The development of cell-mediated immunity after the injection of heat-killed *M. leprae* and of cultivable mycobacteria suggests that protection might be induced; heat-killed *M. leprae* and viable BCG are indeed protective in normal mice and they induce cell-mediated hypersensitivity in the guinea pig. Nevertheless, neither of these preparations alone is active in altering the course of non-reacting patients with progressive disease. Studies of avirulent mycobacteria, particularly in India, have shown the induction of immunological changes in patients with progressive disease, but further characterization of these strains must be awaited. BCG vaccination as an immunoprophylactic procedure has been tested in several studies, but the level of protection, with one exception, has been too low to be considered for control of leprosy.

The differences in response to BCG which have been observed may be due to differences in the mycobacterial flora of the environment or to differing epidemiological patterns, depending upon whether lepromatous or tuberculoid leprosy predominates. The use of a cultivable mycobacteria would possess the great advantage of massive production at relatively low cost. The principal difficulty in choosing an appropriate microorganism is that the specific cross-reacting

antigens of *M. leprae* which are responsible for inducing a protective immune response have not been identified, so there is no way of identifying them in another mycobacterium. Monoclonal antibodies and T-cell lines to diverse antigenic determinants of *M. leprae* may permit the identification of the protection-inducing antigens and their detection in other species in the future.

Recent studies employing a mixture of heat-killed *M. leprae* and viable BCG in the therapy of multibacillary leprosy have demonstrated the efficacy of this mixture in inducing favourable clinical, bacteriological and immunological changes in these patients. A significant proportion of the 300 cases of active lepromatous and borderline lepromatous leprosy treated with eight to ten doses of the mixture developed reversal reactions and positive skin test reactions to *M. leprae*, as well as elimination of the infecting microorganism. Chemotherapy in patients of this type is effective in lowering the bacterial population, but the immunological changes observed — reversal reactions accompanied by clinical improvement and skin positivity — are exceptionally rare.

The mixture was also effective in the immunotherapy of early leprosy of the indeterminate type; 95% of such patients developed strong reactivity to the Mitsuda skin test antigen. The lesions in all of these patients regressed and none developed progressive multibacillary disease. This group is of particular interest since a high proportion progress to multibacillary lepromatous or borderline lepromatous leprosy if not adequately treated.

The mechanism of action of the *M. leprae*-BCG mixture has not been elucidated, but may be related to the local conditions necessary for the effective presentation of antigens by macrophages or for the expansion of appropriate T-cell clones.

The therapeutic effect of the mixture of killed *M. leprae* and BCG in patients with immunological reactivity and low resistance to *M. leprae* clearly suggests that the same mixture might be expected to show prophylactic activity in the contacts of patients at high risk of developing the disease. Indeed, preliminary studies have shown the development of positive skin test reactivity in such individuals, but the follow-up period has not been sufficiently long to evaluate the incidence of new cases of disease.

Future Prospects

The evidence (i) that BCG and heat-killed *M. leprae* individuality induce protective immunity in an animal model, the mouse footpad; (ii) that many years of use have demonstrated the safety of these reagents in human beings; and (iii) that a mixture of heat-killed *M. leprae* and BCG, but neither alone, induce favourable clinical, histopathological, bacteriological and immunological changes in multibacillary leprosy and prevent the progression of early lesions to disseminated disease, has established the basis for initiating additional field trials. The types of trials which should be initiated include additional immunotherapeutic studies in multibacillary disease and, in particular, in Mitsuda-negative indeterminate leprosy, in several areas of the world. Prophylactic vaccine trials should be initiated in individuals at particularly high risk, identified by epidemiological and, if possible, immunological criteria; trials in the general population would be a subsequent step in evaluation. Finally, if other candidate vaccines besides the *M. leprae*-BCG mixture fulfill preliminary prerequisites, they should be evaluated in comparative studies.

Vaccine trials are very costly, not only in terms of production of the vaccines, but in the development of the public health infrastructure necessary to implement preliminary epidemiological studies, to carry out the vaccine trial itself and to evaluate vaccine efficacy by multiple criteria; the support for these trials must be sought at international as well as national levels.

Social Aspects of Leprosy

Social aspects of leprosy have been conventionally understood as socio-economic consequences of acquiring the disease. The problems arising out of social rejection, economic impoverishment and socoial and economic rehabilitation have been the identified social problems. Socio-economic factors for people's noncompliance with leprosy control activities have also been investigated. Human treatment of patients with love, sympathy and compassion has been recommended as the answer to social problems.

With the development of social science theory and methodology, social aspects should include besides social and economic, cultural, religious, management and communication aspects. Since leprosy afflicts humans and is transmitted by humans amongst each other,

understanding life styles of people such as mating patterns of endogamy and exogamy, food habits, rules permitting physical proximity and group interaction become relevant for understanding factors favouring transmission of the disease.

Poverty and health consciousness are usually found in inverse ratio. For the poor, health disorganization is yet another area of disorganization in life. It is thus neglected until it threatens their basic social and economic securities. In leprosy, this happens with the onset of deformities and it is too late. So people resign themselves to their fate, adopting lower levels of aspirations in life and the psychology of defeat.

People are not afraid of physical death as much as of social death, which is ensured by deformities. Man, as a social animal, has to live in human groups in which he seeks his life's fulfillment.

The only hope of cure in leprosy for the common people has been divine intervention. No medical system, indigenous or modern, has been able to satisfy common people about effective tools for cure. This has given rise to many beliefs about leprosy, which have stigmatised the disease. People are always willing to accept all curative techniques from all systems of medicine or faith if they are available at a cost they can afford and prove viable for a reasonable period.

People's participation in control programmes is essential for early diagnosis and continued treatment. They have favoured multidrug therapy since it reduces clinical manifestations of the disease in a short period. All control programmes and tool development programmes should aim at reducing deformities to break the association of leprosy with deformity and social death, which is the root of social stigma. Stigma and fear hinder people's participation in control activities.

Health education should aim at the patient, his or her family and community with an aim to transmit scientific knowledge to the people's culture. Indicators of success of health education and community participation would mean (i) deformity rate reduction, (ii) voluntary reporting, (iii) utilization of services, (iv) rehabilitation.

There exists general apathy about leprosy in the medical profession, which is not conducive to leprosy control. Health workers treating leprosy or diagnosing new leprosy patients are not sufficiently aware of the social and psychological problems associated with the disease. The decision makers and opinion leaders many times share prejudices about leprosy with common people. It is thus recommended that:

1) particularly in endemic countries, medical curricula need to be reoriented to ensure proper training in all aspects of leprosy,

2) orientation of health workers and various leaders in the community to the medical and social aspects of leprosy be done through special programmes.

In view of the involvement of religious organizations in leprosy work, it is further recommended that these organizations should administer information courses for the community. These religious organizations should take the lead in training the voluntary health workers in scientific and social aspects of leprosy.

Since deformity is the main cause of stigma and fear about leprosy, it is necessary that the patients and families be educated to take preventive measures so that deformities do not develop. The socio-economic consequences of deformities need to be made clear to the patients.

It has to be appreciated that the funding agencies are showing greater awareness in not presenting the picture of deformity for raising funds since it strengthens the stigma. It needs to be emphasized that the instinctive association of leprosy with deformity needs to be dissociated, with the help of all media of communication.

The word "leprosy" used by the medical profession generally puts fear in the minds of new patients, who do not like to accept the diagnosis, since patients' perception of leprosy is associated with gross deformities. It is advisable to use available words in local languages which would prevent confusion between early signs of leprosy with mutilation in the mind of patients and families.

The gap between "what the disease is" and "what people believe it to be" needs to be understood by social scientists, medical anthropologists and sociologists, educational psychologists, management and communication experts. Social science research should be encouraged to find better tools for health education and attitudinal changes.

Compassion for the sick is divine only if a leprosy patient gets recognised as a sick person by the community and health workers as in other diseases.

Conclusions and Recommendations

Leprosy is a disease which had been neglected for many years by the scientific community and too often ignored by the world community. There is a resurgence of interest in leprosy in the medical

world for at least two reasons. First, new advances in biomedical science offer better tools with which to attack this ancient affliction of humankind. Second, studies of immunology and pathogenesis as well as social science aspects are providing important insights into fundamental problems with implications far wider than leprosy itself.

New advances in immunology, molecular biology, microbial biochemistry, epidemiology and development of animal models provide great opportunities to understand the pathogenesis of the disease, to detect early infection with *M. leprae* and perhaps to identify those at risk of developing clinical disease, with the hope that intervention can prevent emergence of disease. Candidate vaccines have been developed and are already being evaluated for their ability to provide immunity to patients with the most severe form of the disease, and to prevent individuals in the general population from contracting leprosy. More detailed epidemiological information is needed to define infection rates and identify individuals most at risk in various endemic areas of the world in order to facilitate adequate design for testing the efficacy of vaccines against leprosy.

At the same time, multidrug chemotherapy regimens have been developed and are being used to stem drug-resistant *M. leprae* infection and more effectively treat current patients with leprosy. The emergence of sulfone-resistant pathogens presents an urgency for accelerating the research effort to reduce the transmission of disease in man.

Compassion remains an essential value for approaching the problem of leprosy in social terms, but is insufficient to deal adequately with problems of rehabilitation, integration, acceptance into the community and liberation from the historical stigma. New methodologies in social sciences offer more effective qualitative and quantitative tools with which to understand and approach the social, economic, political and religious problems associated with leprosy in different societies.

To accomplish the task of controlling and hopefully eliminating leprosy for future generations, we believe that support for the following recommendations will be of importance.

A. *At the scientific level:*

1) It must be emphasized and appreciated that there is a crucial relationship between research and control. If we use only the currently available modalities, leprosy will not disappear. It is now that we must

support development of more powerful diagnostic, therapeutic and preventive tools to apply in the future.

2) The recent emergence of sulfone-resistant *M. leprae* indicates the need to adopt widely the WHO recommendations that the most effective current treatment of leprosy requires the universal use of multiple drug chemotherapy.

3) The recent development of vaccines that have demonstrated therapeutic efficacy in patients with some forms of leprosy encourages the hope that they may be effective in preventing healthy individuals from contracting the disease. Because leprosy is a slowly developing disease, and the prevalence and incidence are relatively low even in endemic countries, controlled vaccine trials must necessarily be relatively costly and of long duration (5-10 years). Because of the hope that they offer for preventing and eliminating leprosy, they must be supported and receive adequate priority in health planning.

4) More detailed epidemiological data and methods must be generated in order to make possible early detection of infection and reveal modes of transmission. They are crucial if vaccine trials are to be well designed for use in different endemic areas.

5) Investigation should be carried out to evaluate the possible role and implications of animal reservoirs in disease transmission.

B. *At the political and social level:*

1) Because of the need to link scientific advances in the laboratory to problems of leprosy in the field, multinational scientific cooperation, such as the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, must be supported and strengthened. This kind of cooperation should include the distribution of scarce reagents and materials, such as *M. leprae,* diagnostic and vaccine reagents, laboratory methods, scientific protocols as well as training to appropriate workers in field areas where they can be applied and evaluated. This approach should be incorporated as well into bilateral cooperation programmes.

2) We recognize that leprosy care and control represent fundamentally national responsibilities. Nevertheless, voluntary and religious agencies play unique and important roles, and it is important to strengthen their interaction with governmental programmes. Voluntary and religious agencies offer the possibility of providing not

only patient care but training and educational components that can assist national health efforts to secure the resources and plan for assuming greater responsibility for control and treatment in their countries. The compassionate efforts of voluntary and governmental health workers must be supplemented with greater technical knowledge about the disease and its impact. International agencies can ensure continuity of care in times of economic hardship faced by many leprosy endemic developing countries.

3) Education has a vital role to play in more effectively dealing with leprosy. More useful training about leprosy for medical and postgraduate students and health workers in leprosy endemic countries is required. New social science research approaches provide insight into how best to involve the people and enable them to realize: (i) that leprosy is an infectious disease, not a moral or religious chastisement; (ii) that it can be prevented and cured without the development of deformities, and (iii) that patients with this, like other infectious diseases, when appropriately treated can be productive members of their community. Strong links between health care workers, social scientists, community and religious leaders are important if the new scientific tools such as diagnostic tests and vaccines are to be effectively applied, and if the stigma and fatalism associated with leprosy are to be dispelled.

5) Access to the most appropriate available care and treatment should be recognized as a basic right of all leprosy patients.

TIPOGRAFIA POLIGLOTTA DELLA PONTIFICIA UNIVERSITÀ GREGORIANA
PIAZZA DELLA PILOTTA, 4 - ROMA