

Working Group on:

IMMUNOLOGY, EPIDEMIOLOGY
AND
SOCIAL ASPECTS OF LEPROSY

May 28 - June 1, 1984

CONCLUSIONS



PONTIFICIA
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PRESENTATION

The Pontifical Academy of Sciences held a Working Group from May 28 through June 1, 1984, on the theme: « Immunology, Epidemiology and Social Aspects of Leprosy ».

The Participants in the Working Group, accompanied by the President of the Academy, His Excellency Prof. Carlos Chagas, and by the Director of the Chancellery, Rev. Father Enrico di Rovasenda, were received by His Holiness John Paul II on June 1st.

The Holy Father pronounced a Discourse which is published in the present Document together with the address delivered by the President of the Academy.

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, take the coffee cups they offered me, not knowing the great effort I had to make to be with them.

More recently 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 sufferings, 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, may judge the human element it involves. My thoughts became still more pungent 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 be held were it not for the authoritative way with which Professors Barry Bloom and Jacinto Convit have organized it. I am profoundly grateful for what they did for the Pontifical Academy of Sciences.

I also 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

AUDIENCE OF THE HOLY FATHER

At the beginning of the Papal Audience the President of the Academy, Prof. Carlos 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 efforts have 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 is 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 the lepers. They are an example for a world where unselfishness and munificence are lacking.

Your Holiness, 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 and 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 admiration 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 the 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 hand 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 who 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 he 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 who 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 the 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, accompanied 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.

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 similiary severe measures on sufferers of leprosy as 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 disappearance is unknown, but it occurred before there was any specific treatment availa-

ble. 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

THE SPECTRUM OF LEPROSY

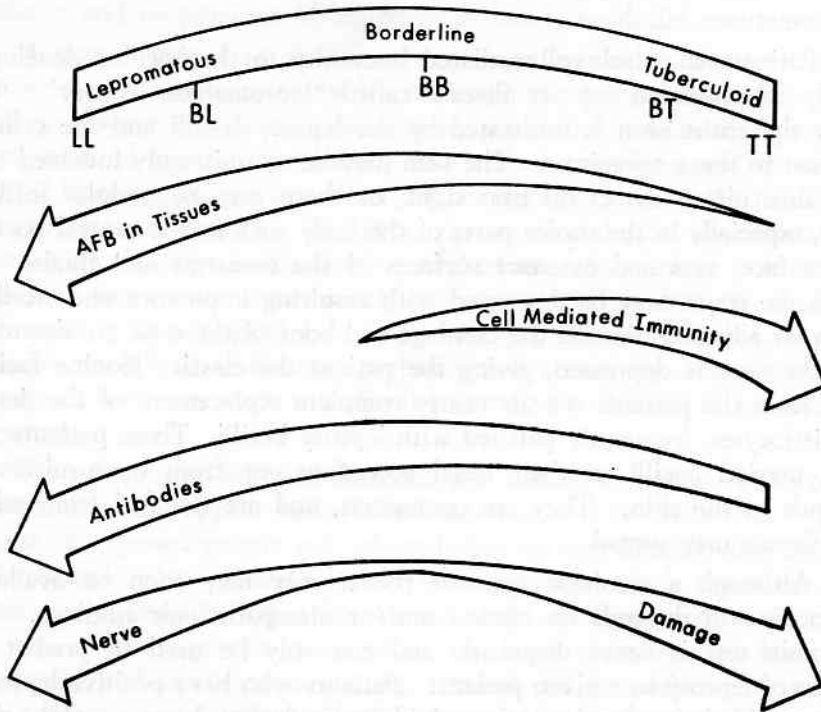


FIG. 1. The clinical and histopathologic types of leprosy vary from the immunologically unresponsive lepromatous (LL) to the high-resistant tuberculoid (TT) forms, with a spectrum of intermediate forms (BL, BB, BT). Numbers of acid-fast bacilli (AFB) in the tissues are greatest in polar LL leprosy and 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.

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 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 on 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 get 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. De-

cline 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 multi-bacillary 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. It therefore suggests that the study of the factors which determine the disease are 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 immunoepidemiological 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 frequen-

cies. 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 implemen-

tation 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 aethiops*) demonstrate that these species are also susceptible to leprosy. The ready availability of rhesus 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 leprous 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 arma-

dillos captured in Louisiana have been found with the disease, with rates of infectivity ranging from 4% 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.

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 dysfunction, 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 deve-

lopments 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 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 sources 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 taxonomic 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 devel-

opment of a highly effective preventive 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 social 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 have been recommended as the answers 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 organiza-

tions 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 to develop 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 encourage 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; (iii) and 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.

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