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Editorials

GROWING POINTS IN LEPROSY RESEARCH

The four papers on "Growing Points of Leprosy Research" in this number of the Review are in line with the more recent policy of the Editorial Board to include, from time to time, invited papers on a particular aspect of leprosy. It was very encouraging that there was a plethora of research topics to choose from, since nowadays progress in all fields of clinical medicine is dependent upon the contributions made by a wide range of biochemical disciplines involved in basic and applied research. The full impact of multi-disciplinary approaches to the field of leprosy research was epitomized at the 10th International Leprosy Congress, Bergen, where, for the first time, there was an almost equal balance between contributions from the more clinical and the more laboratory aspects of leprosy. In order to appreciate and assess the basis on which some of the research efforts are being made and their likelihood of advancing our knowledge of leprosy, this number of the Review also includes the full reports of all the Expert Committees at Bergen.

In the past the field of leprosy has been advanced entirely by a few dedicated, but isolated, workers. Their isolation and the lack of interest by other biochemical disciplines, together with the inability to culture *Myco. leprae in vitro* or *in vivo* had severely restricted progress. Dr Robert Cochrane, for many years closely associated with LEPRA, made a determined effort to stimulate and bring together all the biochemical disciplines which might help to solve the various leprosy problems. Above all, it was his hope that the introduction of "new blood" would bring leprosy into the general stream of clinical medicine and end for all time its isolation. The four contributors to this special number on "Growing Points of Leprosy Research" fully endorse Cochrane's philosophy and objectives, since they represent repectively, biology, epidemiology, immunology and pharmacology and have only recently applied their expertise to the field of leprosy.

The first animal model for studying human leprosy was established in 1960 when Shepard showed that *Myco. leprae* multiplied when inoculated into the mouse footpad. This discovery heralded a new era in leprosy research which has greatly enhanced our knowledge of leprosy. The mouse model, or any other animal model, will continue to play an essential role in leprosy research until it is discovered how to grow *Myco. leprae in vitro*. Therefore, other animal species have been studied and in 1971 Kirchheimer and Storrs reported the successful transmission of *Myco. leprae* to the nine-banded armadillo. In the ensuing three years their intensive studies have fully established the armadillo as an important model for the study of leprosy. In this number Eleanor Storrs, as an authority on the biology and reproductive-physiology of the nine-banded armadillo, presents a resumé of the special features of this mammal together with the latest

information on the type and incidence of leprosy in this animal species. In summary, the results establish the armadillo as another animal model for studying leprosy in which a relatively high proportion of individuals develop progressive, lepromatous type leprosy. Thus the armadillo is the first natural animal host to manifest lepromatous type leprosy, in the mouse this can only be achieved by prior artificial obliteration of their immunological competence. While it is too early to anticipate the full impact of the armadillo in leprosy research, it is already clear that it will be the model of choice for providing a rich source of *Myco. leprae* in the laboratory. The armadillo will never replace the mouse model, but will be complementary, and hopefully, the armadillo will add still further to advances made with the mouse model.

Ellard presents a detailed review and carefully argued case in support of the relevance to man of the experimental chemotherapeutic data based on the mouse footpad model. Ellard justifies his case in drawing attention to similarities between the chemotherapy of leprosy and tuberculosis and the important role that experimental studies on *Myco. tuberculosis* have had on the successful evolution in the chemotherapy of tuberculosis. It is on this basis that he concludes that the chemotherapy of leprosy is at last beginning to be place on an objective bacteriological and pharmacological basis. In drawing attention to the similarities between the chemotherapy of tuberculosis and lepromatous type leprosy, the leprologist is led to ponder over three important problems. (1) While in tuberculosis there are many regimens that when supervised can cure the patient, such regimens fail when applied to routine services in the field in developing countries, because patients fail to take regular treatment—can we be sure that lepromatous leprosy is more difficult to treat with dapsone than tuberculosis with known curative regimens?—do the many failures in mass treatment with dapsone arise because the patients fail to take the drug? (2) Because in tuberculosis it has been fully established that combined therapy is essential in order to avoid more or less universal development of drug resistance with monotherapy, are we any longer justified in giving monotherapy (dapsone) to patients with lepromatous leprosy, since we now know that dapsone resistance does not occur in a significant nimber of lepromatous patients given monotherapy? (3) Since it has now also been fully established that both in man and in the mouse rifampicin is as yet the only bactericidal drug against *Myco. leprae*, if there are no special immunological defects in patients with lepromatous leprosy as compared with patients with fulminating pulmorary tuberculosis, is it now imperative that trials with rifampicin plus dapsone should be undertaken for a limited period of time, and then treatment withdrawn in order to establish once and for all whether the inclusion of a bactericidal drug can significantly shorten the course of chemotherapy in patients with lepromatous leprosy?

Many new methods are now available for measuring the cell-mediated type of immune responses associated with leprosy, which have been brilliantly exploited and applied by Godal. A clear exposition of the lymphocyte transformation and the leucocyte migration inhibition tests is presented by Godal in this issue. Because of the specificity of these tests for *Myco. leprae*, they provide for the first time a means of identifying those who have been infected with *Myco. leprae*. The importance of this new tool for advancing our knowledge of the epidemiology of leprosy is clearly defined in Meade's paper. In fact the preliminary observations of Godal, and their implications, exemplify the need for epidemiologists to exploit new technical developments and progress in other

disciplines referred to by Meade. In this context Meade stresses the importance of the re-awakened interest in the nose as a likely source of infection in leprosy, particularly in view of the new information on the survival up to two days of *Myco. leprae* outside the body. The latter important finding was worked out, again using the mouse model. All these new findings, together with those of Godal, are likely to throw new light on the transmission and epidemiology of leprosy.

These growing points in leprosy offer good prospects for better control and treatment of leprosy. The four papers chosen show clearly the important role that research is playing and underlines the reason why LEPRA decided to support research generously.

R. J. W. Rees

EDITORSHIP AND POLICY

With this number of the *Leprosy Review* Dr Browne becomes Consulting Editor and the Editorial Board is joined by Dr Davey as Chairman. We pay tribute to the distinguished service to Leprology rendered by Dr Browne during the years he has been Chairman of the Editorial Board. In his new position we shall still have the benefit of his vast experience and inimitable personal contributions. It is a pleasure also to pay tribute to the valuable service to the Review rendered in recent years by Dr Duff behind the scenes. As sub-editor, Dr Duff brought to the *Leprosy Review* a lifetime of experience in medical journalism, and the technical excellence of the Review has been due in large measure to his meticulous attention to detail. We offer him our sincere gratitude, and best wishes for his retirement.

At this moment in time it is perhaps appropriate to declare once again the reasons for the existence of this Journal. The *Leprosy Review* came into being in 1930 to articulate and publicize the basic concerns of the British Leprosy Relief Association; namely, (a) the stimulation of research in leprosy, (b) the fostering of responsibility for the eradication of leprosy and the best possible care of those suffering from it, (c) the encouragement of those actually engaged in leprosy control work, through communicating advances in knowledge and the sharing of experience relating to common problems.

These basic concerns still stand, and all need to find expression in the pages of the *Leprosy Review*. On the research side the *Leprosy Review* has a distinguished record. There are few substantial advances in leprology in recent times that did not have their first notice in this Journal. It is fundamental that significant original work should be published without delay. There was a time when publication was possible within six weeks of the arrival of a contribution at the editorial office, as the writer knows from personal experience. Nowadays, printing and publication problems demand a minimum of two and a half months between the receipt of an article and its ultimate appearance in print. This period cannot appreciably be shortened, but in normal circumstances it need not be greatly exceeded. It will be our firm policy to offer publication of original work acceptable to the Editorial Board with an absolute minimum of delay.

The past 15 years have witnessed enormous advances in our scientific knowledge of leprosy. Not only has *Myco. leprae* been rehabilitated. Its unique properties have captured the interest and imagination of bacteriologists and immunologists at many centres, and its ongoing study is in the mainstream of

medical research. Would that a corresponding wave of interest and concern were directed towards the people whose bodies have been invaded by *Myco. leprae* or are at high risk of encountering it. Progress in the control of leprosy lags far behind that already attained in the spheres of microbiology and immunology, and the reasons are not far to seek. The economic importance of leprosy is frequently underestimated. Its ancient and stubborn social implications pose a whole range of problems as varied as they are intractable, and which are outside the normal concerns of medical research. In studying these and in stimulating action in controlling leprosy and caring for those who suffer it, this Journal has a time honoured and independent role to play.

Finally, the large body of field workers engaged in the sometimes thankless task of trying to control leprosy has always been the special concern of LEPRA, and is therefore our special concern too. The tedium of maintaining circumscribed routines may be ennobled by dedication, but it may be sustained creatively if the individual worker continually has access to new knowledge and the experience of others who are similarly engaged. It is an important function of the *Leprosy Review* to serve the field worker in these directions, both where content and distribution are concerned. With this in view, a section devoted to "Leprosy and the Community" is introduced with this issue, presenting reports and material of interest to those directly engaged in leprosy control work. It is hoped to make this a regular feature of the *Leprosy Review*, and develop it further. Contributions and correspondence will be welcomed.

In addition to their value from the standpoint of research, the Committee Reports of the Bergen Congress include a great deal of material which should be essential reading for leprosy workers everywhere. For many years it has been the practice for the Expert Panel and Committee reports of Conferences of the International Leprosy Association to be published in the *Leprosy Review*, and precedent is again followed by the publication in this number of the Bergen Congress Committee Reports in full.

T. F. Davey.

BERGEN 1973–SOME AFTERTHOUGHTS

Another International Leprosy Congress has come and gone, leaving behind it in the mind of at least one participant, precious memories that time will not efface; the coming together of so many friends from across the world; Hansen's microscope; the tribute to his memory around his statue in the Botanical Garden; Grieg's music played on his own piano as the evening light caught the view of fjord and mountain from his house; St Jørgen's hospital, at once so moving and so typical. Then the Congress itself, its crowded sessions, especially in the smaller lecture hall, and the great mass of research material poured out day by day, some of it so relevant and interesting that one frequently wished it was possible to be in two places at once.

The very size of this Congress proclaimed the rehabilitation of leprosy into general medicine. It was a joy to see the old familiar faces of fellow leprologists present in great strength for this historic occasion, but nevertheless a dwindling company among a crowd of colleagues from other medical disciplines, whose presence was a happy augury for the future. The organizational problems surrounding this Congress must have been enormous. The accommodation, transport and entertainment of 700 participants, to say nothing of the 200

associate members, must have been a formidable challenge, and that it went so smoothly is a great tribute to all concerned with the local organization. They deserve our very sincere gratitude.

The technical planning involved in the months preceeding the Congress, with the grouping and final selection of 377 scientific papers, represented an equally formidable task. Profound thanks are due to the Council of the International Leprosy Asociation and their consultants, and especially to Dr Browne, Secretary-Treasurer of the Association, for everything involved in the production of so excellent a presentation.

A few reflections on the Congress may not be out of place. During the sessions it was physically impossible to absorb and make adequate notes on so many matters of interest, except perhaps those falling within the range of one's own immediate concerns. Here the published abstracts of papers were of only limited usefulness. Out of 378 printed abstracts, no fewer than 100 stated intention and methodology, but did not state the findings as they would be presented at the Congress. The requirements of translation and printing demanded a time lag of several months between the submission of abstracts and the actual Congress, and this was therefore inevitable. It would not have mattered, provided the Transactions of the Congress were being published, but no such publication is possible, and as a result participants had no record of findings, many of which they would have wished to preserve. Even if financial considerations prohibit the publication of the Transactions of a large Congress such as this, is it not at least possible after future Congresses to publish at any rate a volume of revised abstracts, containing the findings actually made public at the Congress?

A legitimate question which may be asked is "What was there at this Congress for the clinician and field worker who are engaged at the grass roots level of the fight against leprosy?" A comparision of the numbers of the contributions at recent Leprosy Congresses, according to subjects to which they relate is shown in Table 1.

The striking feature of these figures is the very minor place given to social problems and rehabilitation. In practice these are everyday problems of the field worker, who is frequently discouraged by their intransigence. Any who came to this Congress hoping for help in this sphere must have been disappointed, and some said as much. Every leprosy worker must rejoice at the wealth of interest and expertise now manifest in the spheres of microbiology, immunology and experimental therapeutics. They hold tremendous hope for a future in which we shall have available more dramatically effective drugs, and also a vaccine as effective in leprosy as BCG is in tuberculosis. These fields of research are of great importance and must be given adequate expression in any future Congress, but the fact remains that even better drugs and an effective vaccine will not necessarily greatly change the problems of the leprosy field worker for a very long time to come. His most difficult problems relate to communication, the removal of ignorance, the conquest of prejudice, the creation of concern, the winning of cooperation.

These are not usually regarded as problems in medical research, but if the basic purpose of our coming together as leprosy workers in an international congress is to strengthen the forces combating leprosy throughout the world, these real problems of the public health planner and field worker must also find adequate expression. In leprosy, sociology and medicine meet, two facets of the same individual and community illness.

TABLE 1

Categories of papers presented

Congress	Bacteriology, Pathology, Immunology	Clinical, Therapy, Surgery	Epidemiology, Control	Social Aspects	Rehabilitation	Miscellaneous	Total
Madrid 1953	58	52	29	4	Nil	9	152
Tokyo 1957	32	16	17	7	Nil	6	78
Rio de Janiero 1963	96	54	31	7	5	–	193
London 1968	74	105	36	8[a]	11	7	241
Bergen 1973	172	125	58	5	13	4	377

[a]Psychological aspects only.

It would be unrealistic to advocate the widening still further of the scope of future congresses, planned on the Bergen pattern, by the introduction of substantial sociological material. Is this pattern, however, the only one possible in practice? The same question was asked after the Madrid Congress in 1953, and the succeeding Congress at Tokyyo illustrated one type of answer, in the rigorous limitation of uninvited contributions. Since those days, the pace of expansion and multiplication in research has accelerated, and with its increasing specialization we may well ask whether the day of the comprehensive leprosy congress is over. Certainly those engaged in specialized aspects of research can serve the cause of leprology very significantly by placing leprosy firmly on the agenda of all congresses dealing with the same specialized aspects of general medicine. Increasingly it should be possible at future conferences of the International Leprosy Association to devote relatively less time to microbiology, pathology, immunology, and experimental therapeutics, and more to the direct concerns of leprosy control. India has already taken a lead in this direction. For some time now the biennial All India Leprosy Congresses have consisted of two separate but inter-related parts, (a) the Conference of the Indian Association of Leprologists, lasting for 2-3 days and concentrating on advances in knowledge, with invited papers a feature, and (b) The Leprosy Workers' Conference of the Hind Kusht Nivaran Sangh, following immediately after the first, and devoted to the problems of epidemiology and leprosy control. Here social questions receive the prominence they deserve. There is a general understanding that clinicans and leprologists working in the field do not attend the first Conference to the exclusion of the second, where the great wealth of practical experience represented ensures lively and valuable discussions. Here there is food for thought.

Finally, one practical problem at Bergen cannot be ignored. Amid the hundreds of participants, how many came from western nations and how few there were who directly represented the "third world". African faces were few and far between. The few participants from India grossly under-represented the three million sufferers from leprosy in that great country and did not include some key workers.

Economic questions lay behind this disparity, and even prevented some of those who did attend from staying until the end. It is sad indeed if an international gathering of such importance is deprived of essential voices coming from the parts of the world where leprosy is most destructive of human health and happiness. This situation can surely be prevented.

T. F. Davey.

Lepr. Rev. (1974) **45**, 8-14

Growing Points in Leprosy Research

(1) The Armadillo as an Experimental Model for the Study of Human Leprosy

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The armadillo was selected as an animal model for the study of leprosy because of its low body temperature, availability, presumed weak immunological competence, longevity, and the fact that it regularly produces monozygous quadruplets. Most of these advantages have been realized. At present, 37 armadillos have developed symptoms of leprosy of which 13 have been killed and the disease confirmed by histopathological examination and other tests. These animals have yielded a total of 1255 g of lepromas which contain an estimated 20 g of leprosy bacilli.

The armadillo has great potential for studies on the chemotherapy, immunology and epidemiology of leprosy. It has immediate value for the production of large numbers of leprosy bacilli which could be used for studies on the biochemistry and metabolism of *Myco. leprae, in vitro* cultivation experiments, and preparation of a sufficient supply of standardized lepromin to meet the world's needs.

The nine-banded armadillo (*Dasypus novemcintus,* Linn.), is one of approximately 20 species of armadillos comprising several genera. It belongs to the Edentata, a primitive mammalian order which also includes sloths and anteaters. Edentata are found exclusively in the Western Hemisphere in Central and South America, with the exceptjon of the nine-banded armadillo which ranges from central Argentina to the southern United States. Although little is known about the characteristices of many of the edenates, it ia known that they possess low body temperatures.

The nine-banded armadillo is the first unaltered animal model to develop disseminated leprosy following inoculation with *Mycobacterium leprae* isolated from human tissues (Storrs, 1971; Kirchheimer and Storrs, 1971; Kirchheimer, Storrs and Binford, 1972; Storrs, 1973; Storrs *et al.*, 1973; Storrs, in press; Storrs *et al.*, in press). Leprosy in the armadillo is characterized by a high incidence of susceptibility (at least 40%), bacterial counts as high as 10^{10}/g of tissue and a high degree of pathological involvement. Invasion of the central nervous system and lung by leprosy bacilli have been observed in some armadillos.

At present, 37 armadillos in our colony have developed symptoms of leprosy of which 13 have been killed and the disease confirmed by histopathological examinations and other tests. These 13 animals have yielded a total of 1255 g of lepromas which contain an estimated 20 g of leprosy bacilli.

Because of the magnified form in which leprosy occurs in this species, the armadillo promises to be an excellent model for studies on the chemotherapy, epidemiology and immunology of leprosy and other mycobacterial diseases. Of

immediate importance is the finding that large amounts of infected tissue containing massive numbers of leprosy bacilli can be harvested from infected animals. These can be used in investigations concerned with the biochemistry and metabolism of *Myco. leprae*. A sufficient supply of standardized lepromin could now be prepared from armadillo lepromas to meet the world's needs. In addition to being a model for the study of disease, the armadillo could serve as a source of leprosy bacilli for cultivation studies.

The armadillo is a unique model for the study of leprosy because of a number of practical and scientific considerations. These include availability, low body temperature, suspected weak immunological competence, longevity and the fact that it regularly produces monozygous quadruplets.

Availability

Availability of animals is a very important although mundane consideration in selecting potential models for biomedical research. The nine-banded armadillo is abundant in the southern United States, Mexico, Central America and large areas of South America. These animals have increased remarkably with respect to population and range in the southern United States during the past 50 years. Approximately 80% of the animals brought in from the wild adapt to captivity; the remainder which do not adapt are released. The time allowed for adaptation to captivity prior to inoculation is 3 to 6 months. Armadillo young born in captivity are obtained by bringing in pregnant animals in late autumn; parturition occurs in the spring.

The direct cost of maintaining armadillos is about U.S. $0.37 per day per animal, which includes food, bedding and labour.

Adult armadillos weigh from 3 to 55 kg and are strong but not aggressive and do not attempt to bite. Two technicians can restrain an armadillo for routine technical procedures without anaesthesia and with no mechanical protection other than gloves.

Shipment of animals to locations where armadillos are not native poses no problem. In February of 1972 we received shipments of seven-banded armadillos (*Dasypus hybridus*) and hairy armadillos (*Chaetophractus villosus*) from Argentina. These animals became dehydrated *en route* and a few of them did not survive. However, the majority of animals recovered and all of the survivors are still alive.

While armadillos are not as available, inexpensive to maintain, or easy to handle as rats and mice, they compare very favourably with members of the dog, cat, and monkey families in these respects.

Body Temperature

Most leprologists believe that *Myco. leprae* grows best at low temperatures, since leprosy occurs primarily in the cooler regions of the human body such as the skin, nose, ears, digits and testes (Binford, 1956; Brand, 1959). This was the primary reason for selecting the armadillo as a model for the study of leprosy.

The body temperature (rectal) of the nine-banded armadillo ranges from 30° to 36° C when the ambient temperature is close to 25° C. Johansen (1961) in a detailed study, found the core temperatures of 13 armadillos to range from a low of 34° to 35° C early in the morning to a high of 35° to 36° C around midnight.

The ambient temperature was held constant at 25°C. These temperatures are higher than those reported by Wislocki and Enders (1935) and by Burns and Waldrip (1971). The latter authors found body temperature differences between male and female armadillos. The rectal temperature for fifteen males averaged 33.4°C (range 31.0 to 35.0°C) while for seven females the temperature averaged 31.3°C (range 30.0 to 33.0°C). These temperatures were taken between 0800 and 1200 h during the months of October to January at an ambient temperature of 23°C.

Johansen compared rectal and skin temperatures and oxygen consumption for armadillos exposed to different ambient temperatures ranging from −10° to 40°C. As ambient temperature became lower, skin temperature decreased while oxygen consumption and rectal temperature increased. This temperature increase amounted to about 3.5°C when ambient temperature was decreased stepwise from 30° to −10°C. This overcompensation of the armadillo to a cold stress indicates that the central nervous thermal control is relatively primitive.

At high ambient temperatures both the skin and rectal temperatures increased, and oxygen consumption increased to a level of 400 ml/kg/h and then levelled off. The rectal temperature increased to as high as 38°C at an ambient temperature of 40°C.

Thus it appears that the core temperature may be as low as 30°C in some animals; however, either an increase or decrease in ambient temperature can result in a change in core temperature because of the relatively primitive regulatory mechanism.

Immunological Competence

In reviewing the scientific literature on armadillos, it was observed that these animals had been successfully inoculated with a number of diseases which can infect man including relapsing fever, exanthematic typhus, murine typhus, trichinosis and schistosomiasis (Storrs, 1971). They are also carriers of Chagas disease (Chagas, 1912) and have been reported to be susceptible to African sleeping sickness (Coyle, 1972). Thus, armadillos can be infected with a variety of organisms including spirochaetes, ricettsia, trepanosomes and schistosomes. Because of this, it was suspected that the armadillo might have weak immunological competence.

The papers describing this work were, for the most part, published in South American journals. This older work was summarized in a review by Talmage and Buchanan in 1954 in a Rice Institute Pamphlet Monograph in Biology (Talmage and Buchanan, 1954), but the authors did not draw any deductions from the information they had collected, and in all probability, this pamphlet was not widely distributed.

It now appears possible that the armadillo may be generally susceptible to diseases caused by organisms classified with the Actinomycetales, since in addition to leprosy it has become infected with *Norcardia brasiliensis* (Gezuele, 1972) and *Myco. ulcerans* (Walsh *et al.*, 1973), the causative agent of Buruli ulcer.

Some direct evidence has recently been obtained which suggests that the armadillo might have an immune deficiency which is temperature-related.

It is generally accepted that resistance to leprosy is a function of cell-mediated immunity (CMI). Since it was suspected that the low body temperature of the

armadillo was somehow responsible for susceptibility, it was decided by Purtilo *et al.* (1973) to investigate the effect of temperature on the immune performance of this species. The ability of lymphocytes to transform in the presence of certain mitogenic substances is believed to be a reflection of the immune competence of an individual. With this rationale, these workers investigated the ability of armadillo lymphocytes to transform to phytohaemagglutinin (PHA) and lepromin at both normal human temperature (37° C) and temperatures below this (33° and 28° C) in a range comparable to normal armadillo temperature. They found that lymphocyte transformation was depressed by 66% at 33° C and 81% at 28° C when compared to transformation at 37° C, suggesting that there is an immune dysfunction of the lymphocytes of the armadillo at normal temperatures. Interestingly, the results of a parallel experiment using human lymphocytes also suggested that reduced temperatures had a depressive effect on lymphocyte transformation.

Other investigations by Purtilo and his group showed that from a histological standpoint the tissues of the lympho-reticular system (thymus, lymph nodes, tonsils, etc.) appeared to possess the elements necessary for immune competence. This finding provided additional evidence that the immune deficiency is one of function rather than a result of an anatomical defect.

Thus low body temperature may render the armadillo highly susceptible to leprosy for two reasons: (a) it provides an optimum temperature for growth of *Myco. leprae,* and (b) this temperature may depress the activity of the CMI system of the armadillo. It is emphasized that these are hypotheses which will have to be verified by in-depth studies.

Longevity

It has been speculated that leprosy may require 3 to 5 years to develop in man following inoculation by *Myco. leprae* (Skinsnes, 1964). Thus, the use of a long-lived animal model in which leprosy develops over a prolonged period of time is advantageous. Also, a long-lived model would be preferable for studies on chemotherapy, since leprosy is a chronic disease which requires treatment with drugs over a period of many years. Its chronicity and the limitations of available chemotherapy are illustrated by the finding that of 22 patients at the U.S. Public Health Service at Carville, Louisiana, U.S.A., in whom Promin treatment was initiated in 1941, 10 still had active leprosy 30 years later (Faget *et al.*, 1966). Therefore, in order to assess adequately the efficacy of new drugs, the animal model employed should have a long life span and develop lepromatous leprosy. The armadillo satisfies both of these requirements since its life span is estimated to be at least 12 to 15 years, and it develops severe disseminated disease 10 to 40 months after inoculation with *Myco. leprae.*

This estimate of life span of at least 12 to 15 years is based on the facts that the armadillo requires two years to reach sexual maturity, and the period of gestation totals nine months, which includes a three-month period of delayed blastocyst implantation. Thus, it matures less rapidly than dogs or cats, which have life spans of about 15 years.

Armadillos which were captured as full grown adults in 1968 were still alive in the Gulf South Research Institute colony in late 1973; hence these animals must be at least 7 years old. Three of the first 4 animals to be inoculated with leprosy bacilli (not viable in the mouse footpad) in December of 1968 are still alive,

indicating that they must be at least 6 years old since these were also adults, at least 2 years old, when captured.

Monozygous Quadruplets

The nine-banded armadillo regularly produces monozygous quadruplets derived from a single fertilized ovum. The monozygosity of armadillo quadruplets has been well established by the embryological investigations of Newman and Patterson (1910), Hamlett (1927) and Enders (1966). In our laboratories we have never observed a mixed set of young; they are always all males or females. The seven-banded armadillo, which is very closely related to the nine-banded armadillo, regularly produces 8 to 16 monozygous young (Benirschke, 1968).

It must be emphasized that although the monozygous young are in all probability identical genetically, they are not necessarily completely identical immunologically, biochemically, or morphologically. Anderson and Benirschke (1962) found that sygenic grafts of skin between monozygous quadruplets were ultimately rejected although at much slower rates than allografts. Storrs and Williams (1968) made biochemical and morphological measurements on 16 sets of monozygous quadruplets and concluded that there were significant differences within sets. However, the differences within sets were usually smaller than the differences between sets. All of the measurements were made at birth or on animals delivered by Caesarean section just before birth to minimize environmental influences. They speculated that the differences observed within sets might arise from cytoplasmic inheritance. There is a greater opportunity of this occurring in the armadillo than in man because of the unique embryological development of the armadillo which is illustrated in Fig. 1.

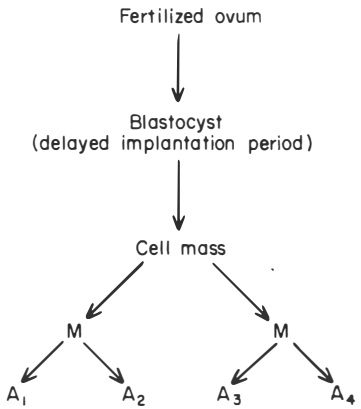

Fig. 1

Cell division of the fertilized ovum takes place and a blastocyst is formed which remains quiescent for a period of 14 to 16 weeks. After implantation, the cell mass develops 2 buds. These subsequently redivide to yield 4 cell masses which develop into the armadillo embryos.

Although these monozygous quadruplets may not be entirely identical somatically they are nevertheless very similar, and can be used to test the hypothesis that susceptibility to leprosy is inherited.

Therefore, 11 sets of monozygous quadruplets, one year old, were inoculated

with leprosy bacilli according to the schedule shown in Table 1. All conditions were kept constant except for the number of animals inoculated. In 3 cases all members of the sets were inoculated, and in 8 cases only 2 of the 4 animals were inoculated in order to preserve the genomes should the inoculated members develop leprosy.

TABLE 1

Inoculation schedule for monozygous quadruplet armadillos

Monozygous set no.	Sex	Inoculated	Uninoculated
1	♀	2	2
2	♀	2	2
3	♀	2	2
4	♀	2	2
5	♂	2	2
6	♂	2	2
7	♂	2	2
8	♂	2	2
9	♂	4	0
10	♂	4	0
11	♂	4	0

Six months after inoculation all 4 members of set number 9 were positive for acid and fast bacilli at the sites of inoculation (abdomen) while all of the other animals were negative. The probability of this happening by chance is 1 in 20,475. However, the disease did not develop uniformly in all 4 animals. At the time of writing, 2 of these animals have developed small nodules and the other 2 rather large nodules.

The diagram showing when divisions of the cell masses take place indicates that there are 2 sets of twins within each group of 4; A1 and A2 may be more similar to each other than to the other group of twins (A3 and A4).

It is assumed that differences in immunological competence within sets will be least apparent when resistance to infection afforded by the genome is low. In these cases, the differences in resistance between individuals may not be great enough to prevent all the animals from developing leprosy. However, when resistance provided by the genome is high, the time required for leprosy to develop in animals within sets could vary, since small differences in immunological competence between individuals could be magnified. with some being just below the borderline of infection and others just above it, However, since this work with monozygous young is only in the early stages of development, evidence for this hypothesis will have to await further results.

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Growing Points in Leprosy Research

(2) Epidemiology

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In spite of limited progress in leprosy epidemiology over recent years, the opportunities for new and potentially fruitful approaches are now good. The need for further epidemiological work arises mainly from the failure, so far, to achieve the primary prevention of leprosy on any meaningful scale by any of the means theoretically available, including the interruption, by means of environmental changes, of its transmission. Re-awakened interest in the nose as the likely source of infection in leprosy, new information on the probable survival time of *Myco. leprae* outside the body, epidemiological similarities between leprosy and tuberculosis, and anthropological methods for measuring contacts between leprosy patients and their family and social circles, are points which should help in the design and conduct of studies of the environmental and other factors, besides *Myco. leprae* itself, involved in leprosy transmission. The potential value of lymphocyte transformation testing as a way of identifying those infected by *Myco. leprae* calls for further intensive study, much of it by epidemiological means. Another field in which the epidemiologist must collaborate with workers in different disciplines is in assessing the effectiveness of chemotherapy, whether by sulphones or newer preparations such as rifampicin, and in keeping the question of antibiotic resistance in leprosy under review.

The Committee on Advances in Epidemiology of the Tenth International Leprosy Congress in Bergen, 1973, concluded that there had been few major developments in the epidemiology of leprosy in the previous five years. Its forecast for the future, however, was more optimistic, reflecting the real new opportunities for epidemiological work in leprosy that now exist. Many of the potential openings depend on testing and exploiting recent technical developments and progress in other disciplines. In this respect, leprosy is in the same position as many other chronic diseases for which population-based study methods are appropriate—that further progress depends largely on working links between epidemiologists and those with other skills, the contribution that the epidemiologist on his own can now make being rather limited.

Leprosy Control

What can and ought to be done by epidemiological methods is largely determined by the present world leprosy position, and the interpretation of what has been achieved since the widespread introduction of the sulphones in the late 1940s and early 1950s.

Without doubt, many assumed that sulphones would be effective not only in treating patients with clinically manifest leprosy, but also in preventing the spread of the disease to others. This hope was partly based on the decline in tuberculosis observed in many (mostly economically developed) countries after the introduction of streptomycin. This particular comparision was, of course, inappropriate since mortality from tuberculosis in many of the Western countries concerned had been falling for some years before streptomycin became available. Vital statistical data on tuberculosis and leprosy for countries where both were endemic were simply not available at the start of the antibiotic era, but it is unlikely that similar changes in tuberculosis mortality were occurring in these non-Western countries. Circumstances in which comparisons between the two diseases may or may not be helpful need careful thought; an example is discussed later.

At all events, the phrase "leprosy control" has, by common usage, come to have at least two different meanings, and the resulting confusion has created difficulties that are only now being resolved.

On one hand, the term has been applied to mass treatment programmes whose chief objectives have been the detection and treatment of as many people with leprosy as possible, the potential benefit to the *individual patients* concerned being the reason for these programmes. There is little doubt that these schemes have generally succeeded in their main purposes, by providing treatment for those who would otherwise not have received it, and in most cases by reducing the prevalence of the disease. Nevertheless, only limited efforts have been made formally to assess the impact of mass case detection and treatment. While information on bacteriological changes following sulphones is available, comparatively little has been done to measure clinical and social costs and benefits. This subject, developing rapidly in relation to other diseases and the health services of many countries, assumes much more than academic importance with the arrival of rifampicin, the first bactericidal anti-leprosy antibiotic. For, vastly expensive as this drug is compared with dapsone, the indications are that it may have to be used for much shorter periods than the latter. If established, this development could mean potentially large savings in long-term projects based on dapsone, and the ability to divert resources into other health services. These changes are, of course, not by any means certain, but their possibility is something that leprosy epidemiologists with interests in applied aspects need to be aware of in the coming years—and if they do occur, the cause of integrating leprosy services into general health services will be considerably advanced. There are, of course, many schemes around the world that could study problems and developments in this field.

On the other hand, "leprosy control" has been used in a primary preventive sense to suggest that leprosy incidence (i.e. the rate at which new cases appear) might also decline as a result of treating established cases; in this instance, it is the benefit to *those at risk but hitherto unaffected* that is under consideration. Whether or not mass treatment programmes have accomplished this as well as helping those with clinical leprosy is still an open question. On the whole, however, the consensus view is that incidence has not declined in areas where such programmes have been in operation.

If we assume, therefore, that primary prevention is not likely to be achieved by the chemotherapy of overt disease (and this is the only safe assumption in the absence of firm evidence), what other possibilities are there? First, vaccination;

the results of the three major BCG trials are now well-known. In Uganda (Brown, Stone and Sutherland, 1968; Stone and Brown, 1973), protection against leprosy by BCG is about 80%, in New Guinea (Scott and Wigley, 1966; Russel, 1973) about 50%, and in Burma (Bechelli *et al.*, 1970, 1973 *a, b*) about 20%. (Different levels of protection occur at different ages; the figures given are for all ages studied.) These results refer to tuberculoid disease; virtually no information on protection against lepromatous disease is available. Overall, it is difficult to assess the impact that BCG (which most health services probably want to use against tuberculosis anyway) would have on leprosy incidence. The development of a specific anti-leprosy vaccine is obviously desirable, but not very likely at present.

Secondly, chemoprophylaxis is effective in reducing leprosy incidence (Dharmendra, Noordeen and Ramanujam, 1965, 1967; Noordeen, 1969), but calls for the long-term administration and taking of dapsone in doses which (in leprosy patients, at least) are associated with the development of resistance. As a means of preventing leprosy in isolated (e.g. island) communities, chemoprophylaxis may be effective and feasible (Sloan *et al.*, 1971), but its long-term effectiveness and practicability in endemic areas is obviously doubtful.

Finally, leprosy workers suprisingly often overlook the historical lesson that the modification of environmental factors favouring the spread of infectious diseases has been successful in their prevention much more frequently than individually-directed measures (such as immunization). Indeed, this has already happened with leprosy, in so far as the disease disappeared from previously endemic areas (such as Northern Europe) for reasons which, though quite unclear, were almost certainly nothing to do with steps taken by, or directed at, specific individuals in the population at risk. In fact, one of the great advantages of identifying and modifying the environment in which an infectious disease spreads is that changes can often be made (e.g. in water supplies) which do not require the active participation of the whole population. It is to this area of study that leprosy epidemiology is now increasingly turning, through studies of the way in which leprosy is transmitted, and of factors associated with susceptibility or immunity to the clinical disease.

Transmission

The often-quoted assertion that leprosy is transmitted by prolonged, intimate skin-to-skin contact has never been tested. This postulated view of the mode of spread was probably largely derived from the obvious cutaneous clinical signs of the disease. That *Myco leprae* can be recovered from several tissues has been known for a number of years, but it is only recently that interest in the nose and nasal secretions as sources of infection has been re-awakened. Thus, Pedley (1970, 1973) has convincingly demonstrated that not only are insignificant numbers of bacilli shed from the intact skin of lepromatous patients (they are shed from broken skin lesions—these, however, are unusual) but that very large numbers are shed from the nose and upper respiratory tract; the acid-fast bacilli concerned have been identified as *Myco. leprae* (Rees and Ridley, 1973). Moreover, it also appears (Barton *et al.*, 1973) that the clinico-pathological changes in the nose are often more advanced than might be expected from the extent and degree of neural and cutaneous involvement.

Together, these findings begin to build up a composite picture for the possible mode of spread of leprosy that has not hitherto been available, at least on the

basis of scientific evidence (Davey and Rees, 1973). For not only do they suggest a source of infection—they also offer a potential explanation for the apparent failure of chemotherapy in overt disease also to assist with the primary prevention of leprosy in endemic areas. The early lepromatous patient, shedding millions of *Myco. leprae* from nasal lesions disproportionately advanced compared with other manifestations of the disease, may perhaps infect as many people in his family and social circle as he can before he is diagnosed; his treatment may by then be largely irrelevant so far as his ability to spread the disease further is concerned. On this basis, the only way in which chemotherapy could prevent as well as cure would be if a high proportion of lepromatous patients, often with little or nothing in the way of skin manifestations, were diagnosed at the early stages of nasal involvement—from a practical viewpoint, a difficult task.

Spread involves not only a source of infection, but also a portal of entry. Here, analogies with tuberculosis may be helpful. Clearly, *Myco. leprae* could be spread by sneezing, coughing, spitting and unhygienic nose-cleaning methods—in many respects, therefore, by way of droplets as in tuberculosis. In this context, therefore, the figures in Table 1, showing great similarities in bacterial loads from the nasal secretions and sputum of patients with lepromatous leprosy and open tuberculosis respectively are of considerable interest. Clearly, the portal of entry could still be the skin, but equally, *Myco. leprae*-laden particles could also be inhaled or swallowed. Table 2 compares attack rates for the two diseases in household contacts; again, the figures are of the same general order, especially in the younger age-group. Clearly, these comparisons prove nothing, but they do suggest, really for the first time, scientific ways of studying leprosy transmission,

TABLE 1

Mean numbers (log_{10}) of viable Myco. leprae. *and* Myco. tuberculosis *in nose-blows or sputum*

Organism and source	No. of observations	Mean (log_{10})
Myco. leprae 24-h nose-blow output	13	6.95
Myco. leprae single nose-blow	17	6.84
Myco. tuberculosis 12-h sputum output	107	7.69

Adapted from Rees and Meade (1974).

TABLE 2

Average annual age and sex-specific attack rates for tuberculosis and leprosy in family contacts, S. India

Age	Male		Female	
	Tuberculosis	Leprosy	Tuberculosis	Leprosy
0-4	4.0	4.4	3.8	5.6
5-14	1.8	7.3	1.6	2.1

Adapted from Rees and Meade (1974).

and they are certainly compatible with a mode of spread for leprosy similar to that of tuberculosis. The openings here for the epidemiologist, either in collaboration with the microbiologist, or at least with awareness of work in this field, are obvious. They should also be enhanced by the results illustrated in Table 3, which indicate the likely length of time that *Myco. leprae* can survive outside the body. Prospective incidence studies of leprosy, necessary to elucidate the "risk factors" associated with the onset of clinical disease (Meade, 1971) should obviously consider information of this sort in planning what variables might usefully be studied, and how they could be measured. Table 3 suggests, for example, that since *Myco. leprae* can probably survive 2 or 3 days outside the body, the lepromatous patient and the person he infects need not be in the same place at the same time; Hausfeld (1970) has described how contacts outside (as well as within) the immediate family circle can be measured in ways that could usefully take account of the distribution of survival times of *Myco. leprae* outside the body.

TABLE 3

Survival of Myco. leprae *in dried nasal secretions*

Exposure to drying (Days)	Viability (infectivity for mice, %)	No. of tests
0	100	3
1.0	100	3
1.75	10	2
3.0	0	2
7.0	0	1
10.0	0	1

Mean temperature: 20.6°C; mean humidity: 43.7%.
Rees, 1973 (personal communication).

End-points; Infection and Clinical Disease

One of the leprosy epidemiologist's problems has always been the definition of "end-points" in relation to the onset and diagnosis of leprosy. The appearance or non-appearance of clinical leprosy as an end-point suffers the disadvantages that, first, diagnosis is often difficult, especially in the early stages, and secondly that the appearance of clinical disease is obviously the final stage in a process of infection and its sequelae that may have been going on for many years. The lepromin skin test may (or may not) be of value in forecasting susceptibility to lepromatous disease, but cannot be interpreted, as the tuberculin test can, as an index of previous infection (or artificial protection). Thus, the development of lymphocyte transformation testing (Godal and Negassi, 1973) is of great potential importance. If this technique is as specific for infection by *Myco leprae* as early results indicate, it offers a means whereby those who have been infected can be identified and also of comparing those infected who do or do not go on to clinical disease. A good deal of work needs to be done before the technique can be accepted as valid, and much of it will have to be in the field, the epidemologist working closely with the immunologist. Apart from specificity for *Myco. leprae*, the reproducibility of the technique needs study; assuming these are satisfactory (and that the method can be adopted for field conditions—a difficult, though

probably not impossible task) information on the proportions in endemic areas with positive tests is crucial. For if virtually the whole of a population shows transformation at very early stages (to take a somewhat extreme example) the discriminatory value of the technique would be limited, since all it would really show is that most people have been infected, and the problem of which individuals succumb to clinical disease and which do not would remain. The finding of more gradual changes in positive responses by age, however, with the consequent identification of distinct infected and uninfected groups, might well make the technique as valuable as tuberculin testing in tuberculosis. The possible effects of "superexposure" (Godal and Negassi, 1973), arising from prolonged exposure to lepromatous disease, in giving false negative lymphocyte transformation results clearly calls for intensive study, also in field surveys.

At the same time, the value of clinical disease, or its absence, should not be overlooked as an end-point. What matters to the individual is not whether he has been infected or not, but whether he has clinical leprosy. There are other examples, such as ischaemic heart disease or lung cancer, where the clinical end-point, rather than the pathological, has had to be used (for obvious reasons) without obscuring epidemiological associations between these diseases and their postulated causes.

Resistance to Sulphones

Finally, the leprosy epidemiologist must play an increasing part in studying the emergence of resistance to sulphones. This development has been known for several years, and was to be expected (again, by analogy with tuberculosis) in a monotherapeutic situation. Whether the sulphone resistance problem will become a major one is difficult to foresee; it turns out that because of the very long time-periods needed for reasonably complete data-collection, it is difficult to say whether intervals from the start of chemotherapy to resistance are falling (as many believe they are) and even more difficult to tell whether the incidence of resistance is increasing, and if so, at what rate. Relative youth at the start of treatment, and treatment with low doses of sulphones are associated with the later emergence of resistance (Rees *et al.*, 1973), and it is almost certain that other associations can be identified by properly designed and conducted studies. The whole crucial problem of sulphone resistance is not one that the clinician, microbiologist, epidemiologist or statistician can solve on his own, and is yet another example of the way leprosy research on any particular issue is increasingly involving several disciplines. The same is true of the clinical trials that are now needed (partly, though not entirely, as a result of the growing concern over the potential implications of sulphone resistance) to assess the clinical and microbiological effects of rifampicin, and the most effective ways of using it in a service context.

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Growing Points in Leprosy Research

(3) Immunological Detection of Sub-clinical Infection in Leprosy

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The evidence for the presence of sub-clinical infection in leprosy, based on information acquired by the lymphocyte transformation test (LTT) and the leucocyte migration inhibition test (LMIT), is reviewed. These methods appear to have sufficient specificity to be useful as monitors of immune responses elicited by *Mycobacterium leprae*. The results obtained suggest that sub-clinical infection commonly follows exposure to *Myco. leprae* and therefore indicate that leprosy is more highly infectious than denoted by prevalence and incidence rates. Some observations imply that the intensity of exposure may modify host responsiveness to *Myco. leprae*.

In most, if not all, infectious diseases, apparently only a proportion of those who become exposed to the germ will develop the disease, while the rest will combat the infectious agent by developing effective immunity before it has time, either directly or indirectly, to cause overt disease. Such individuals are said to pass through the stage of sub-clinical infection. In some infectious diseases, e.g. poliomyelitis and tuberculosis, sub-clinical infection is a common outcome after exposure, while in others, such as smallpox, sub-clinical infection is a very rare event.

The epidemiological understanding of an infectious disease is dependent, to a very large extent, on how precisely the relationship between the infectious agent and each individual of a given population can be determined. At any one time subjects may be classified into either of the following categories:

(A) Not exposed.

(B) Exposed

(1) Non-immune: These individuals are incubating the germ but have not yet mounted an effective immune response.

(2) Immune: Such individuals may or may not harbour the germ. Their characteristic feature is that they have recovered and mounted an effective immune response subsequent to: (a) sub-clinical infection (no history of disease), or (b) clinical infection.

(3) Clinical disease.

The methods available for classification of a subject into either of the above-mentioned categories vary from one disease to the other. In general they are of three kinds:

(A) Detection of the infectious agent. This can be done quite accurately in

diseases where the germ is harboured in an organ easily accessible for microbiological examination, such as the upper respiratory tract in the case of diphtheria. However, often the target organ is inaccessible to direct examination (e.g. lungs in tuberculosis) and the proportion of carriers, therefore, cannot be precisely determined.

(B) Detection of immune response. In diphtheria the presence of an effective (or protective) immune response may be assessed by toxin neutralizing skin reactivity (Schick test). However, in many other diseases, where the immune response to the infectious agent may be monitored, the response may be associated with, but not directly related to, protective immunity. This apparently applies to the tuberculin test in tuberculosis.

(C) When the above methods were lacking or unsatisfactory, attempts have been made to acquire information about the frequency of sub-clinical infection by searching for minor pathological changes in the target organ, e.g. slight alterations in liver function tests indicating sub-clinical hepatitis.

It should be noted that the estimation of the total proportion of a population which has been exposed to an infectious agent is usually dependent on all three categories of tests. Thus, only a proportion of exposed individuals can be detected by any one kind of test alone.

In leprosy also these three diferent types of approach have been applied.

(A) *Detection of leprosy bacilli.* Following the observations of Figueredo and Desai, (1949), Taylor, Elliston and Gideon (1965) searched for acid fast bacilli in the ear lobes of contacts of leprosy patients. They found 7/71 (10%) of the contacts of lepromatous patients and 2/80 (2.5%) of the contacts of tuberculoid patients to be positive for acid fast bacilli, while out of 50 contacts examined in a leprosy non-endemic area none were found to be positive. Although direct evidence that these bacilli were in fact leprosy bacilli still appears to be lacking, "positive" contacts have subsequently been found to have a sixfold increased risk of acquiring leprosy (Chatterjee *et al.*, 1973). This suggests not only that the acid fast bacilli were leprosy bacilli but also that many, if not most, of these "carriers" were in the incubation period of the disease.

(B) *Detection of immune response to* Myco. leprae. Previously the most widely used immunological test for examination of the immune response to *Myco. leprae* was the late (Mitsuda) lepromin test. However, because the test has been found to be positive in individuals not exposed to leprosy (see Rees, 1964) it has been disregarded as a useful test for detection of immune responses elicited by *Myco. leprae.* Moreover, even with the early (Fernandez) reaction, which is read after 48-72 h, positive reactions have been observed in subjects from non-endemic areas (see Rees, 1964, Shepard and Saitz, 1967, Waters, 1973), although strong reactions appear to be much less common among non-contacts, including TB patients, than leprosy contacts (Rotberg, Bechelli and Keil, 1950). With the Fernandez reaction Waters found that only 1 out of 65 tuberculin negative volunteers reacted positively, while approximately 1/3 of the tuberculin positive subjects showed positive reactions. These results indicate that there is a considerable degree of cross-reactivity between *Myco. tuberculosis* and autoclaved *Myco. leprae.* However, Myrvang (1973), who has done lepromin testing on a small number of contacts and non-contacts in Addis Ababa, found non-contacts uniformly negative with the Fernandez reaction, even though many responded strongly to BCG *in vitro.* In contrast, a high proportion (50%) of occupational contacts responded to lepromin by the Fernandez reaction.

(C) *Detection of sub-clinical pathological changes in leprosy.* It has been claimed that a large proportion of contacts have an enlargement of the larger auricular nerve (Karat, personal communication).

From these studies it appears difficult to draw any definite conclusions either because the results are conflicting, as is the case with the lepromin test, or because their relationship to leprosy remains unclear. Thus, there would appear to be a need for new methods to be found for the study of the epidemiology of leprosy.

Recently, methods by which it has become feasible to measure immune responses associated with cell-mediated immunity to *Myco. leprae* have been established *in vitro.* They include the lymphocyte transformation test (LTT) and the leucocyte migration inhibition test (LMIT). I shall now turn to discuss in some detail these tests and observations made in contacts of leprosy patients in order to try to reveal their potential as epidemiological tools in leprosy.

Detection of Cell-mediated Immunity to *Myco. leprae in vitro*

It is now a well-established fact that lymphocytes carry antigen receptors on their surface. When exposed to an antigen which can interact with the receptors, the lymphocyte, being either a T or a B cell, will enlarge and start to divide. This phenomenon is called blastoid transformation or simply lymphocyte transformation. Lymphocyte transformation may be monitored *in vitro* by counting the number of transformed cells morphologically or measuring the associated DNA synthesis by uptake of radioactive thymidine. If the stimulated cell is a B cell the end result will be antibody synthesis and generation of many B cells with the same specificity. If the stimulated cell is a T cell, a more complex pattern and only partly understood chain of events will follow bringing about both cell-mediated immunity and a delayed-type hypersensitivity reaction *in vivo.* One of the early results of T cell stimulation is the liberation of molecular mediators (hereafter called lymphokines). The lymphokines have a number of key functions in the expression of cell-mediated immunity, one being their capacity to stimulate the macrophages to increased antibacterial activity (Godal, Rees and Lamvik, 1971; Fowles *et al.*, 1973). The production and release of these lymphokines can be monitored *in vitro* by various tests, of which their ability to inhibit macrophages from migrating out of a capillary tube is the best established method. In man there is no easy access to macrophages, except for blood monocytes which are present in too small numbers for ordinary capillary tube methods. In search of methods applicable to man, the migration of buffy coat leucocytes (mainly granulocytes) has become utilized. However, the mechanism of this test and the involvement of lymphokines are not yet fully established. Moreover, it has been shown that humoral immune reactions can modify the test. Thus, it is evident that neither LTT nor LMIT is specific for delayed type hypersensitivity reactions. However, both tests have been found in man, in a number of test sytems, to correlate to delayed type hypersensitivity reaction. For more detailed information the reader is referred to recent reviews on the subject (Bloom, 1971; David and David, 1972; WHO, 1973).

The practical conclusions to be drawn from these observations are that neither the LMIT nor the LTT can *a priori* be judged as *in vitro* correlates to delayed type hypersensitivity and cell-mediated immune reactions. The existence of such a relationship has to be established in each individual test system.

Information regarding the relationship between LTT and LMIT delayed

hypersensitivity and host resistance (cell-mediated immunity) is derived, in leprosy, mainly from studies of leprosy patients. It may, therefore, be pertinent to review briefly these studies before discussing the results obtained using these tests in contacts and non-contacts of leprosy patients.

LTT and LMIT in Leprosy Patients

Immune responsiveness to *Myco. leprae* has been studied throughout the clinical and histopathological spectrum of leprosy both by LTT and LMIT (Myrvang *et al.*, 1973). By both these methods, as well as the early and late lepromin reaction, the responses continuously decreased from the polar tuberculoid (TT) group to the polar lepromatous (LL) group. Thus, the overall picture revealed was that these tests are correlated to histological and clinical signs of host resistance. It is most likely that all these phenomena are related to the expression of T cell function to *Myco. leprae* antigens in these patients. On the contrary, B cell functions, as examined by the presence of precipitating antibody to other mycobacteria (*Myco. leprae* is not available in large enough quantities for the test), gradually increased from the TT to the LL end of the spectrum (Myrvang and Feek, 1973).

LTT and LMIT in Healthy Contacts of Leprosy Patients

(a) MEDICAL ATTENDANTS

Out of 122 medical attendants who had been working with leprosy patients, 71 (58%) were found to respond to *Myco. leprae* by LTT $\geqslant$ 2%.* Thirty-six of the 122 medical attendants tested were non-Ethiopian residents working at leprosy institutions in various parts of the world, who had come to ALERT to participate in courses organized there. Twenty out of the 36 (56%) responded positively. Fifty-two individuals belonging to the medical attendant group were examined by LMIT. Thirty-seven (71%) were found to give rise to $\leqslant$ 80% migration in the presence of *Myco. leprae* (Myrvang, 1973)

(b) HOUSEHOLD CONTACTS

Out of 105 subjects living in the same hut or compound as a leprosy patient, 49 (47%) responded by LTT to *Myco. leprae.* The majority were family members of the patient and living in the same straw hut as the patient. Out of these 88 could be sub-divided, according to the diagnosis of the patient, into contacts of tuberculoid or indeterminate patients (29) and lepromatous (BL-LL) patients (59). Out of the 29 tuberculoid contacts, 18 (62%) responded to *Myco. leprae* by LTT, while only 24/59 (41%) of the lepromatous contacts gave a positive response (Godal and Negassi, 1973). Further subdivision of the contacts of lepromatous patients provided suggestive evidence that contacts of treated patients responded better than contacts of untreated patients and that spouses behaved similarly to genetically related contacts. This was a most unexpected observation as obviously untreated lepromatous patients are the most infectious ones.

* It should be noted that this definition of a "responder" deviates from that of our recent publications (Godal, Löfgren and Negassi, 1972; Godal and Negassi, (1973) where the cross-reactivity to *Myco. tuberculosis* was also taken into account (this will be discussed below).

Only 12 household contacts have been examined by LMIT (Myrvang, 1973). Six (50%) gave a positive reaction. The restricted numbers investigated did not allow meaningful subdivision according to the diagnosis of the patient.

LTT and LMIT in Non-contacts

(a) SUBJECTS FROM NON-ENDEMIC AREAS

None of 26 individuals tested within 2 months of their arrival in Addis Ababa responded by LTT and all of 10 similar subjects were negative with LMIT.

(b) SUBJECTS LIVING IN ENDEMIC AREAS WITHOUT ANAMNESTIC EVIDENCE OF CONTACT WITH LEPROSY PATIENTS

Out of 45 subjects who had lived in Ethiopia for more than 1 year, 13 (29%) responded by LTT, while none out of 7 of a similar group gave a positive response by LMIT to *Myco. leprae* (Myrvang, 1973). The LTT group was heterogeneous concerning duration of stay. Thirty-one were expatriates who had lived in Ethiopia between 1 and more than 10 years and 14 were Ethiopian medical personnel (nurses and dressers), most of them were working at the TB centre in Addis Ababa.

On the Specificity of LTT and LMIT

The most striking difference between the results obtained with LMIT and LTT and those obtained previously with the early lepromin reaction, was the uniform lack of response among definite non-contacts, i.e. individuals from non-endemic areas. This would indicate that LTT and LMIT are more specific than the early lepromin reaction. Thus, what is the evidence that LTT and LMIT are specific to *Mycò. leprae vis-à-vis Myco. tuberculosis* (var. *humanus* and BCG)?

(1) The average respone to *Myco leprae* among 12 nurses and dressers at the TB centre in Addis Ababa, who had been working with tuberculosis patients for more than 4 years, was only 3.08% as compared with a response of 21.1% to BCG. Since only two of them had been BCG vaccinated, this finding indicated that the tubercle bacillus only has a limited cross-reactivity with *Myco. leprae* in the LTT (3.08/21.1 = 14.7% cross-reactivity) (Godal, Löfgren and Negassi, 1972). Since these individuals had been living in the endemic area all their lives, it was argued that these figures could show too high values as the subjects could have been exposed to *Myco. leprae* as well.

(2) A group of 8 subjects, who showed initially a low response to BCG (1.08% mean) and to *Myco. leprae* (0.34%), was vaccinated with BCG. This was followed by a rapid increase to a maximum of 9.16% one month after vaccination, while the response to *Myco. leprae* remained low, showing a maximal response of 1.28% also one month after vaccination.

(3) In a study undertaken in Norway the response to *Myco. leprae* was studied in BCG vaccinated subjects (Closs, 1973). The responses to *Myco. leprae* were found to be related to the tuberculin reactivity of the subject and the mean cross-reactivity to *Myco. leprae* as compared to BCG was 27%. However, the study is not strictly comparable to our studies in Addis Ababa as a micro-LTT method was used.

All these observations indicate that there is a high degree of specificity to

Myco. leprae v. *Myco. tuberculosis* in the LTT. However, the studies of Closs, in particular seem to indicate that responses to *Myco. tuberculosis* may influence the responses to *Myco. leprae* and that the level of cross-reactivity may vary according to technique used. The influence of threshold level selected for cross-reactivity between *Myco. tuberculosis* and *Myco. leprae* on the proportion of responders in various groups is shown in Table 1. By increasing the threshold of cross-reactivity from 0 to 50%, the proportion of response to *Myco. leprae* falls from 29 to 2% while more than 30% of contacts remain responsive even at a 50% level. This is in spite of the fact that the non-contact group had a higher mean response to BCG than both the contact groups.

Another question is whether other mycobacteria in the environment in Addis Ababa include a mycobacterium with a much higher cross-reactivity to *Myco. leprae.* This seems unlikely for the following two reasons.

(1) The proportion of LTT responders among staff in Ethiopia (60%) is virtually the same as the proportion of responders among occupational contacts from outside Ethiopia (56%).
(2) A striking difference in responders to *Myco. leprae* between Ethiopian staff at ALERT has been found between those who are working with patients as compared to administration staff (Godal and Negassi, 1973).

The LMIT has only been studied in a more limited number of subjects. However, there appears to be no correlation in any group between responses to *Myco. leprae* and BCG. Thus, the LMIT might turn out to have even a higher degree of specificity than LTT (Myrvang, 1973).

These findings suggest that both LTT and LMIT appear to have sufficient specificity to become promising tools in epidemiological studies of leprosy. However, the specificity of the tests needs careful attention in each case. It might perhaps be improved by using sub-optimal concentrations of *Myco. leprae* and more purified antigenic preparations, as there is evidence that a more purified antigen increases the specificity of the Fernandez reaction (Dharmendra, 1948).

Although our observations at present do not allow any detailed analysis between the *in vitro* tests and the Fernandez reaction, the results suggest a higher specificity in the *in vitro* tests. One factor which may explain this difference is that fresh *Myco. leprae* is used in LTT and LMIT. Thus, it is possible that denaturation by autoclavation may make the antigens of *Myco. leprae* less specific in the Fernandez reaction.

Epidemiological Implications

The results obtained with LTT and LMIT have provided a considerable amount of new evidence that sub-clinical infection occurs frequently in leprosy; in fact it appears to be the most common outcome after exposure. This concept is not new as a similar conclusion has been reached by the common observation that only a few of those who live together with a high infectious patient will acquire the disease (see Skinsnes, 1964). Our observations suggest that such individuals are not resistant, but develop resistance subsequent to infection.

It appears that leprosy is more contageous than indicated by the prevalence and incidence rates. However, the degree of infectiousness cannot be precisely determined for two reasons. Firstly, as outlined above, immunological methods will only detect a proportion of the exposed part of any population. Secondly, the interpretation of our results will depend on threshold level for cross-reactivity

TABLE 1

The influence of various threshold levels of cross-reactivity between Myco. leprae *and BCG on per cent responders by lymphocyte transformation among contacts and non-contacts of leprosy patients*

Threshold level of cross-reactivity (*Myco. leprae*/BCG x 100)	% responders to *Myco. leprae* (≥ 2%)				% responders to BCG (≥ 2%)	Mean responses to BCG (% transformation)
	0%	15%	30%	50%		
Non-contacts from non-endemic areas	0	0	0	0	53	3.59
Non-contacts living in endemic areas ≥ 1 year	29	24	9	2	78	13.80
Occupational contacts	58	53	38	31	84	11.57
Household contacts	47	44	39	35	73	8.40

to *Myco. tuberculosis.* If 15% is chosen, our data would indicate that a considerable proportion of individuals would become exposed without their knowledge when living in endemic areas. While if a threshold of 50% is chosen, only very few non-contacts living in an endemic area remain as responders. However, a considerable proportion of contacts would still be classified as "exposed".

In fact, since the LTT appeared in our hands to be quite specific to *Myco. leprae,* the cross-reactivity being in the order of 15% or less, I would favour the interpretations based on a 15% cross-reactivity level. Further support for this high degree of infectivity in leprosy may be found in the observation that only a small proportion of individuals know their source of infection (Badger, 1964) and the observations that patients with active lepromatous leprosy shed as many bacilli from the upper respiratory tract as an open case of tuberculosis (Davey and Rees, 1973). These observations may sound very alarming to medical personnel concerned with leprosy. However, it must be stressed that these observations do not change the fact that in any case only a very small proportion of medical attendants develop the disease.

The high proportion of response found among contacts of tuberculoid patients may be interpreted in two ways:

(1) Tuberculoid patients are infectious;
(2) Both the tuberculoid patient and the contact may have been exposed to an unknown lepromatous patient in the community.

Although the second explanation would seem more likely than the first one, our observations do not permit distinction between these two possibilities.

The low proportion of response found among contacts of active lepromatous patients was unexpected and would appear paradoxical. However, there have been similar findings with lepromin which showed that children who had close contacts with lepromatous patients had negative lepromin tests more often than children who had not had such contact (see Dharmendra, 1948). These findings raise several questions concerning risk factors in leprosy, other than exposure alone, as contributing factors in the susceptibility to leprosy, namely:

(1) Role of genetic factors.
(2) Intensity and nature of exposure: (a) initial dose, (b) duration of exposure, (c) route.
(3) Nutritional status of host.
(4) Age.

Recent genetic studies on twins suggests that genetic factors, although possibly contributing, do not play a decisive role in leprosy (Chakravartti and Vogel, 1973). Since spouses of lepromatous patients also responded poorly, genetic factors alone would not appear to explain our observations (Godal and Negassi, 1973).

Since our observations may indicate that contacts tend to recover when the patient is put on treatment, their suppressed response may be related to intensity of exposure, perhaps in combination with other suppressive factors on the immune system such as malnutrition.

These possibilities are at present hypothetical and can only be rejected or supported by further studies, not only in man but perhaps in experimental animals where the conditions can be much more precisely regulated to give specific answers in this very complex field.

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Growing Points in Leprosy Research

(4) Recent Advances in the Chemotherapy of Leprosy

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Recent advances in the chemotherapy of human and experimental leprosy are reviewed. These advances are begining to place the treatment of leprosy on an objective bacteriological and pharmacological basis. The relevance of these recent studies to designing more effective and more conveniently administered regimens for the successful treatment of lepromatous leprosy is discussed.

Introduction

Several recent reviews provide excellent testimony to the decisive contribution made during the past decade by the mouse footpad model to advances in the treatment of leprosy (Shepard, 1969*a*, Rees and Weddell, 1970; Rees, 1971; Shepard, 1971*a*, *b*; Pattyn, 1972; Rees and Waters, 1972; Rees, 1973). It has provided methods for assessing the efficacy of established drugs and of successfully screening new compounds for potential use in the treatment of human leprosy. Through its use the chemotherapy of leprosy is at last beginning to be placed on an objective bacteriological and pharmacological basis.

For an anti-leprosy drug to be effective in man, well tolerated doses must produce concentrations in the body that at least temporarily exceed its minimal inhibitory concentration against *Myco. leprae*. The administration of each successive effective dose to a patient results in some viable drug-sensitive leprosy bacilli ceasing to multiply and in others being killed. The relative importance of these two effects depends on whether the drug is primarily bacteriostatic or bactericidal. The cell-mediated defence mechanisms of the body can also kill leprosy bacilli, although their ability in this respect decreases progressively as one moves from the tuberculoid to the lepromatous end of the clinical spectrum of leprosy. As effective treatment is continued the proportion of viable *Myco. leprae* steadily falls. In lepromatous patients this proportion can be estimated by inoculation into normal mice, inocula containing as few as 0.1% viable bacilli being infectious. By employing the mouse as an *in vivo* culture system to detect viable *Myco. leprae*, reductions of up to 99% can be measured in the numbers of viable bacilli in lepromatous patients. However this end-point may still be equivalent to as many as 10^7 viable *Myco. leprae* and if treatment were terminated at this point relapse would almost certainly occur. Non-viable leprosy bacilli gradually become morphologically degenerate so that the bacterial killing can be monitored indirectly by determining the rate of fall of the morphological index. Although such a procedure is relatively simple to carry out and gives

immediate results, it is only about a tenth as sensitive as the mouse inoculation method. Furthermore, by its very nature, it necessarily underestimates both the absolute and relative rates of killing of *Myco. leprae* by actively bactericidal drugs. The acid-fast fragments of morphologically degenerate *Myco. leprae* are then slowly removed, a process followed by measuring the rate of fall of the bacterial index. Although such a measure may be fundamentally correlated with the remission of the lepromatous patient's histological and clinical symptoms, it is inherently incapable of distinguishing between the relative efficacies of different antileprosy drugs.

Significant numbers of naturally drug-resistant leprosy bacilli are however to be expected among the large bacterial populations harboured by patients with untreated lepromatous leprosy. In these patients the number of viable *Myco. leprae* may total 10^{10}-10^{11}. In tuberculosis the proportion of naturally resistant bacilli can vary from about 1 in 10^6 to 1 in 10^8 according to the drug studied. When only a single drug is given the drug-resistant leprosy bacilli may ultimately multiply to such an extent that the patient relapses and inocula may once more become capable of infecting mice. Their multiplication in the mouse will however only be prevented, if at all, by giving much higher dietary concentrations of the drug than are required to suppress the growth of strains of *Myco. leprae* derived from untreated patients.

Treatment of Leprosy

DAPSONE

Feeding 0.0001% dapsone (DDS) in the diet to mice results in continuous plasma concentrations of about 0.01 μg/ml and completely inhibits the multiplication of strains of *Myco. leprae* from untreated patients. Since multiplication was not inhibited when the dose was lowered to 0.00001% it was estimated that the minimal inhibitory concentration of dapsone against *Myco. leprae* was between 0.0001 and 0.01 μg/ml (Shepard, McRae and Habas, 1966; Rees, 1967*a*, *b*; Shepard, 1967*a*; Shepard, Tolentino and McRae, 1968; Ellard *et al.*, 1971; Ozawa, Shepard and Karat, 1971). The minimal inhibitory concentration of dapsone against one strain of *Myco. leprae.* has been determined with greater precision in Lewis rats and shown to lie between 0.0015 and 0.004 μg/ml (Peters *et al.*, 1972*b*). Kinetic studies in the mouse have consistently demonstrated the ability of dapsone to cause significant growth delays, but the results have been interpreted by some as due to the induction of prolonged bacteriostasis and by others as the result of limited bacterial killing (Shepard, 1967*a*, *b*; 1969*b*; Holmes, 1972; Holmes and Hilson, 1972; Levy, 1972). However the ability of doses of 0.01% dapsone given once-weekly or 0.1% given every 14 days in preventing the multiplication of *Myco. leprae* (Rees cited Shepard, 1967*a*; Pattyn and Saerens 1974), despite its rapid elimination in the mouse (Ellard *et al.*, 1971; Ozawa, Shepard and Karat, 1971; Levy *et al.*, 1972*a*), strongly suggests that dapsone is capable of inducing prolonged bacteriostasis in *Myco. leprae.*

Previous colorimetric methods for the determination of dapsone based on reaction with *p*-dimethylamino-benzaldehyde or on diazotisation followed by coupling with *N*-1-naphthyl-ethylene-diamine, were too insensitive and unspecific to determine accurately its plasma concentrations. Highly specific fluorimetric methods have however been recently developed that are capable of measuring plasma dapsone concentrations of down to 0.01 μg/ml (Glazko *et al.*, 1968; Ellard and Gammon, 1969; Peters, Gordon and Colwell, 1970) or even to 0.001 μg/ml

(Murray, Gordon and Peters, 1971). A gas-chromatographic procedure has also been described for dapsone (Burchfield *et al.*, 1973), while a simple urine-test method has been developed which has revealed the potential seriousness of irregular self-adminstration of the drug by out-patients (Ellard, Gammon and Harris, 1974; Ellard *et al.*, 1974*b*).

Dapsone is rapidly and completely adsorbed in man. The only metabolite demonstrated so far in the plasma is monoacetyl-dapsone (MADDS) and slow or rapid acetylators of dapsone can be distinguished according to the ratios of acetylated to free drug found in the plasma (Gelber *et al.*, 1971; Peters *et al.*, 1972*a*; Ellard *et al.*, 1974*c*). It has not however been possible to establish whether this metabolite has intrinsic anti-leprosy activity because it is rapidly and completely deacetylated in the mouse (Levy *et al.*, 1972*a*). Dapsone is eliminated relatively slowly in man. The dapsone half-lives of patients can differ significantly (range 14-53 h), but are not related to their acetylator phenotype (Peters *et al.*, 1972*a*; Gelber and Rees, 1973; Ellard, Gammon and Harris, 1974).

The treatment of lepromatous patients with doses of dapsone ranging from as little as 1 mg a day to 300 mg twice a week results in the proportion of viable leprosy bacilli falling to less than 1% of the initial value over a period of about 3 months and in morphological indices falling to baseline values within 4½-6 months (Waters and Pettit, 1965; Pettit and Rees, 1967; Shepard, Tolentino and McRae, 1968; Pearson and Pettit, 1969; Ellard *et al.*, 1971).

Small numbers of viable *Myco. leprae* do however persist, often in preferred sites such as peripheral nerve or striated muscle (Pearson, Rees and Weddell, 1970), despite many years of continuous dapsone treatment (Waters *et al.*, 1973). Since these persisting bacilli may retain their sensitivity to dapsone (Waters *et al.*, 1973), and since experimental studies in the mouse, rat, dog and sheep have demonstrated that dapsone readily penetrates these and other tissues (Francis, 1953; Shepard and Chang, 1964; Peters, 1973; Weddell *et al.*, 1974), it is probable that these bacilli had remained dormant throughout the treatment period. Perhaps the sites in which they were situated had protected them from the extremely limited cell-mediated defence mechanisms displayed against *Myco. leprae* by lepromatous patients. These findings readily explain why lepromatous patients must be treated for so many years if permanent cures are to be achieved.

Relapses due to the appearance of dapsone-resistant leprosy bacilli were first demonstrated in Malaya some 10 years ago (Pettit and Rees, 1964). Other dapsone-resistant strains of *Myco. leprae* have since been isolated from relapsed lepromatous patients from many different parts of the world (Pettit, Rees and Ridley, 1966, Rees, 1967*a, b*; Shepard, Levy and Fasal, 1969). During the past 10 years some 2.5% of the lepromatous patients who began treatment with dapsone in Malaya from 1949 to 1963 have relapsed with proven dapsone-resistant leprosy after from 6 to 26 years of treatment (Meade *et al.*, 1973). Pharmacological studies indicate that among these patients relapse with dapsone-resistant *Myco. leprae* was not associated with either the rate of acetylation of dapsone or its elimination from the body (Ellard *et al.*, 1972; Gelber and Rees, 1973).

ACEDAPSONE

The demonstration that two-monthly injections of 6 mg/kg acedapsone (*N,N'*-diacetyl-dapsone, DADDS), a slow-release form of dapsone, suppressed the multiplication of *Myco. leprae* in the mouse (Shepard, 1967*a*) led to its evaluation for the treatment of human leprosy. Doses (225 mg) of acedapsone given

intramuscularly once every 11 weeks enable dapsone plasma concentrations of between about 0.03-0.06 μg/ml to be maintained (Glazko *et al.*, 1968; Ozawa, Shepard and Karat, 1971; Russell *et al.*, 1973), and are therapeutically effective although the initial rate of fall in the number of viable *Myco. leprae* is rather slower than when 50 mg dapsone is given daily (Shepard, Levy and Fasal, 1968, 1972*a*).

LONG-ACTING SULPHONAMIDES

These compounds are only weakly active against *Myco. leprae* (Ellard, Gammon and Rees, 1970), and are inactive against dapsone-resistant strains (Adams and Waters, 1966; Rees, 1967*a*; Pattyn *et al.*, 1972). Since they are considerably more expensive than dapsone their continued use in the treatment of leprosy appears unjustified.

RIFAMPICIN

The sensitivity of *Myco. leprae* to rifampicin was first demonstrated in the mouse by Rees, Pearson and Waters, (1970), its minimal inhibitory concentration being about 0.3 μg/ml (Holmes and Hilson, 1972). Subsequent kinetic studies revealed rifampicin's powerful bactericidal activity, infections apparently being sterilized by feeding 0.01% of the drug for 30 days (Holmes, 1972; Holmes and Hilson, 1972), 0.03% for 2 days (Shepard *et al.*, 1971), by giving 2 doses of 25 mg/kg separated by 70 days or a single 40 mg/kg dose (Shepard, Levy and Fasal, 1972*b*, *c*). In lepromatous patients the bactericidal activity of 600 mg rifampicin daily was equally impressive. Morphological indices fell to base-line values within 4 weeks (Rees, Pearson and Waters, 1970)and after only 3-7 days treatment viable bacilli could no longer be recovered (Shepard, Levy and Fasal, 1972*b*, *c*). Similar results were obtained when a single dose of 1500 mg rifampicin was given (Levy, Shepard and Fasal, 1973). Rifampicin is excellently absorbed in man, and its pharmacology has recently been studied using extremely sensitive microbiological methods (Dickinson *et al.*, 1974).

CLOFAZIMINE

Although the multiplication of *Myco. leprae* is prevented by feeding mice 0.0001% clofazimine (Shepard, 1969*c*), its minimal inhibitory concentration cannot be estimated because of the marked accumulation of the drug by reticulo-endothelial cells (Barry, 1969). In man the therapeutic response obtained with daily doses of 200-300 mg clofazimine is similar to that achieved with dapsone (Pettit and Rees, 1966; Pettit, Rees and Ridley, 1967; Levy, Shepard and Fasal, 1972*b*). Clofazimine also aids the control of *erythema nodosum leprosum* (Browne, 1965; Helmy, Pearson and Waters, 1972), although many light-skinned patients find the marked skin pigmentation caused by prolonged treatment unacceptable. Intermittent clofazimine treatment is highly successful in mice (Shepard *et al.*, 1971; Banerjee and Hilson, 1973), but results in man have been disappointing (U.S. Leprosy Panel/Leonard Wood Memorial, 1972). Its pharmacology in both mouse and man appears complex (Banerjee *et al.*, 1974; Levy, 1974).

THIAMBUTOSINE–OTHER DIPHENYL THIOUREAS–THIACETAZONE

Thiambutosine (Ciba 1906; *p*-butoxy-*p'*-dimethylamino-diphenyl-thiourea), thiocarlide (Isoxyl; *p,p'*-diisoamyloxy-diphenyl-thiourea), a number of other

diphenylthioureas and thiacetazone have all been shown to prevent the multiplication of *Myco. leprae* in the mouse, although their minimal inhibitory concentrations have yet to be determined (Pattyn and Royackers, 1965; Rees, 1965, 1967*b*; Gaugas, 1967; Shepard, 1967*b*; Hilson, Banerjee and Holmes, 1971; Pattyn and Wagner, 1972). These drugs are well tolerated in man, and showed initial promise in the treatment of human leprosy, but after 2-4 years' treatment relapses occurred due to the appearance of drug resistant *Myco. leprae* (Lowe, 1954; Davey, 1958, 1960; Quyen, Buu-Hoi and Xuong, 1960; Griffiths, 1965; Leading Article, 1965; Rees, 1965; Garrod and Ellard, 1968; East African/British Medical Research Council, 1970; Miller *et al.*, 1970). Cross-resistance is shown to these drugs by both *Myco. leprae* and *Myco. tuberculosis* suggesting they have a common mode of action (Rees, 1967*a*, *b*). Studies against *Myco. tuberculosis* indicate that they are likely to be purely bacteriostatic (Dickinson and Mitchison, 1966*a*, *b*). Specific chemical methods have yet to be developed to enable the plasma concentrations of the diphenyl thioureas to be determined. Pharmacological studies indicate that thiacetazone is well absorbed in man (Ellard *et al.*, 1 1974*a*), but both thiambutosine and thiocarlide are poorly absorbed (Ellard and Naylor, 1961; Emerson and Nicholson, 1965).

ETHIONAMIDE

This drug displays significant bactericidal activity against *Myco. leprae* in the mouse but is unfortunately not well tolerated in man (Fox *et al.*, 1969; Shepard, 1969*b*, *c*, 1972; Rollier and Rollier, 1972). More sensitive analytical methods are needed to enable its minimal inhibitory concentration against *Myco. leprae* to be determined.

Discussion

Regimens, if they are to be of a widespread use in the treatment of leprosy, need to be highly effective, cheap, easily administered and of low toxicity. The accepted practice of treating patients with tuberculoid and borderline leprosy with dapsone alone is convenient and successful. However in lepromatous patients, with large populations of leprosy bacilli and poor immunological response, there is a strong case for commencing treatment with combined chemotherapy in the hope of preventing subsequent relapse through the appearance of drug-resistant *Myco. leprae* (Rees, 1973). Obviously one of the drugs given must be dapsone. The recommended oral dose is 50-100 mg daily, since lower doses are no less toxic (Pearson and Pettit, 1969; Shepard, Levy and Fasal, 1972*a*; Pearson and Helmy, 1973; Russel *et al.*, 1973) and may encourage the growth of dapsone-resistant mutants of *Myco. leprae*. If at all possible these daily dapsone doses should be given under strict supervision since experience with other diseases demonstrates how irregular self-medication can be (Fox, 1962, 1968, 1972). An alternative treatment procedure, which might be of considerable value in urban situations, would be to give out-patients weekly supervised doses of 300 mg dapsone orally. If regularly taken such doses should maintain continuously inhibitory dapsone concentrations, and all multiplication of dapsone-sensitive *Myco. leprae* would probably be prevented even if the occasional dose were missed. Once and twice-weekly treatment schedules have been successfully used for tuberculosis patients in the Third World (Fox, 1968, 1971, 1972).

The companion drug of choice is rifampicin. However in view of its extremely

high cost the amount of rifampicin treatment that can be given is very limited. The results already obtained nevertheless indicate that as few as 3-7 daily doses of 600 mg rifampicin or even a single dose of 1500 mg rifampicin can reduce the number of viable *Myco. leprae* in lepromatous patients to less than 1% of their original total (Shepard, Levy and Fasal, 1972*b*, *c*; Levy, Shepard and Fasal, 1973).

Unfortunately the mouse footpad inoculation method is incapable of detecting the lethal action of further rifampicin doses so that their immediate benefit cannot be evaluated. However since studies with *Myco. tuberculosis* indicate that rifampicin only kills growing bacilli (Dickinson, Jackett and Mitchison, 1972), and since the great majority of such bacilli are probably killed by the first few doses of rifampicin, it would appear that continuing rifampicin treatment for more than a few weeks would be unlikely to justify the cost incurred. Thiambutosine at a dose of 1500 mg daily might also be employed as a companion drug for dapsone, but it would not be expected to aid the killing of *Myco. leprae* substantially. For the treatment of patients with proven dapsone-resistant strains of *Myco. leprae* combinations of rifampicin, thiambutosine or clofazimine are recommended.

When treatment has been continued to the stage that only the occasional viable leprosy bacillus can be detected, oral dapsone therapy might be conveniently replaced by intramuscular injections of 225 mg acedapsone given once every 3 months and continued until all signs of active leprosy have disappeared and a permanent cure seemed to have been achieved.

The knowledge gained from recent controlled clinical trials and experimental studies in the mouse should be of considerable assistance in designing regimens that are less likely to fail through the appearance of dapsone-resistant strains of *Myco. leprae*. Whether rifampicin will be more effective than dapsone in eliminating persisting leprosy bacilli remains to be established. If it were at all active in this respect it might significantly reduce the numbers of years treatment required to achieve the permanent cure of lepromatous patients. Ultimately however, despite the immense difficulties involved, the success of this and of any other new treatment procedure must be established by means of controlled clinical trials of many years duration and involving many patients.

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Reports of Committees

Committee 1: Advances in Experimental Leprosy

Members: R. J. W. Rees *(Chairman)*; C. H. Binford; J. Convit; W. F. Kirchheimer; Y. Matsuo *(By correspondence)*; S. R. Pattyn; G. Munoz; Rivas *(By correspondence)*; C. C. Shepard; E. E. Storrs; A. G. M. Weddell.

1. INTRODUCTION

This report covers the five years since the last International Leprosy Congress. However, before reviewing these advances and their relevance to leprosy in man, it is necessary to consider, on the one hand, the contributions made from studies on experimental models in the successful fight against other infectious diseases and, on the other hand, the particular difficulties in developing any experimental models for studying leprosy. In no field of medicine has greater progress been made than with the infectious diseases, particularly those caused by bacteria but also some viruses. This progress in knowledge, whether on the microbiological, pathological, preventive or therapeutic side, has evolved, in the first instance, from studies on the cultivation and *in vitro* properties of the causative organisms and only subsequently on experimental animal models. Unfortunately, leprosy has remained an exception, because *Mycobacterium leprae* has still not been cultured *in vitro* and only since 1960 has an animal model been available. Therefore, once animal models were available for studying leprosy it was reasonable to assume that they would also be applicable to leprosy in man. In the first instance, the mouse footpad infection was systematically exploited and has enabled the same topics to be studied in leprosy as in other bacterial diseases affecting man. However, the mouse model had also to be adapted for studying the bacteriological characteristics of *Myco. leprae,* which for other bacteria are studied *in vitro*.

From these general and particular considerations the field of experimental leprosy has been developed and has rapidly advanced, all within the last 13 years, almost entirely based on animal models using the mouse and more recently, the rat and the nine-banded armadillo. Our report summarises the relevance, importance and suitability of these animal models in contributing to knowledge of leprosy in man.

2. ANIMAL MODELS

2.1. Mouse. Shepard in 1960 presented unequivocal evidence that infections with *Myco. leprae* could be transmitted to animals by showing that *Myco. leprae* multiplied locally when inoculated into the footpads of mice. This claim has been

fully substantiated on hundreds of strains of *Myco. leprae* in laboratories throughout the world. By applying standardized techniques the footpad infection has provided a sensitive and reproducible *in vivo* model for bacteriological studies on *Myco. leprae.* However, bacterial multiplication in the footpad is limited to increases of 100-fold and confined to the first 6-8 months following inoculation. Although *Myco. leprae* infections in other rodents, including rat and hamster, are similar to the mouse, practical reasons favour the mouse as the standard model.

In 1966 Rees introduced the immunologically suppressed mouse model on the assumption that multiplication was limited in the normal mouse by the development of immunity to *Myco. leprae* infection. Pure-line strains of mice are used (mainly CBA) and made immunologically deficient by adolescent thymectomy (T) followed by total body irradiation (900R), requiring syngeneic bone marrow replacement. In T/900R mice *Myco. leprae* continue to multiply beyond the 6-months period, giving eventual yields of bacilli 10-1000-fold higher than in normal mice. These observations in mice have been confirmed in other laboratories. To simplify the T/900R procedure, lead shielding of a limb, or T followed by 5 fortnightly exposures to 200R, has been used successfully. Both modifications avoid bone-marrow replacement and permit the use of outbred mice.

Thus two distinct mouse models were developed initially for bacteriological studies of *Myco. leprae.* Subsequently the models were exploited to study the evolution and pathogenesis of experimental leprosy throughout the animals' life-span (2-3 years), following inoculation of *Myco. leprae* locally into the footpad or ear, intraperitoneally or intravenously and, in limited experiments, animals exposed to aerosols or nasal drops.

2.2. Rat. Footpad infection with *Myco. leprae* in the intact rat is similar to the one in the mouse. In the neonatally thymectomized Lewis rat, however, the bacillary population reached levels 100-fold higher than in the intact animal. Following intravenous inoculation, spread to peripheral sites (footpad, ear, tail and nose) occurs. The advantage of these immunologically impaired animals is that they do not develop runting disease. Subtotal body irradiation appears to further depress their immunological capacity.

2.3. Armadillo. The nine-banded armadillo (*Dasypus novemcinctus,* Linn.), a primitive mammal, possesses some unique biological characteristics, which could make it a valuable animal model for leprosy research. Among the biological features particularly relevant to leprosy are: (a) low body temperature (32-35); (b) long life-span (12-15 years) and regular production of litters of monozygous quadruplets.

Kirchheimer and Storrs reported disseminated infection with *Myco. leprae* in an armadillo in 1971. Further results in the short period available have shown at autopsy that about a third of dermally inoculated armadillos become systematically and heavily infected before 37 months, In these animals the histology was of the human lepromatous type, including nerve involvement. In the other inoculated animals there was no evidence of infection, including some observed up to 42 months. In addition the two intravenously inoculated armadillos have developed disseminated infection within 30 months.

The evidence for the identification of the organism grown in the armadillo as *Myco. leprae* is based on: (1) Mouse footpad inoculation; (2) Failure to grow *in vitro*; (3) Lepromin testing; (4) Dopa-oxidase activity; (5) Pyridine extraction; (6) Histological picture and (7) Immuno-diffusion test.

3. CHARACTERISTICS AND CLINICAL IMPLICATIONS OF ANIMAL MODELS FOR RESEARCH IN LEPROSY

The main work and advances have come from the mouse models because they were first to be developed.

Unless otherwise stated, the succeeding report is based on the mouse model.

3.1. Bacteriological characteristics. The growth pattern and rate of multiplication of *Myco. leprae* (mean generation time 13 days) in the mouse footpad of normal and T/900R mice is completely reproducible for all primary isolates of bacilli from leprosy patients including drug resistant strains, or after serial passage in mice. These characteristics now form a basis for the identification of *Myco. leprae.*

Important recent applications of these criteria are:

(a) Monitoring the viability of *Myco. leprae* used to inoculate other animals and the identification of the acid-fast organism subsequently recovered.

(b) Identification as *Myco. leprae* of acid-fast bacilli in nasal discharges and their survival up to 1.75 days in discharges allowed to dry outside the body.

(c) Identification of *Myco. leprae* in various arthropods fed on leprosy patients or recovered from arthropods in the vicinity of cases with untreated leprosy.

(d) Monitoring *in vitro* attempts to cultivate *Myco. leprae.*

Until *Myco. leprae* are cultured *in vitro,* the only, but relatively small, laboratory source of *Myco leprae* has been from mice. Susceptible armadillos can now provide large yields of bacilli which will be of the greatest importance for future studies on *Myco. leprae.*

3.2. Clinical implications. Although there are small variations in the growth pattern of leprosy bacilli in mice, the same variations are seen in bacilli obtained from bacilliferous patients in different parts of the world. There is no evidence from these obervations that the geographical variation in the clinical form of leprosy is caused by variations in the virulence of different strains of *Myco. leprae.*

3.3. Chemotherapeutic applications. Very great advances have been made in chemotherapy entirely based on the mouse models and which are reported in detail by the Committee on Experimental Chemotherapy. However, it is important to make clear that drug-resistant variants (to dapsone and thiambutosine) have the same infectivity and pathogenicity in the mouse as sensitive strains. All studies on the significance and incidence of drug resistance in leprosy should be based on tests using the mouse footpad model. On the other hand, basic studies on the frequency of drug resistant mutants in populations of *Myco. leprae* could only be studied in highly susceptible animals with bacillary populations comparable to those found in man. The susceptible armadillo is the animal model most likely to provide this important information.

3.4. Pathological characteristics. A detailed picture of the pathology and pathogenesis of *Myco. leprae* infections in the mouse models has evolved from histological studies of tissues taken at regular intervals throughout the life-span of the animals (based on CBA mice). To correlate the histology with the bacteriology during the evolution of the infections, paired organs or tissues divided equally were used for the respective assessments.

The main findings are summarized:

(a) Although a lesion is first localized to the site of inoculation, systemic spread eventually occurs, with overwhelming evidence that it is haematogenous in origin,

since bacilli are found in the lining cells of capillaries haphazardly throughout the body. There are, however, sites of predilection, including the dermis of footpads, ears and tail, the nose, the testes and dermal and peripheral nerves. Although nerves become infected later than the other sites they are always involved by 20 months. The nose and testes are the sites most frequently and heavily infected. These same sites of predilection follow intravenous or intraperitoneal inoculation of *Myco. leprae.*

(b) The late cellular and bacterological patterns of response to *Myco. leprae* mimic those seen in human leprosy as defined by the Ridley-Jopling classifications. Thus by 20 months in the normal mouse, there is a well-developed epithelioid granuloma resembling BB to BT type leprosy and in T/900R mice the lesions resemble BB to LL type leprosy. Cellular changes in nerves mimic the complete spectrum of human disease from TT to LL.

(c) Nasal involvement, particularly in T/900R mice, is associated with positive nasal smears and histologically shows, unlike the dermis, the juxtaposition of the granuloma to the surface epithelium giving exit of bacilli to the exterior.

(d) Histological studies on immunological models have shown that established lepromatoid leprosy in T/900R mice changes to a BB or BT picture when the mice are given syngeneic lymphnode cells or thymus grafts. These changes are associated with an influx of lymphocytes into the lesions, destruction of bacilli, oedema and later collagen deposition. Similar changes are seen in nerves and are followed by destruction of axons.

(e) *Myco. leprae* has the same predilection for nerves in the mouse as in man, a characteristic shared by no other species of mycobacterium. Early nerve infections show bacilli in Schwann and perineural cells, later axons and perineural cells are destroyed and at both sites this is followed by deposition of collagen. Special studies have shown that leprosy neuritis in mice is associated with a defect in the blood-nerve barrier, since markers, such as trypan blue and ferritin, readily diffuse through the endoneural capillaries. This defect plus the destruction of the perineural sheath would seriously change the endoneural environment, thus diminishing nerve conductivity and also allowing the entry of macrophages and lymphocytes.

(f) In all the mouse models striated muscle fibres were frequently seen to contain bacilli. In human leprosy although smooth muscle such as arrector pili and dartos are frequently infected, striated muscle is less so.

Preliminary histological studies in susceptible armadillos also show the importance of haematogenous spread, including infection of nerves, nose with positive nasal discharges and most other sites common to man and mouse. In the armadillo the cellular picture at autopsy resembles LL type leprosy. However, in the armadillo, atypical sites, including the lung, are heavily infected, possibly because of lower body temperatures.

3.5. Clinical implications. The significance of these models for studying clinical leprosy is that they reproduce, or can be adapted to reproduce, many of the features of leprosy in man. They particularly provide models for studying early phases of the evolution and pathogenesis of leprosy that can never be undertaken in man. These features are of particular importance for studying the pathogenesis of leprosy neuritis and possible routes of infection via the lungs, nose or gastro-intestinal tract. Mice provide precise models for unravelling the immunological complexities of leprosy, bearing in mind that the majority of patients with leprosy are in the TT to BB range and these are the types of leprosy seen in

normal mice. The armadillo, on the other hand, may in addition provide models for studying innate susceptibility and resistance and their possible genetic bases.

4. CONCLUSIONS

The report summarizes the considerable advances that have been made in experimental leprosy using animal models in a period of only 13 years. Thus, animal models are proving to be as valuable in leprosy as they have been for studying other human infections. The particular merits of the various animal models available for studying leprosy are discussed.

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Committee 2: Advances in the Microbiology of *Myco. leprae*

Members: Y. Yoshie *(Chairman)*; W. L. Barksdale; P. Draper; E. Freerksen; J. H. Hanks; N. E. Morrison; M. Nakamura; F. F. Wilkinson *(By correspondence)*.

This report has been prepared by members of the Committee on Microbiology.

The report summarizes the progress made in the field of general microbiology of *Myco. leprae* during the past 5 year period since the 9th International Leprosy Congress in London in 1968. *Myco. lepraemurium* has been included in the review as an interim model for *Myco. leprae*. Progress has been made in four areas: cytology; metabolism; cultivation; and the identification of *Myco. leprae*.

1. CYTOLOGY OF *MYCO. LEPRAE*

1.1. Morphological Index (solid ratio). The utility of the morphological index (MI), based on the proportion of solidly staining *Myco. leprae* cells has been exploited particularly to follow the initial antimycobacterial drug action in patients during chemotherapy. The present MI does not distinguish the infectious from the non-infectious patient. No unified opinion has been formulated regarding the question whether the ratios of solid staining bacilli are associated with viability in the bacteriologic sense. Further studies appear necessary.

1.2. Pyridine-extractable acid-fastness. Myco. leprae in section or smears lose the property of acid-fastness, but not gram-positivity when extracted with pyridine. The acid-fastness of *Myco. lepraemurium, Myco. tuberculosis* and *Myco. intracellulare,* is not affected by this procedure. It has been suggested that a differentiation between *Myco. leprae* and other mycobacteria is possible by using Ziehl-Neelsen staining after extraction with pyridine. Further studies are needed with *Myco. ulcerans* and *Myco. marinum* from human lesions, with *in vitro* grown mycobacteria and with senescent populations of cultivable mycobacteria.

1.3. Electron microscopy. Studies with the combined use of electron microscopy and chemical and biological techniques were caried out. Miscellaneous information such as the band structure and peptido-glycolipid filaments on

the surface of *Myco. leprae,* chemical components of the cell wall of *Myco. lepraemurium* and the electron-transparent capsule-like outer zone around the bacilli were obtained.

As a significant discovery, the mycolic acids in the cell wall of *Myco. lepraemurium* were demonstrated to differ from corynemycolic or nocardic acids. The characteristic mycolic acid-arabinogalactan-murein in the cell wall of *Myco. lepraemurium* resembles that in other members of the genus mycobacterium such as *Myco. tuberculosis bovis* and strain BCG. The discovery of mycolic acid in *Myco. leprae* isolated from human tissues likewise indicates that this pathogen is a mycobacterium.

In the field of electron microscopy, further chemical and biochemical information would permit the interpretation of the relationship between structure and function or the physiologic state of *Myco. leprae.*

2. METABOLISM OF *MYCO. LEPRAE*

The extraordinary long generation time of 12-14 days in the mouse footpad has been regarded as one of the characteristics of *Myco. leprae.* No information is available to explain this slow rate of metabolism. One difficulty in metabolic studies on *Myco. leprae* is that of obtaining adequate supplies of cells and a second is that of collecting all the bacilli as suspensions without tissue contamination.

Fragmented reports have appeared indicating the presence of various enzymes in *Myco. leprae.* Among these, *o*-diphenoloxidase has been suggested to be unique to *Myco. leprae,* being distinct from plant and mammalian enzymes. Concentrates of *Myco. leprae* prepared from lepromatous material actively oxidized 3, 4-dihydroxyphenylalanine (DOPA) to pigmented products. This specific metabolic activity has been proposed as an identification test for *Myco. leprae.*

Ribulose diphosphate carboxylase activity was demonstrated in the supernatant from disrupted *Myco. leprae* collected from lepromatous tissues. It appears to be important if confirmed, because this enzyme occurs otherwise only in autotrophic bacteria and green plants.

Recent evidence has suggested an incorporation of tritiated thymidine into leprosy bacilli in cultures of human lepromatous macrophages. If the observation is confirmed, this is an important advance, because it implies that the organisms were synthesizing DNA. Further studies of this type are needed.

2.1. Metabolism of Myco. lepraemurium. Since the last congress, knowledge of the metabolism of *Myco. lepraemurium* increased dramatically. The major advance is in our knowledge that the overall energetics of the organism operate independently from those of the host. It has been demonstrated that *Myco. lepraemurium* contains a cytochrome-linked pathway for oxygen utilization. Due to the limited rate of terminal electron transfer, the assimilation and oxidation of exogenous substrates occurs very slowly and does not result in marked stimulation of oxygen uptake.

Experiments using isotope-labelled substrates and cell-free extracts of *Myco. lepraemurium* have confirmed the following facts:

(1) An extraordinarily slow rate of aerobic metabolism based upon a host-independent tricarboxylic acid (TCA) cycle. All enzymes of the TCA cycle were demonstrated, the pyruvate and α-ketoglutarate dehydrogenases being rate limiting. Although the TCA cycle may contain an alternative pathway at the

∝-ketoglutarate step, a conventional TCA pattern of isotopic distribution arose during substrate oxidation.
(2) There appears to be a lack of capacity to oxidize glucose, even though its incorporation into cellular material was established.
(3) Short-chain fatty acids, in contrast to medium-chain fatty acids, cannot be utilized for lipid synthesis.

Studies on energetics have been further advanced by the development of ultrasensitive methods for determining ATP (energy levels) in host-grown microbes. Host ATP has been eliminated and the quantitation of ATP refined to require only 1/60th the number of bacterial cells employed in the most sensitive methods hitherto available. The method has been applied thus far to demonstrate the potential losses of ATP during extraction, purification, prolonged refrigeration, and the growth potential of *Myco. lepraemurium* in cultivation studies. These methods have been designed to investigate the energetics of *Myco. leprae.*

3. CULTIVATION PROBLEM

3.1. Cultivation of Myco. leprae. Four cell-free systems have been described for the cultivation of *Myco. leprae in vitro.* These are: (a) a U-tube divided by a fine sintered glass membrane and using a conventional medium for mycobacteria, (b) an inorganic medium suitable for autotrophic bacteria, (c) semi-soft agar media, and (d) media enriched with substance of mycobacterial origin. These experiments have not been successfully repeated by other investigators.

Attempts at cultivation in cell cultures were carried out using cell lines of human origin, cell strains derived from human tissues, cell strains derived from animals, and mouse macrophages. No proliferation of the bacteria was noted.

Recently, evidence has been obtained regarding a limited multiplication of *Myco. leprae* within the macrophages derived from human peripheral blood cells. The applicability of the method is restricted by limited survival of the host cells. The majority of host cells did not survive beyond 60-80 days in most cultures.

3.2. Cultivation of Myco. lepraemurium. Extracellular growth of *Myco. lepraemurium* was obtained in cell-impermeable diffusion chambers implanted in the peritoneal cavities of mice. The generation time observed was 11 days. The division time was shortened to 8 days when macrophages were included in the chambers.

Noteworthy reports on the growth of *Myco. lepraemurium* in cell-free medium have appeared recently and reproducible results have been obtained by some other investigators.
(1) A pale yellow, R type macroscopic colony was produced on 1% egg-yolk solid medium after more than 3 months of cultivation at 37°C. Subcultures have been continued for 10-16 generations. Low plating efficiencies indicate a need for further studies.
(2) From 30-300 fold multiplication of *Myco. lepraemurium* (Hawaiian strain) was noticed at 30°C in Kirchner's medium containing calcium pantothenate, α-ketoglutaric acid, cytochrome *c* hemin and L-cysteine. Successive cultivation through serial transfer is required. Corroboration is desired in order to determine if specific growth factors are needed.

4. ADVANC S IN IDENTIFICATION OF *MYCO LEPRAE*

The WHO Expert Committee on Leprosy 1970 made a report on the identification of *Myco. leprae* as follows:

> "In all the cultivation work, it is important to prove the viability of the purported growth and to identify it by the methods now available (the inoculation of mouse footpad, lepromin test, enzymatic studies of DOPA oxidation, and serological identification of nodular extract antigen)."

The pyridine sensitivity and the specific *o*-phenoloxidase in *Myco. leprae* have already been described.

It has been observed that leprosy nodular extract (NE) contained at least two antigens which were differentiated from human serum proteins by the immunodiffusion test. One of these antigens was a heat-stable polysaccharide, and the other was a heat-labile protein which gave a single precipitation line with anti-NE serum absorbed with human serum. In as much as this antigen is highly specific for *Myco. leprae,* serological identification of *Myco. leprae* by the technique of immuno-fluorescence should become practicable with antiserum prepared against the antigen.

Committee 3: Advances in Experimental Chemotherapy

Members: C. C. Shepard *(Chairman)*; G. M. Ellard: L. Levy; V. A. Opromolla; S. R. Pattyn; J. H. Peters; R. J. W. Rees; M. L. R. Waters.

1. INTRODUCTION

Progress in the last decade in leprosy now allows the same topics to be studied in leprosy as in other bacterial diseases. They are:

(a) Screening of new drugs, and determination of minimal effective dosage (MED).

(b) Characterization of anti-leprosy activity: bactericidal, bacteriostatic, or bacteriopausal (prolonged bacteriostasis).

(c) Methods of measurement of drug in blood and tissue, and determination of minimal inhibitory concentration (MIC), pharmacokinetics including repository effect.

(d) Toxicity in relation to MIC.

(e) Metabolism of the drug.

(f) Short-term clinical trials to determine whether the drug is also active in man.

(g) Long-term clinical trials to determine whether the drug's activity continues to smear-negativity.

(h) Very-long-term follow-up to see if smear-negativity is maintained or if drug-resistant *Myco. leprae* eventually emerge.

These steps should be followed in the development of anti-leprosy drugs. Patients should not be deprived of standard dapsone (DDS) therapy in order to test compounds that have not been tested against *Myco. leprae* in animals or compounds that appear on the basis of results in animals to be clearly less efficacious than standard therapy.

2. DRUG SCREENING AND CHARACTERIZATION OF ANTI-LEPROSY ACTION

2.1. Experimental model. In the absence of significant growth of *Myco. leprae in vitro*, all work must be done in animals. Most research has been done in the mouse model. This infection is very consistent. Genetically uniform mice are readily available and easily maintained in standard conditions. Hence, the mouse continues to be the animal of choice. Other animals may be useful when particular findings must be checked in another species. For studies requiring larger populations of *Myco. leprae*, the thymectomized-irradiated mouse, the neonatally-thymectomized rat and the armadillo may provide suitable animal models.

2.2. Methods of study. The continuous method of drug administration (from the day of infection to the end of the experiment) reveals whether a drug is active against *Myco. leprae*. The kinetic method (administration of drug during a limited period, beginning early in the logarithmic phase of growth of bacilli), determines whether a drug produces bactericidal, bacteriostatic or bacteriopausal effects. Administration of drugs in graded dosages allows the MED and MIC to be determined.

2.3. Results of drug screening and characterization. With these methods, more than 200 drugs have been tested. Only a few have exhibited bactericidal (or bacteriopausal) activity and these few appear to include most of the drugs of real promise in leprosy. These drugs include:

(a) DDS and other sulphones giving rise to DDS in the gut or in tissues.

(b) Rifampicin. The related antibiotic streptovaricin is distinctly less active.

(c) Clofazimine (B 663) and another phenazine dye, B 1912.

(d) Long-acting sulphonamides. These compounds appear to have MIC's close to toxic blood levels in man.

(e) Ethionamide. In the dosage apparently required to man, gastrointestinal distress is frequent.

2.3.1. MIC of DDS. This was found to be 0.01 to 0.001 μg/ml (microgramme/ml) in the mouse, corresponding approximately to an oral dosage of 1 mg a day in man. This finding in mice led to the introduction of treatment with acedapsone (DDADS), which releases DDS at a steady rate of 2.5 mg daily, following injections of 225 mg every 75 days. The therapeutic efficacy of this regimen and that of 1 mg oral DDS given daily, confirmed these predictions. It needs to be emphasized that this study of 1 mg daily was carried out to compare the MIC of DDS in mouse and man, and not to evaluate, or encourage, very low dose DDS therapy as a practical therapeutic regimen.

2.3.2. Bactericidal effect of rifampicin. The curves of blood concentration in the mouse and in man are very similar, and studies of the anti-*Myco. leprae* effect of per-kilo dosages in mice have been predictive of the results in man. With the kinetic method in mice, rifampicin, was found to produce as much bactericidal effect in a few days as DDS in a few months. Bactericidal rates for these two drugs in man appear to be the same as in the mouse.

2.3.3. Clofazimine. Studies of the MIC of clofazimine have not been practical because the drug is very unevenly distributed in the tissues; thus, blood and tissue levels may not accurately reflect the concentration of drug in the immediate environment of the organism.

2.3.4. Demonstration of drug-resistant *Myco. leprae*. The mouse provides the only method of proving drug resistance. DDS-resistant *Myco. leprae* have been demonstrated in mice from some patients who have relapsed on prolonged DDS

therapy. By contrast, DDS-sensitive organisms have been isolated from relapsed patients who have, in fact, stopped taking the drug. Studies have shown that 1 to 10% of sulphone-treated patients eventually undergo relapse caused by DDS-resistant *Myco. leprae.* Combinations of anti-leprosy drugs appear to offer the most promise for the prevention of these relapses. Thiambutosine- and thiacetazone-resistant *Myco. leprae* have been isolated from patients who have relapsed after therapy with these drugs.

3. PHARMACOKINETICS AND METABOLISM OF DRUGS

Comparative studies of the pharmacology of drugs in the mouse and man are necessary for understanding their anti-leprosy actions.

3.1. DDS. In man there are great individual differences in the rate of DDS elimination. The half-life (T ½) of the drug varies from 5 to 50 h. Among patients with relapses caused by DDS-resistant *Myco. leprae,* there is a significant excess of persons with very short half-lives. Since it is not possible to determine the T½ of all patients, regimens need to be designed so that they will take care of patients with shorter T½. Fifty mg DDS daily would ensure blood levels continuously well in excess of the MIC, whereas 350 mg once weekly (the same total dosage) would not. For this reason, it is insufficient to describe dosage merely in terms of the total weekly intake.

The only metabolite of DDS found in human blood is monoacetylated DDS (MADDS). Humans have been found to be genetically polymorphic in their acetylation capacities, resulting in rapid and slow acetylators. Rapid acetylators have higher ratios of MADDS/DDS in their plasma, but do not eliminate DDS more rapidly, so *a priori* one would not expect the acetylator status to affect the response of leprosy patients to DDS. Nevertheless, some studies, but not others, have suggested an excess of rapid acetylators among patients with relapses caused by DDS-resistant *Myco. leprae.*

3.2. Rifampicin. Pharmacokinetic studies of rifampicin are complicated because the half-life of rifampicin varies with drug concentration and because blood levels tend to decrease after the patient has been receiving the drug for several weeks.

3.3. Clofazimine. Similar studies with clofazimine have not been possible because the drug is accumulated in the tissues.

TRIALS IN MAN

4.1. Background. Applications of experimental chemotherapeutic findings to man has been inadequately understood. For a better understanding, the bacterial populations in human leprosy have to be considered (Table 1). A lepromatous patient with a Bacterial Index (BI) of 4+ (Ridley) and a Morphological Index (MI) of 10%, may be estimated to have 10^{11} *Myco. leprae* in his body, of which 10^{10} are viable. For example in line 3 of the table, after 1 to 3 months of DDS treatment, the MI is less than 1%, so that the number of viable *Myco. leprae* is less than 10^9. If mouse inoculation is negative, the number of viable organisms is less than a hundredth of its original value and may be estimated to be less than 10^8. With each decrease of the BI by 1 unit, the corresponding numbers of bacilli fall to a tenth of the prededing value (decrease by one exponent). When the BI is less than 2+, measurement of the MI or inoculation of mice with standard numbers of bacilli is not possible, so that measurement of the proportion of viable bacilli is impossible. Consequently it is not technically possible with present procedures to

TABLE 1

Estimated number of Myco. leprae *in typical lepromatous patients at various times during response to regular DDS therapy*

	Findings			Interpretation	
	BI	MI	Mouse inoc[b]	Total *Myco. leprae*	Viable *Myco. leprae*
1 Untreated	4+	10%	Pos	10^{11}	10^{10}
2 Dapsone 1-3 mths	4+	1%	N.D.[c]	10^{11}	10^{9}
3 1-3 mths	4+	< 1%	N.D.	10^{11}	$<10^{9}$ [d]
4 1-3 mths	4+	< 1%	(Pos)[e]	10^{11}	10^{8}
5 1-3 mths	4+	< 1%	Neg	10^{11}	$<10^{8}$
6 *ca.* 1 year	3+	< 1%	N.D.	10^{10}	$<10^{8}$
7 *ca.* 1 year	3+	< 1%	Neg	10^{10}	$<10^{7}$
8 *ca.* 2 years	2+	< 1%	Neg	10^{9}	$<10^{7}$
9 *ca.* 2 years	2+	< 1%	Neg	10^{9}	$<10^{6}$
10 *ca.* 3 years	1+	N.P.[f]	N.P.	10^{8}	$<10^{7}$ [g]
11 *ca.* 5 years	0	N.P.	N.P.	$\leqslant 10^{7}$	$<10^{6}$ [g]
12 Required for cure					0?

[a] When carried out according to the specifications described for "solid ratios" so that the proportion of "solid" bacilli is the same as the proportion of bacilli infective for mice.

[b] When 1×10^{3} to 1×10^{4} bacilli are inoculated.

[c] Not done.

[d] For example, $<10^{9}$ means that the number may lie between 0 and 10^{8} (inclusive).

[e] Weakly positive (long incubation period and irregular results in mice), indicating that the number of viable *Myco. leprae* is near the limit of detectability.

[f] Not possible.

[g] Since it is not possible to determine the MI with a BI of less than 2+, the estimate of viable *Myco. leprae* is based on the supposition that not more than 10% of the total are viable. This does not imply an increased number of viable *Myco. leprae*.

estimate the number of viable *Myco. leprae* present in the body at any number less than 10^{9}. These considerations allow one to understand how there can be many viable bacilli present in the body if treatment is stopped after the MI has reached baseline values and infectivity for mice can no longer be demonstrated. To explain relapse in a patient, it is clearly not necessary to assume that non-solid bacilli have become viable. Similarly, in a patient with negative smears, it is not necessary to assume that non-acid-fast viable forms of *Myco. leprae* exist, since there could be as many as 10^{6} typical, viable but undetected *Myco. leprae* present in the body. The survival of living *Myco. leprae* during treatment appears to occur by two mechanisms. One, which is not unusual with other drug-bacteria combinations, is the survival of a small fraction of drug-sensitive bacilli in the continued presence of the drug. Such bacilli do not multiply, and since they are dormant or metabolically inactive, they remain relatively insensitive to the drug, until they resume normal metabolism. Moreover, the location of the bacilli in the tissues may be important, and some believe the location of *Myco leprae* in nerve or muscle favours their survival. Because of the large numbers of bacilli present, factors affecting even a very small fraction of the population of *Myco. leprae* become important.

The second, unrelated, mechanism of survival of *Myco. leprae* is drug-resistance. A small fraction of bacilli is genetically insensitive to the drug and can multiply in its presence. Again, because large numbers of bacilli are present in lepromatous leprosy, a small resistant fraction may constitute a large number of bacilli.

4.2. Clinical trials. In the treatment of leprosy, distinct differences exist between (a) the rate of loss of viability and (b) the rate of disappearance of acid-fast bacilli. Nearly all drugs that have been tried in leprosy were selected on the basis of their ability to carry out process (a), and such drugs do not affect process (b). During early treatment, (a) is much faster than (b).

Except for special studies in relapsed patients, all trials should be carried out in previously untreated lepromatous patients.

4.2.1. Short-term trials. These are carried out to confirm in man laboratory results of the anti-*Myco. leprae* effect of a drug. Two criteria may be applied:

(a) Measurements of the MI. These provide immediate results, but are difficult to standardize between laboratories, and are technically demanding.

(b) Mouse inoculations. They provide firm evidence of bacterial viability, are more sensitive than measurement of the MI, but they require greater investment of personnel and facilities, and results are available much later. Mouse inoculations may show more rapid bactericidal effect than do MI measurements, probably because changes in bacterial morphology may lag by perhaps two weeks behind loss of ability to multiply, a difference particularly evident with rifampicin.

Short-term trials may now be limited to a period of 6 months, or even much less, depending upon the regimen. The BI changes little in this period and is therefore of no value in such trials.

4.2.2. Long-term trials ("5-year trials"). These are carried out to determine whether a drug's activity continues until smear negativity and clinical and histological quiescence are reached. Not many patients on standard DDS treatment reach this stage within 5 years. For practical reasons, these trials usually need to involve commitments by appropriate organizations to ensure long-term continuity. Mouse inoculations are particularly helpful when treatment failure is suspected, in which case tests of drug-sensitivity provide crucial information. Measurements of the MI, if they can be performed reliably, may provide the first indication of treatment failure.

4.2.3. Very-long-term studies. Because of the very long generation time of *Myco. leprae,* a complete picture of the therapeutic efficacy of a drug cannot be obtained unless patients are followed for very long periods, perhaps for the rest of their lives. Therefore leprosy services that successfully practise very long-term follow-up of lepromatous patients can provide invaluable information on the final efficacy of regimen. As pointed out, smear-negativity does not signify that the patients is free of bacilli, but rather that the number of bacilli in the body is less than 10^7. The minimal number of viable *Myco. leprae* needed to cause a relapse in a lepromatous patient may be very small, since such a patient would not be expected to possess immunity against *Myco. leprae.* Therefore, treatment may need to be continued indefinitely. In these studies, it will be essential to determine whether relapse is caused by drug-sensitive or drug-resistant *Myco. leprae.* Experience with sulphone therapy has shown that such relapses may occur 5 to more than 20 years after the commencement of treatment.

5. CONCLUSIONS

The application of the mouse model has at last placed the chemotherapy of leprosy on an objective bacteriological and pharmacological basis. It has provided sensitive procedures for the assessment of new drugs, the response to treatment, and the detection of drug-resistance. It has also led to clarification of the theoretical basis of long-term and very-long-term clinical trials. These are difficult and expensive to carry out, but without them the final value of a regimen cannot be determined.

Committee 4: Advances in Immunopathology

Members: O. G. Skinsnes *(Chairman)*; T. Godal; M. Abe; C. K. Job; J. H. M. Pearson; D. S. Ridley; M. Ulrich; R. S. Weiser *(By correspondence)*.

Since the last Congress panel report in 1963, great strides have been made in the understanding of the immunopathology of leprosy. These advances, however, have been possible because of the great amount of pathologic information available from the work of the past century which has given direction to and formed a basis for the application of newer techniques and hypotheses in immunopathology generally.

Leprosy still remains clinically and histologically the best characterized infectious disease which covers the range from a stage of effective immunity at one end to a state of profound immunologic deficiency towards the infectious agent at the other.

Although advances in animal transmission of *Myco. leprae* have contributed significantly to the understanding of pathogenic mechanisms in leprosy, recent progress in basic medical research has provided methods by which it has become feasible to study in detail the host parasite interaction in the leprosy patient himself. This fact makes it increasingly important to establish and support laboratories in leprosy-endemic areas where immunopathological studies may not be undertaken on materials from leprosy patients. Such studies may not contribute to our understanding of disease processes in leprosy and related diseases but also give a lead to better care and control of the disease.

1. CLASSIFICATION

The classification adopted by the Sixth International Congress, Madrid, still seems operative, adequate and in conformity with new developments in understanding. Essentially, this classification recognized the two polar immunopathologic expressions of leprosy as "tuberculoid" and "lepromatous" with an interlying spectrum of variable manifestations, termed "borderline" (dimorphous) in place of the previously adopted "intermediate" and a category designated "indeterminate" of use particularly in early cases where the eventual classification characterization is not clear. This classification has been neatly summarized and correlated with its clinical, immunologic and morphologic expressions [*Lepr. Rev.* (1962), **33**, 119-128; *Int. J. Lepr.* (1966), **34**, 255-273] with the convenient code designations of TT, BT, BB, BL and LL added.

It is recommended that this system of classification and notation be generally used, and for ease of communication that this system be utilized in publications.

It is recognized that some workers and groups of workers feel that on occasion additional designative terms are necessary. It is suggested that when such are used, their relative position in the classification scale be stated and they be clearly defined either in terms of the full scale of immunopathologic and microbiological characterizations now used in classification, or, if they be used for clinical convenience, that this be stated. For reference purposes it is recognized that both the "Lucio" and the "histoid" expressions of leprosy are unexplained variants at the lepromatous end of the classification scale and it is desirable that these terms be retained and used appropriately.

The term "lazarine" leprosy has historical associations with both ulceration seen in "Lucio" leprosy and otherwise seen, often in association with debilitation. It is recommended that, since the cause of ulceration in "Lucio" leprosy is recognized to be vascular thrombosis with dermal infarcation, that the designation "Lucio phenomenon" be retained for this manifestation and the term "lazarine" be reserved for complicating ulcerative manifestions, particularly as associated with debilitation.

2. HISTOPATHOLOGY IN LEPROSY

The use of the biopsy for the diagnosis and classification of leprosy is well established. The significance of neural involvement in leprosy has long been recognized and is increasingly coming to the fore. It is urged that no histopathologic report on skin biopsies relating to the possibility of leprosy be regarded as complete or acceptable unless mention is made of evaluation of nerve involvement. It is of importance that all biopsies include full thickness of the dermis to provide inclusion of adequate cutaneous nerve samples.

3. MEASUREMENT INDICES IN LEPROSY

3.1. Bacteriologic Index (BI). The BI in use is of proven value. Variations in the standards employed in different laboratories impair its usefulness as a comparative measurement. Nevertheless, its standardized use in the form of log scale increments is recommended.

3.2. Morphological Index. This index, expressed as the percentage of solid form bacilli among the total counted, has come to be generally used as a measurement of the percentage of viable organisms present, and therefore as a measure of therapeutic response. Variations in its performance and in staining related thereto in various laboratories precludes its usefulness as a precisely comparative measure. The statistical confidence interval [*Int. J. Lepr.* (1971), **39** 857-862] is considerably greater when 100 bacilli are counted than when 200 are the basis of enumeration. The difference appearing when 200 is less significant and it seems reasonable to suggest, in balance, that the counting of 200 bacilli gives a more valid percentage whereas the counting of 400 is probably not worth the extra time and effort required. In patients in relapse it is important to utilize one or more of the most active lesions.

3.3. Histopathologic Index (HI). Also known as the Biopsy or Numerical Index. Based on the examination of an acid-fast strained paraffin section cut at 5 μm thickness, this assay utilizes the Bacterial Index system of bacterial concentration combined with an assessment of the proportion of the specimen occupied by bacilliferous lesion. Under controlled conditions it is more accurate than the slit smear index and has proved its value in research. It has not generally found a place in the routine management of patients.

4. SIGNIFICANCE OF VISCERAL LESIONS

The presence of bacillemia in leprosy postulated by the First International Leprosy Congress and subsequently demonstrated by a number of workers has recently been shown to be virtually continuous in untreated lepromatous leprosy. The circulating bacilli have been shown to be, in part at least, viable.

Significant morphologic evidence of leprous lesions in visceral organs, most particularly the liver, spleen, adrenal glands, bone marrow and lymph nodes has also been long available. More recently, however, biopsy studies have reiterated and extended the recognition that the visceral lesions essentially reflect the morphologic characteristics of the immunopathologic skin lesion type including episodes of lepra reaction. Such studies have also demonstrated that viable *Myco. leprae* are present in lepromatous leprosy in the liver and bone marrow, and it is therefore to be expected that they are present also in other areas of deposition. Though morphologic evidence suggests that these lesions may be viable evidence is not conclusive and that the presence of viable bacilli in these organs, though it may be supportive of this conclusion, can also be interpreted as merely the presence of recent haematogenous bacillary deposition.

Laryngeal lesions, at one time not infrequent and troublesome enough to require tracheostomy, have virtually disappeared under sulphone therapy. In contrast, nasal lesions, though also responsive to sulphone therapy, have increasingly been noted as a probable source of discharge bacilli for the spread of leprosy.

The nasal lesions in untreated lepromatous patients infiltrate cartilage and bone which form the framework of the nose, resulting in its collapse and deformity in some of them. Infection by secondary organisms may hasten this process of destruction. Similarly in the small bones of the hands and feet specific leprous osteomyelitis may be responsible for the bone erosion. But in this instance, more than often invasion by secondary organisms is responsible for loss of tissue, including bones. There are also the superimposed vascular alterations following nerve paralysis which create a complex pathogenic process. In addition, factors such as disuse atrophy, pressure atrophy etc., combine to produce the severe deformity that may be seen in these patients.

The involvement of the eye in lepromatous patients is a serious complication. There is infiltration of the iris, ciliary body, sclera and episclera by macrophage leproma. During the reactive phase there may be infiltration of the iris and cilary body by neutrophils with fibrinous exudate into the anterior chamber resulting in loss of vision. Anaesthesia of the cornea and lagophathalmos due to paralysis of the 5th and 7th cranial nerves respectively found in all forms of leprosy, may lead to corneal ulceration and ultimate loss of the affected eye.

5. PATHOLOGY OF NERVE INVOLVEMENT IN LEPROSY

Peripheral nerve involvement is a characteristic finding in all forms of leprosy, although the nature of the lesion varies depending on the type of this disease. In lepromatous leprosy the predominant picture is the invasion of the nerve by a large number of organisms which are present in perineural cells, Schwann cells and intraneural macrophages. There is also intraneural proliferation of all collagen and oedema. Inflammatory response bacillary antigen both intra- and peri-neurally and the nerve parenchyma is replaced by tuberculoid granuloma which in some instances may even caseate and form an abscess. *Myco. leprae* are demonstrable

with difficulty. In borderline leprosy the appearances are very variable, depending on the exact type of the disease.

Further, the nerve involvement is generalized in lepromatous and borderline leprosy and localized to one or few nerves in tuberculoid cases. However, the route of entry of organisms into the nerves is still a matter to be elucidated.

The onset of paralysis is slow and insidious in lepromatous leprosy, taking several years, and may improve under effective chemotherapy. In tuberculoid leprosy, however, the onset is comparatively rapid and usually irreversible. In borderline cases also the nerves are rapidly damaged and very severe and rapidly developing paralysis can occur in the presence of reactions.

The mechanism of destruction in the tuberculoid part of the spectrum is a delayed type hypersensitivity reaction to bacterial antigen in the nerve parenchyma. In lepromatous leprosy, although the presence of a large number of organisms ultimately causes much destruction, the exact pathogenic sequence of events is yet unclear. The reactions which may complicate all forms of leprosy commonly contribute to further damage.

Nerve damage is often permanent and disabling, and therefore of paramount practical importance in leprosy. Advances in the prevention and management of nerve damage are only possible as a result of increased understanding of the various mechanisms involved. Further research in this field therefore deserves high priority.

6. REACTIONS IN LEPROSY

A "reaction" in leprosy is regarded as a hypersensitivity phenomenon and does not include phenomena associated with the simple extension or regression of the infection. Biopsy studies are of value in elucidating whether or not such a reaction is taking place and for determining its nature. On occasion biopsies are essential.

Two types of reaction are well recognized, namely *erythema nodosum leprosum* (ENL) in lepromatous leprosy, and reversal reactions in borderline leprosy. ENL is associated with the infiltration of neutrophils as in the Arthus reaction. Necrosis and ulceration may follow. The presence of immune complex deposits have been reported in ENL lesions, together with alterations of complement levels in serum. Confirmation is awaited, but the precise nature of ENL remains to be fully elucidated. Reversal reactions are associated clinically and histologically with an increase of cell-mediated immunity which can be demonstrated by lymphocyte function tests. In experimental animals reversal reactions can be precipitated by the injection of syngeneic lympoid cells.

A number of other reactions are liable to occur and lack of fundamental knowledge precludes their classification. These include:

(a) Reactions in tuberculoid leprosy which are presumably an expression of delayed hypersensitivity;

(b) Reactions in borderline leprosy associated clinically and histologically with a downgrading within the immunological spectrum or with no change in immunity, though the results of lymphocyte function tests are variable;

(c) Reactions in lepromatous leprosy which vary in form from a simple localized neutrophil infiltration or necrosis in a hyperactive nodule to severe ulcerating lesions associated with thrombosis and dermal infarction in the "Lucio phenomenon". The relation of these lepromatous reactions to ENL remains to be determined.

Further studies of lepra reactions are regarded as important. It is recommended

that the most promising approach is a controlled longitudinal study with combined clinical, histological and immunological observations before, during and after the period of reaction. A further possible means of advance lies in the study of the antigenic structure of *Myco. leprae* since the antigenic components involved in the reactions are not yet determined. Two polysaccharides designated *beta* and *delta* have been demonstrated and a protein antigen able to elicit delayed type hypersensitivity has been isolated.

A most serious and possibly fatal sequel of severe lepromatous leprosy is the development of renal lesions, including amyloidosis. It is not yet clear to what extent this is due to ENL or to other forms of reaction. It is urged that renal biopsies on selected patients should be included in studies of reaction where facilities permit; and that the kidneys of patients who come to necropsy following reaction should be made available for study.

7. LEPROMIN

The following antigenic preparations of *Myco. leprae* appear at present to be used in the study of delayed (skin) hypersensitivity to *Myco. leprae* [*Bull. Wld Hlth Org.* (1973), in press]:

(a) Suspension of whole autoclaved homogenized leproma ("integral" lepromin).
(b) More purified bacillary suspensions ("bacillary" lepromin).
(c) Non-coagulated soluble bacillary proteins ("leprolins").
(d) Defatted and disrupted bacillary suspension ("Dharmendra antigen").

While lepromin containing whole bacilli elicits both an early (Fernandez) reaction (48-72 h) and a late (Mitsuda) reaction (3-4 weeks) "leprolins" and Dharmendra antigen elicit mainly an early reaction and none or a weak late reaction.

The early reaction indicates existing hypersensitivity to the injected antigens. The late reaction, on the other hand, allows sufficient time for the test subject to become sensitized by the injected antigens. Thus, the late reaction may not only measure existing delayed type hypersensitivity, but perhaps also provide information about the test subject's capacity to initiate and/or amplify the response to the injected antigens. The high incidence of late lepromin positive individuals in leprosy non-endemic areas is in agreement with this view. The late reaction, therefore, does not indicate whether a subject has previously been exposed to *Myco. leprae* or not. Its primary importance appears at present to be limited to the determination of prognosis in leprosy patients. Further information about the lepromin reaction may be found in a recent WHO Report [*Bull Wld Hlth Org.* (1973), in press].

It is recommended that in publications relating to their use, the type of antigen used and the nature of the reaction measured should be clearly specified.

It is urged that, if current reports of massive *Myco. leprae* proliferation in the armadillo continue to show validity, efforts be made to develop and utilize this source of bacilli for the preparation of standardized lepromin and leprolin that could be made universally available.

8. THE USE OF BCG IN THE IMMUNOPROPHYLAXIS OF LEPROSY

In the absence of additional information, this panel echoes the recommendation of the WHO Expert Committee on Leprosy [*Fourth Report, WHO Tech. Rep. Series No. 549,* (1970)] to the effect that it is premature to recommend the

general use of BCG vaccination and that final recommendation be postponed until the results of the controlled studies in progress achieve definitive evaluation.

9. IMMUNE RESPONSIVENESS IN LEPROSY

The concept of a host-determined immunologic spectrum in leprosy has received steadily increasing clinical and pathologic support during the last decades to the point where leprosy today stands forth as a unique immunopathologic disease model. The immunologic support for this concept was initially based on delayed hypersensitivity skin testings. More recently a considerable number of other immunological methods recently applied in studies on humoral and cellular immune responsiveness in leprosy include:

9.1. Humoral immune responsiveness

(a) Quantitative examination of serum immunoglobulin levels.
(b) Semi-quantitative determination of antibody production to TAB (typhoid-paratyphoid A and B) after active vaccination.
(c) Presence of anti-mycobacterial antibodies in serum by fluorescent antibody and gel precipitation techniques.
(d) Detection of antibody-coated bone marrow derived lymphocytes (B-cells) by immune fluorescence.

9.2. Cell-mediated immunity

(a) Delayed skin sensitivity to microbial antigens such as PDD and "artificial" antigens such as dinitrochorobenzene and picryl chloride.
(b) Detection of sheep red cell rosette forming lymphocytes (T-cells).
(c) Blastoid transformation of peripheral blood lymphocytes. This may be measured by morphologic examination of stained lymphocytes or more quantitatively by uptake of radioactive thymidine in such cells.

Substances used to stimulate lymphocytes may be divided into three categories:

I. Non-specific mitogens such as phytohaemagglutinin.
II. Antigens not related to *Myco. leprae.*
III. Antigenic preparations derived from *Myco. leprae.*

(d) Production and release of molecular mediators (lymphokines) from sensitized lymphocytes. These may be monitored by various techniques, including migration inhibition of autologous, homologous or heterologous phagocytes.

It should be noted that the last two groups of tests cannot *a priori* be judged as measurement of cell-mediated immune responsiveness as humoral immune responses can influence the results of these tests.

While the findings suggest that humoral immune responses are unimpaired in leprosy patients, there is increasing evidence of a depression of cell-mediated immunity in certain categories of such patients. The degree of depression appears to increase continuously from the TT to the LL end of the spectrum. Circulating antibody to mycobacterial antigens, on the other hand, increases towards the lepromatous end of the spectrum. In addition to this immunological imbalance in lepromatous leprosy which is specific to *Myco. leprae,* a non-specific depression of cell-mediated immunity has been reported in various studies. In contrast to the specific depression which does not recover as a result of anti-leprosy chemotherapy, the non-specific depression may become reduced by treatment.

10. MACROPHAGE FUNCTION IN LEPROSY

Most tissue macrophages are derived from blood monocytes. In the tissues, macrophages can adopt a wide variety of morphological forms. The resulting pleomorphism is well exemplified in leprosy where macrophages may appear as epithelioid, multinucleate, histiocytic or foamy cells. This differentiation and this influx into tissues appears to take place as a result of various stimuli, including products of activated lymphocytes.

Some laboratories have reported a lack in the capacity of lepromatous macrophages to lyse autoclaved *Myco. leprae* while other groups of workers have been unable to substantiate this finding.

Whether the deficiency of macrophages in lepromatous leprosy to dispose of the leprosy bacillus and its lipid degenerative products is a defect in the macrophage population *per se* or due to lack of stimuli from other cells, is not yet clear.

It would appear that the eventual solution to the problem will involve the concepts and techniques of both immunopathology and cell enzymology.

Committee 5: Advances in Epidemiology

Members: M. F. Lechat *(Chairman)*; P. B. Arcuri; J. A. Cap; Z. Castellazi; R. A. Feldman; R. S. Guinto; T. W. Meade; S. K. Noordeen *(Unable to attend)*; J. Walter.

1. INTRODUCTION

The Committee feels that there have been few major advances in the epidemiology of leprosy in the past five years. This report therefore deals mainly with suggestions for future work, after a brief initial review of recent developments.

2. ADVANCES IN PAST 5 YEARS

2.1. Analysis of data. There has been much work in many areas of the world on the statistical analysis of data on diagnosed cases of leprosy. However, much basic information is still wanting (especially in the absence of the ability to idemtify persons infected with *Myco. leprae*), on the characteristics of individuals, households and communities that are associated with the transmission of leprosy.

2.2. Control

(i) A number of studies have been indicated that the treatment of lepromatous and borderline cases has significantly reduced the subsequent incidence of leprosy in household contacts, especially children.

(ii) Some evidence from active control programmes suggests reductions in prevalence which might be expected eventually to influence incidence rates. However, long periods of intensive chemotherapeutic control and careful evaluation will be needed before it can be generally accepted and agreed that widespread falls in incidence have been achieved.

(iii) The need to clarify what is meant epidemiologically by "control" has become increasingly clear. The term does not include the treatment of cases presenting sporadically to clinics, etc. "Control" includes attempts to reduce

prevalence by the systematic treatment of existing cases in the programme area, and, finally, to reduce incidence. The interactions of epidemiology and control need to be continually reviewed.

2.3. New laboratory techniques with epidemiological implications. Recent developments in other disciplines (e.g. immunology, bacteriology) may well offer epidemiologists the prospects of being able to detect infection by *Myco. leprae,* as well as clinical manifestations of leprosy, and of studying host-parasite relationships more effectively than hitherto. At present, however, these possibilities have not been fully tested and validated in the field, and it is hoped that steps to do so will soon be taken.

3. FUTURE WORK: SUGGESTIONS

3.1. Population-based studies

(i) Prevalence studies, characteristic of the bulk of current epidemiological studies in leprosy, should, in certain instances, be extended to, or re-planned as, prospective incidence studies, with the necessary follow-up investigations. Since it is not possible to detect infection epidemiologically, such studies will have to be based on newly arising clinical cases.

(ii) The main objective of work of the sort proposed is the identification of risk factors whose modification or use may contribute to the control of the disease.

(iii) The factors studied should cover all the attributes likely to be relevant to the onset of leprosy in the groups under study, i.e. probably need to include a wider range of constitutional and environmental variables, including information on intercurrent diseases, than has generally been the case so far. Because the incidence of leprosy is low, projects of this sort require very large numbers and long follow-up periods, which need to be related to the endemicity of leprosy in the study areas.

(iv) Strict attention must be paid to the development and use of standardized criteria and procedures so that the results of different studies may usefully be compared.

(v) Clear distinctions must be drawn between case-finding (the detection of established as well as new cases) and incidence, in order to avoid possible confusion (especially in the early stages of a prospective study) as to whether incidence is really changing or not.

(vi) In addition to observational studies, opportunities afforded by on-going field surveys for epidemiometric model building and computer simulations of onset and natural history should be taken.

(vii) Population-based studies of the sort suggested are likely to pay dividends in other ways, by providing sampling frames for the collection of biological material, the conduct of clinical trials, and for a range of other purposes.

(viii) Field research programme should take full account of the medical requirements of all diagnosed leprosy patients.

(ix) The need for large study populations presents problems, especially in countries where skilled and semi-skilled manpower and other resources are limited. However, the experience and achievements of groups who have attempted large scale studies make it clear that these can be carried out. In addition, individual investigators or small teams who can carry out well-planned epidemiological studies of particular problems, especially where exceptional conditions or opportunities exist, should be encouraged.

4. INTERNATIONAL CO-ORDINATION: VOLUNTARY AGENCIES

The role that international bodies such as the World Health Organization and voluntary agencies can play in contributing to the general co-ordination and comparability of large-scale, long-duration studies and of smaller undertakings requires special emphasis.

Committee 6: Therapy

Members: J. Languillon *(Chairman of meeting)*; K. Ramanujan *(Chairman by correspondence)*; J. Barba-Rubio; J. C. Gatti; N. Torsuev *(By correspondence)*; A. B. A. Karat *(By correspondence)*; J. R. Trautman.

"It has been said that it is now a practical proposition to control leprosy in this generation and eradicate it during the next. All that has to be done is to ensure that an adequate number of the correct pills pass down the throat of patients for a significant length of time" (Walker, 1973).

1. TREATMENT OF UNCOMPLICATED LEPROSY

1.1. Diamino-diphenyl-sulphone (DDS). The parent sulphone, DDS, continues to hold sway as the drug choice in the management of uncomplicated leprosy; its low cost and infrequency of the emergence of sulphone resistant cases, when given in conventional doses, are its special features. Its slow bacteriostatic action and the consequent necessity to administer it over long periods of time and its inability to quickly clear the body of bacilli are some of its inherent drawbacks.

Under DDS therapy, even after the complete disintegration of bacilli in the skin, intact bacilli have been reported to be still present in smooth muscle and superficially located striated muscle (Leiker, 1971), liver, bone-marrow and lymph nodes. This may perhaps explain why relapses tend to occur even while the patient continues on the drug.

Unanimity has not been reached with regard to the optimum effective dose of DDS, frequency of administration of the drug, its relationship to the occurrence of reactive states and continuation of treatment after attainment of the inactive state, but the Committee recommends treatment of lepromatous cases for life.

1.2. Other drugs. Less effective bacteriostatic agents such as thiambutosine, streptomycine and thiosemicarbazone are used less frequently in the treatment of leprosy.

Long-acting sulphonamides have the advantage of weekly administration by the mouth. Some leprologists claim to have obtained good results with these drugs particularly in tuberculoid forms of the disease and its complicating neuritis. However, since serious and even fatal complications have followed the use of these drugs in the treatment of other diseases, the drugs should be used with caution in mass leprosy campaigns.

1.3. Clofazimine. A notable advance in the therapy of leprosy was the demonstration of the activity of clofazimine against *Myco. leprae.* The drug has bacteriostatic as well as anti-inflammatory properties.

The initial reports of Browne bearing out the anti-inflammatory properties of clofazimine (Browne, 1965) were followed by the demonstration of the

anti-mycobacterial activity by Pettit, Rees and Ridley (1967) in the human and Shepard (1969) in the mouse footpad. The extensive clinical experimental studies of Ross and his colleagues established the efficacy of clofazimine in sulphone-resistant cases. Clofazimine has established its value in the treatment of lepromatous leprosy but its high cost and the easy availability of the safe effective and cheap DDS militate against its use in the treatment of uncomplicated lepromatous leprosy.

1.4. Diacetyl-diamino-diphenyl-sulfone (DADDS). An initial short-term trial with this drug in the Philippines (Shepard, Tolentio and McRae, 1968) and a subsequent longitudinal clinical trial in New Guinea (Russel *et al.*, 1971) and Micronesia (Sloan *et al.*, 1971) have yielded satisfactory results. Although the initial reports are encouraging about the therapy on schedule in underdeveloped areas, the possiblity of the emergence of sulphone resistance, occurrence of relapses and the possible danger that this preparation may perpetuate a reactive state in cases in which the drug has triggered such a state have to be borne in mind.

1.5. Rifampicin. The newest entrant into the therapy of leprosy is a very potent antibiotic. Rees and his colleagues, after establishing its efficacy in mouse footpad infection with *Myco. leprae,* used the drug in active and sulphone-resistant lepromatous cases (Rees, Pearson and Waters, 1970) and found it effective, It is expected that the rapid killing of *Myco. leprae* would prevent the slow release of intracellular antigens of *Myco. leprae* and thus eliminate or markedly reduce the incidence of complications of immunocomplex deposition such as ENL. Although no toxic effects have been reported by these workers, there have been conflicting reports about its hepato-toxicity and the occurrence of thrombocytopenia (Proust, 1971). In view of its high cost and limited availablity, it would be wise to restrict its use to selected cases.

2. COMBINED THERAPY

Concurrent administration of drugs such as thiambutosine, long-acting sulphonamide, thiosemicarbazone, clofazimine and rifampicin along with DDS have been tried in the treatment of leprosy with a view to obtaining a synergistic effect and also to prevent the development of sulphone resistance. The results of the trials are not uniform—some found the combined treatment better than DDS alone, while others did not notice any substantial difference.

3. TREATMENT OF COMPLICATIONS ASSOCIATED WITH LEPROSY

3.1. Reactions in leprosy. With the advent of sulphone therapy, the incidence of the reactive states has been on the increase with the manifestations becoming more severe and serious.

The first major breakthrough in the management of reactive states in lepromatous leprosy was the introduction of corticosteroids (Roche *et al.*, 1951). Although this drug dramatically relieves the agony of severe reactions, the attendant undesirable side effects and drug dependence pose serious therapeutic problems.

The indication for the use of corticosteroids in the management of the distressing complications associated with leprosy has declined with the introduction of thalidomide (Sheskin, 1965). The effectiveness of thalidomide in controlling the acute exacerbations in lepromatous leprosy has been confirmed.

In Dimorphous and RTL reactions, it is reported to be much less effective. The major drawback of this drug is its teratogenic effect when administered to pregnant women.

While the concensus of opinion amongst workers is that the drug produces a spectacular effect in acute lepra reaction, there is no unanimity regarding the effect of the drug in neuritis, ocular and joint manifestations. In many instances these complications respond more readily to corticosteroid therapy possibly because of its more generalized anti-inflammatory effect.

In recurrent lepra reaction, a maintenance dose of 50 to 100 mg/day of the drug is reported to keep the reaction under control. Further experience with the drug has shown that under its protective cover, steroid-dependent cases can be weaned from steroids and sulfone-sensitive cases continued on treatment with DDS.

With Browne's report of a possible anti-inflammatory action of clofazimine in lepromatous leprosy, a new hope opened up for lepromatous patients who were subjects of recurrent necrotising reaction. The controlled clinical trials of Karat *et al.* (1970) confirmed the beneficial effects of the drug in lepra reaction. Similar reports have also appeared from Hastings, Warren and Trautmman and many others. However, the beneficial effect of clofazimine takes as long as 8-12 weeks and sometimes high dosages, to become manifest, and hence in severe cases with necrotizing lesions it will be necessary to combine clofazimine with corticosteroids or thalidomide until the acute phase is controlled. The significant improvements in the general health of these severely ill patients have been well documented.

While it is not effective in quickly controlling the acute reactive states, clofazimine has been observed to suppress not only the recurrent reactive episodes, but also permits withdrawal of steriod in steroid-dependant cases. Also it increases a tolerance to DDS in sulphone-sensitive cases while simultaneously exerting a benificial effect on the disease process. Long-term studies are necessary to determine whether once the reactive states are controlled and the patient is able to take DDS in adequate doses, clofazimine can be withdrawn. It is a matter for serious consideration whether this drug could be safely used in cases of recurrent severe lepra reaction with overt renal involvement.

4. SULPHONE RESISTANCE

The occurrence of drug resistance, one of the anticipated outcomes of chemotherapy, has now been established in lepromatous cases (Pettit, Rees and Ridley, 1966) on DDS therapy. Inadequate dosage and irregular treatment appear to be contributing factors. This condition poses serious therapeutic problems. Clofazimine and rifampicin either alone or in combination with DDS (or other drugs such as thiambutosine and ethionamide) have been found to be effective in the management of these cases. However, emphasis should be laid on the prevention of this clinical state by adequate DDS therapy.

5. CHEMOPROPHYLAXIS IN LEPROSY

Chemoprophylaxis using DDS orally (WHO, 1970) and DADDS (Walker, 1973) has been found to yield satisfactory results. The value of chemoprophylaxis in the prevention of the development of lepromatous leprosy, its duration, the optimum dose and the frequency of adminstration are yet to be determined.

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Committee 7: Leprosy Control

Members: L. M. Bechelli *(Chairman)*; M. L. Brubaker; C. Estrada Silos; P. Kapoor; M. R. Labusquiere; E. Rasi; H. Sansarricq; C. M. J. Vellut.

Despite substantial and sometimes even striking gains in many fields of leprology, progress in leprosy control has not kept pace—mainly because of the present unavailability of an ideal drug or specific vaccine. Control continues to focus on the patient or those more prone to develop leprosy. The population at higher risk is known, but the means to protect it are not yet available or still under study, and active drugs are badly needed to make a greater impact on the load of infectiousness. Hopefully, the preparation of a specific vaccine and/or the obtaining of favourable results in chemoprophylaxis can make primary prevention possible. The prevalence and duration of leprosy, plus its unique characteristics and socio-economic implications, call for special priority in public health programmes and in research.

Because there was no major breakthrough necessitating special changes in the guidelines and methodology of leprosy control, the relevant reports prepared by the Committe of Leprosy Control (Rio, 1963) and by the WHO Expert Committee on Leprosy (1966 and 1970) are generally valid today. Therefore our

attention will be focused only on certain aspects of control which need more emphasis or represent an addition to the previous guidelines.

There are definite indications that where an effective case-detection and case-holding programme has been developed the total number of patients and the annual detection of new cases has been reduced. It also appears that with such programmes larger proportions of early, non-deformed patients are detected who can be easily treated, helping ultimately in reducing the quantum of infection in the community. There is, however, a good number of new cases in spite of efficient work. This requires epidemiological investigation and also the need to find ways and means to improve present methodology.

1. MEDICAL MEASURES

1.1. Case-finding. To control leprosy it is essential to diagnose the early cases prone to develop lepromatous leprosy and the early lepromatous cases; this requires good training and experience of the relevant staff. For such diagnosis bacteriological examination should be done on all patients.

In the surveillance of contacts, the criteria recommended by WHO Expert Committee (1966) should be adopted. School surveys are useful in highly endemic areas.

Mass survey is an important method for case detection. In non-hyperendemic areas it has limited value. In such areas the most effective and practical case-finding method is contact tracing, not only limited to household contacts.

The above methods of case detection should be supported by health education and where possible, by multiple purpose surveys.

Where mass surveys are undertaken, they should be multipurpose, as performed in several countries, and advantage should also be taken for health education in leprosy and other diseases. In this way, such surveys would be relatively less expensive and yield better results and public acceptance.

1.2. Out-patient care. Irregularity of treatment continues to be one of the most important drawbacks in control, in spite of the efforts to prevent it. The cause of absenteeism should be investigated by social and behavioural scientists.

Efforts should be made to take the treatment to the patients, near their homes, even if this must be done once a month. Advantage should be taken during the visit for health education and contact examination and other activities including prevention of disabilities of comprehensive medical care.

1.3. In-patient care. Facilities for temporary hospitalization for acute illness must be provided. However, institutional isolation of infectious cases, even temporary, is no longer recommended.

1.4. Medical rehabilitation. Prevention and treatment of disabilities by simple physiotherapeutic methods merits greater attention and should be part of the out- and in-patient care. Reconstructive surgery should be undertaken in general rehabilitation centres, surgical and orthopaedic services, including university hospitals.

1.5. Release from control. This should be a continuing activity to avoid inflation of the prevalence and of keeping patients under control for a longer time than needed, thus increasing the work load and expenses.

1.6. Protection of the healthy population with special reference to contacts and children. The Committee noted with great interest the findings so far reported by the groups investigating the preventive effect of BCG in Uganda, Karamui and Burma. Similar interest was shown in the chemoprophylaxis trials.

In view of the findings so far available from these trials, the Committee considers it premature at this stage to recommend BCG vaccination or chemoprophylaxis as a regular part of the leprosy control measures. Further research is still needed in these important subjects.

2. HEALTH EDUCATION

Although it is most important to remove fear and irrational behaviour about leprosy, it still seems that health education is too often a neglected subject in most countries. The attitude of the medical and health workers is often the first stumbling block. Health education is a most important aspect of leprosy control and should be given high priority.

With regard to terminology and approach, all aspects of culture and language call for attention. To be effective and create a positive feeling for action, health education must be in a language people understand.

The cause of prejudice should be investigated to develop a better methodology for overcoming it.

3. TRAINING

In spite of all the emphasis given to this crucial measure, in a number of countries leprosy training for medical officers is neglected. Initial training and refresher courses and in-training should be conducted regularly for the various types of workers. Refresher courses should be repeated at regular intervals. Seminars and symposia should be frequently organized for all levels of workers.

Training in leprosy for undergraduate and postgraduate students is not receiving adequate attention, for which the leprosy campaign suffers. The efficiency of the teaching and learning processes should be evaluated.

4. ADMINISTRATIVE MEASURES

4.1. Planning. Many projects have not yet established quantitatively defined objectives for the different activities. Each project should have realistic objectives, feasible with available resources, and defined in terms of quantity, areas and time. When defining objectives in quantitative terms, special attention should be given to the following priorities: treatment and follow-up of infectious and indeterminate patients and surveillance of contacts of the infectious patients.

Control measures, specialized or integrated, should aim at reaching a country-wide coverage within the shortest possible time.

4.2. Quantification of the problem. Data collection. The data available on the prevalence in many countries do not represent the real situation, because the case-finding has not reached the desired level and sometimes because the number of patients released from control is small, thus inflating the rates. More realistic figures and baseline information are required for planning and evaluating programmes.

A uniform definition of terms is a basic requisite in a system of leprosy statistics: the information collected should allow comparisons between the various areas of the country and also between different countries and continents.

4.3. Integration. The principle of integration of leprosy control activities into the general health services is widely accepted, as are the difficulties recognized in

achieving it. One of the questions is how to prepare the polyvalent personnel both at medical and paramedical level.

Complete integration may not be feasible at the present time in many countries, however desirable it might be. If integration is attempted too soon. the leprosy work will be the first to suffer most.

> "Full integration will be attained only as a result of a long drawn-out process and for this reason countries should be encouraged to take the first step as early as practicable . . ." (WHO Expert Committee on Leprosy, 1970),

after appropriate training and motivation of all the staff concerned. It should be started and studied in a pilot test area. Where feasible, leprosy control programmes should be combined with other control programmes.

4.4. Evaluation. Constant evaluation should be carried out in all projects, especially where control work has been undertaken for 10 years or more, or in areas that appear to have achieved a reduction in incidence and prevalence.

Detection of a large number of early cases the success of the programme, but does not necessarily mean that leprosy is increasing. Detection of such benign cases and subsequent early release from control reduces the prevalence rate, apparently indicating that leprosy is being controlled. However, this does not mean that the source of infection has been removed from the community and further control measures must be continued.

4.5. Supervision. In most countries, adequate supervision by medical officers and senior auxiliary staff is lacking or is unsatisfactory. It is essential that such supervision be provided and exercised for all activities connected with leprosy control.

5. OPERATIONAL RESEARCH

The Committee notes with interest the efforts to develop techniques which can be useful in the detection of the high risk groups. Subjects relevant to immediate and/or long-term public health action should preferably be chosen and should include test runs of optimum solution given by the epidemiometric model. Efforts should continue to develop an epidemiological model to provide forecasts of the impact of the programmes on the natural course of leprosy and its control.

Studies should also be undertaken regarding the methodology to be applied in urban leprosy control.

Studies on reactivation and relapses are needed to determine the criteria and length of treatment required for releasing patients from control.

6. RESULTS THAT MIGHT BE EXPECTED FROM THE PRESENT CONTROL METHODS

Where the methodology is currently and persistently applied and where there is co-operation of all concerned and where there has been motivation of the population, it can be expected that there will be an increase of early benign cases, a decrease in the number of disabilities, a slow and progressive decrease of infectious cases and finally a gradual fall in the detection rate. The whole thing is such a long process that it requires a long time to achieve the end result. This prospect can only be improved by intensifying research.

Committee 8: Rehabilitation

Members: O. W. Hasselblad *(Chairman)*; J. J. Arvelo; P. W. Brand; M. I. Bly; A. E. Carayon; T. N. Jagadisan; S. Karat; R. O. Manzi; J. M. Mehta; W. F. Ross; A. Samy; K. Saikawa; N. Hasselblad *(Secretary)*.

1. INTRODUCTION

We must begin by pointing out an anomaly in the use of the term "Rehabilitation" in relation to leprosy treatment. By tradition all those aspects of patient care which relate to the prevention of physical disability have been grouped under "Rehabilitation" along with corrective surgery and other definitive rehabilitation techniques, managed by a surgeon and his staff, while the treatment of the disease itself has been managed by specialists in leprosy control. The result has often been that when a rehabilitation team is not available, the physician in charge of the control project has felt that techniques related to the management of disabilities are not considered to be his responsibility. Thus patients are deprived of aspects of *primary patient care* which might have saved them from progressive crippling deformity and social, economic, psychological and vocational disability.

We wish to emphasise that the special techniques that have been developed to prevent physical disability are absolutely basic to the medical care of every patient who has suffered peripheral nerve damage, whether or not a definitive Rehabilitation Team is available. Appropriate techniques can be carried out without expensive equipment or specialized personnel. The essentials are extra time spent by the auxiliaries on each patient and additional expenditure on such devices as protective and therapeutic footwear.

The extra cost is compensated for by the improved cost-effectiveness that results from better attendance of the patients who will recognize that trophic ulcers are healed and that felt needs met, beyond which personal experience and that of their neighbours teaches it could not be accomplished by medication alone.

Conversely, the ultimate cost of caring for the totally disabled patient whose disability has not been prevented, is many times more than the very small amount saved by withholding the care which should have *prevented* the disabilities. That the public and governments are deeply conscious of the burden of this cost of caring for the totally disabled is demonstrated by the large sums of money collected and provided for their care whether in or out of institutions as compared to the amount budgeted for the control of the disease.

Moreover the continuing accumulation of newly disabled patients from among the ranks of patients treated in mass campaigns is regarded by new patients as evidence of failure of control programmes. Failing to care for the patient as an individual becomes a valid reason for discontinuing treatment.

To ensure that staff, responsible for control of leprosy, assumes full responsiblity for techniques of disability prevention, it is essential that new dialogue be instituted between physicians in charge of control programmes and those specialists in rehabilitation who have been mainly concerned with the problems of disability. It is not sufficient to state that the responsibility must be transferred; there is a great deal of experience that needs to be communicated and every opportunity for such communication must be taken advantage of.

The total care of leprosy p ıtients may thus be considered under these headings:

1.1. Primary patient care. The large majority of patients need no other care than this, and prevention of disability should be carried out by all staff of the leprosy control programme.

1.2. Rehabititation. Patients with substantial established disability require a planned programme to restore maximum ability to function as self-respecting and respected persons. Frequently vocational training and counselling is required to discover means of self-support consistent with their residual abilities. Many of these activities require specialized trained personnel.

1.3. Social welfare. Given relatively limited resources, it is not feasible to attempt rehabilitation of all disabled patients. For the totally disabled it must be accepted that permanent provision for their care be made, consistent with human dignity and decency. In principle the creation of segregated facilities for whatever reasons, for patients whose disabilities arise from a particular disease such as leprosy, must be deprecated. Such facilities may have served a useful function in the past but their continued existence perpetuates a public image that leprosy is a disease apart and its victims are to be excluded from the life of the community. In addition, the influence of any type of categorical segregation facility on the patients themselves is almost always dehumanising and unjust.

1.4. Comprehensive community health planning. The management of leprosy is severely handicapped by community social attitudes. The methodology of management has tended to place the patient at risk in regard to his self image and that of his community which should be supportive of his welfare. Informed studies reveal that the majority of patients prefer the risk of disability to segregation and alienation from home, community and whatever margin of economic security he has been able to maintain. The patient is always a person in relationship. New forms of health care delivery systems need to be examined which will include the treatment of leprosy among other priority health needs of the community and not as a separately vertically structured programme.

2. PRIMARY MEDICAL CARE

Primary medical care, so far as prevention of disability is concerned, begins with the attempts to prevent damage to the peripheral nerves. This depends, in the first place, on health education directed toward the patient to make him constantly aware of early danger signs and that he be prepared to report such signs to the auxiliary worker, even in the absense of neuritic pain. From the time of diagnosis the patient must learn to actively participate in his own treatment and prevention of disability. Equally important is the alertness of the medical auxiliary to understand early danger signs and to act promptly as they appear. The treatment may then consist of the use of anti-inflammatory drugs, splintage of affected parts, and in selected cases, decompression of swollen nerves or constricted blood vessels by surgical intervention. This sequence of monitoring events and timely intervention is the ultimate responsiblity of the supervising physician who alone can insure an inter-relationship of confidence between patient and auxiliary worker.

Primary medical care includes the prevention of *progressive* disabilities. Thus it is important that the physician aims to cater for all complications which may lead to disability, to give immediate and effective care using the most feasible methods that will enable the patient to return to normal activity as quickly as possible.

It is important to recognize that effective treatment for 90% of the complications related to eyes, anesthesia and paralysis, is simple, inexpensive, and

can be administered by specifically trained auxiliary medical workers in peripheral clinics or at home. These methods have been tested and found successful in domiciliary based leprosy control programmes. The auxiliary medical worker can be trained and motivated to offer such services adequately and effectively under the supervision of a physician who himself has had adequate training and who cares. In practical terms this approach means:

(1) Health education directed towards securing the patient's full participation in the methods of prevention of disabilities progressing from early danger signs of complications.
(2) Immobilization of limbs with even minor injuries, wounds and ulcers.
(3) Simple care of early eye complications.
(4) Provision of protective footwear including suitable modifications as indicated.

Essential to the delivery of primary medical care is the adequate training of physician and auxiliary medical worker in order to fulfil their decisive responsibilities. International training centres are now available where physicians can be exposed to both didactic teaching and active demonstration programmes in which management and prevention of disability is an integrated element in routine treatment. Several centres nationally and internationally situated, offer similar training opportunities for various categories of auxiliary medical workers. However, essentially it is the responsibility of the trained physician or supervisor to provide in-service training for those for whom he is responsible. Training is a continuous process in which every level of worker must be involved through refresher courses, training programmes designed to up-grade the standard of performance, and most important of all is the need for constant interaction between the supervised and supervisor.

3. REHABILITATION

Rehabilitation is the process of being involved in assisting the handicapped individual to reach his "maximum potential for normal living, physically, psychologically, socially, vocationally." However, before a patient is referred to a rehabilitation service, it must be insured that he has passed through the services of *primary medical care,* regardless of the degree of disability when first seen by a physician or auxiliary medical worker. The physician responsible for primary care must first fulfil his responsibilities in his own area of competence. Rehabilitation is a specialized activity requiring advanced skills on the part of those engaged in it.

Reconstructive surgery which has formed a large part of previous reports of this panel, is not considered in detail this year. This is not to minimize its importance, but to emphasize that it should not ordinarily be considered part of the responsibility of the leprosy control team. This is a special discipline which requires years of training. The surgeon who undertakes such training should ordinarily use his expertise for reconstructive surgery of any deforming disease including leprosy. Ideally, rehabilitation services should be integrated in order to make the maximum use of skilled manpower available.

In areas of high leprosy endemicity there may be a place for a full-time leprosy surgeon, but rarely for a physician who is a part-time surgeon.

Similarly, in Vocational Rehabilitation, it is not ideal for a physician or even a social worker to undertake to train patients for the skills required to become self-supporting in their future life. This is a field for vocational counsellors,

industrialists, agriculturalists, engineers, business men, marketing specialists, and placement officers. Such experts may often be persuaded to give part time service voluntarily to assist in this important and even decisive activity in successful rehabilitation.

In the area of the specialized skills of physiotherapy and occupational therapy, training in the management of disabilities arising from leprosy is also required. However, it is a sufficiently narrow field that it has been proven practicable to use technicians who are trained by qualified therapists, and who then devote their whole time to the physical problems of leprosy including the mobilization of stiff joints and splintage of injured limbs, re-education after surgery and the special training of patients to work without damaging their hands and feet.

Every leprosy control and rehabilitation programme also needs a shoemaker. With training and experience such a skilled individual may make a most valuable contribution and should be regarded as a full member of the professional team.

Many disciplines are required in leprosy rehabilitation. It is imperative that personnel be recognized for the particular skill they can bear as a member of a team. Mutual respect among members of the team is of primary importance to insure that the patient remains the object of the care offered rather than the exercise of professional prerogatives.

We recognize that full integration is impractical at this time but as a first step, all centres that are able to offer comprehensive rehabilitation services to leprosy patients should accept a proportion of those with disabilities arising from causes other than leprosy. Centres which have so far excluded leprosy patients should similarly be encouraged to accept a proportionate number of such cases. This is not a simple matter, however. Few general rehabilitation workers and medical personnel have had experience in dealing with the problems posed by patients with anaesthetic limbs. Special training of all grades of staff will be required to enable them to adapt their skills and basic techniques to the needs of leprosy patients. It is particularly advocated that medical universities and teaching hospitals realise the importance of ensuring that both student and staff are exposed to the rehabilitation needs of leprosy patients.

4. SOCIAL WELFARE

We recognize that substantial numbers of leprosy patients are so severely disabled that rehabilitation is not a practical possiblity. They are, nevertheless people, and have a basic human right to live with dignity and self-respect. They need care. Their needs are often primarily social and thus are deserving of the best possible social welfare service that the community in which they live can provide, equal in every way to services offered those whose physical, social and economic disabilities derive from other causes. Facilities designed for the care of only those whose disabilities arise from leprosy are to be deprecated. There is evidence to suggest that serious disadvantages arise in attempting to care for the totally and permanently disabled in institutions primarily meant for the short term care of medical and surgical complications of patients requiring primary medical care and definitive rehabilitation services.

The social welfare services ought to be integrated, providing for the needs of those whose disabilities arise from causes other than leprosy as well as those whose disabilities do arise from leprosy. Ideally these severely disabled patients should be cared for in their own families. Where homes cannot be found or where

families cannot accept the patient, substitute families should, if possible, be provided.

In this connection we have considered alternate uses for the traditional type of leprosarium or sanatorium.

(1) A gradual phasing out of the segregated facilities and the development of Leprosy Hospitals as the base hospitals for leprosy control programmes.
(2) Such institutions may become hospitals that offer general medical services if in an under-served area.
(3) Some may assume the responsibility for providing specialized care of the permanently disabled, regardless of the cause of disability.
(4) Where there is a general hospital in the vicinity of the leprosarium, the hospital activities including short-term care of leprosy complications should be integrated with the general hospital. In some instances additional facilities will be required to become an integral part of the hospital and sharing all facilities for patient care.

5. COMPREHENSIVE COMMUNITY HEALTH PLANNING

It is well to recognize that in many communities, attitudes toward leprosy patients are unsatisfactorily conditioned by the presence of severely disabled patients who are non-productive and hence a costly burden to the community. Attitudes are also conditioned by outmoded methods of leprosy control that segregate the patient and isolate his care from the public health services offered to the community for other diseases.

There is evidence to suggest that the provision of good, primary medical care that includes leprosy treatment and management, helps to change public attitudes. Prejudicies fade away when the public observes that the medical profession accepts responsibility for the care of the leprosy patient as any other. Community attitudes will also be favourably influenced when it is observed that the leprosy patient may continue as a self-respecting contributing and thus, respected member of the community.

In addition, a systematic approach to Health Education in the community is important. This is necessary in order to ensure that the desired changes in attitudes actually take place. This will involve a careful diagnosis of the situation, preferably by social scientists with special training in this field. There will be particular emphasis on the discovery of beliefs in the community about the causation of the disease, their specific attitudes to leprosy and those whose lives have been interrupted by it, their specific attitudes toward deformity. Only through such in-depth understanding can it be expected that health education methods will be devised to alter attitudes. Leaders of community opinion will be identified and special efforts directed toward them. This must begin with the medical and auxiliary medical professions.

Diagnosis will be followed by the definition of specific measurable goals. Planning is necessary and the advice of specialists in education should be sought to determine the most suitable means of bringing about measurable changes in attuitudes.

The use of trained volunteers for the actual execution of the programme should be explored as should the possibility of using carefully chosen leprosy patients as health educators.

Into all such health education programmes should be built means of evaluation to determine effectiveness and to determine needs for effective methods.

6. SUBJECTS FOR FURTHER INVESTIGATION

(1) The problem of neuropathy.
(2) A systematic and widely acceptable approach to the training of staff.
(3) Operational research to evaluate the methods in use for the health care delivery systems to leprosy patients.
(4) Social anthropology and patient psychology studies as a basis for a better understanding of the patients' viewpoints in order to develop better patient health education.
(5) Study of comprehensive Community Health Planning projects into which leprosy treatment has been integrated to determine whether they offer more efficient means of case-finding and case-holding as well as the prevention of social and vocational dislocation.
(6) Surrounding or in the vicinity of many leprosy institutions, communities of discharged patients have settled. In other instances there are selfmade communities, citizenship in which is determined only by having had a direct or indirect association with leprosy. In many instances the members of the community will have become socially and economically marginalized by a long term stay in a leprosy institution. How may the development of such communities be prevented? What practical methods may be used to restore individuals and families into normal community life?

7. RECOMMENDATIONS

(1) That arrangements be made for further exchanges between personnel involved in leprosy control and rehabilitation so as to define more effectively the role of primary medical care and the prevention of disabilities in leprosy control programmes.
(2) That the International Leprosy Association be requested to include a combined meeting of panels on Leprosy Control and Rehabilitation in the next Congress.
(3) The problem of peripheral neuropathy is of sufficient importance to warrant the arrangement of a separate section to discuss this subject at the next Congress and that the International Leprosy Association be so requested.
(4) To foster a wider dissemination of information concerning advances in management and research of leprosy, voluntary agencies are encouraged to provide subscriptions to the major leprosy journals for medical universities throughout the world.

Lepr. Rev. (1974) **45**, 74-77

News and Notes

LEPROSY RESEARCH IN OXFORD

Delegates at the recent Congress in Bergen must surely have been heartened to see evidence of continued efforts in leprosy research from Professor A. G. M. Weddell's group in the Department of Human Anatomy, Oxford. This work started over 10 years ago in cooperation with the National Institute for Medical Research in London, when Dr R. J. W. Rees began sending tissues for histopathological examination, with particular reference to the mechanism of nerve damage in leprosy. Tissues from the NIMR itself have come mainly from the mouse model, but the work has expanded to include a wide range of human biopsy material from the Leprosy Research Unit of the Medical Research Council in Sungei Buloh, Malaysia. Numerous publications pay testimony to the value of the mouse model in leprosy research, to useful parallels between the pathology in man and mouse, and to the special place of the mouse in experimental work on drug metabolism, dapsone resistance, BCG, bacillary viability and immunology.

In recent years the work of Dr Elizabeth Palmer and D. G. Jamison has been carried on by Drs Rosa Edwards (microbiologist), Janny Boddingius (electron microscopist) and Colin McDougall (clinician). In association with Professor Weddell their main interests are now (1) the mechanism of nerve damage in leprosy, with special reference to the integrity of the perineurium and its permeability; (2) the ultra-structure of the leprosy bacillus in the treated and untreated patient, the effect of anti-leprosy drugs on the morphology of the bacillus, and the patterns of phagosomes and lysosomes which occur at different stages of lepromatous disease; (3) the physicochemical penetration of anti-leprosy drugs into mammalian peripheral nerves; (4) the histopathological and bacillary changes, as seen on light microscopy, in skin, nerve, muscle and scrotum following various drug regimes; and (5) the histopathology of lepromatous leprosy in the nose.

The opening of an Annexe by Dr R. G. Cochrane on 11 August 1970, made available 6 beds for the admission of leprosy patients at the Slade Hospital in Oxford. Although the total is small, some highly bacilliferous patients have been admitted during the past 3 years for diagnosis, classification and treatment; in the course of this basic service to the patient and referring physician, biopsies have been taken for light- and electron-microscopy, studies have been carried out on the excretion of bacilli from the lepromatous nose, and valuable information obtained on the clinical and histopathological response to drugs, particularly Rifampicin.

The Oxford research workers wish to record their sincere thanks to LEPRA for continuing financial help with salaries and scientific equipment.

HIND KUSHT NIVARAN SANGH—ANNUAL REPORT FOR 1972

The Annual Report for 1972 of the Sangh is, as usual, interesting and informative. Although much of the Report covers routine activities, factual accounts of courses of training, the preparation of publicity material and the like, an imaginative reading between the lines provides some indication of the significant progress achieved over the years. In matters of health education, radio talks, the dissemination of literature and posters (in railway stations), and the special efforts for World Leprosy Day, the record for 1972 was well up to the standard set in previous years.

Leprosy in India is resuming publication under the Editorship of Dr Dharmendra after a regrettable lapse and irregular publication. Data on legislation on leprosy, deriving from the central Government and the states, are being collated and examined with a view to discovering lacunae and inconsistencies. The State Branches of the Sangh have shown commendable initiative and energy.

Much remains to be done in India if the considerable leprosy problem is to be tackled with hope of success. *Leprosy Review* sends to *Hind Kusht Nivaran Sangh* its congratulations and best wishes for the future.

ELEP MEDICAL COMMISSION

At the meeting of the Medical Commission held in Brussels on 14 December 1973, reference was made to the death on 2 December of Dr L. P. Aujoulat, *ex-Ministre,* and a former Chairman of the Commission. Dr Aujoulat was perhaps the best-known and the best-loved French doctor in African francophone territories. His very extensive knowledge of public health problems in the tropics, based on a lifetime of intimate personal acquaintance with ordinary villagers and political leaders, was of recent years freely placed at the disposal of those concerned especially with leprosy.

More emphasis will in future be given to health education through World Leprosy Day, and the social aspects of leprosy will receive wider publicity. The need for regularity of treatment will be stressed in radio broadcasts in many countries.

The Medical Commission reviewed and assessed several applications for research grants, and evaluated the feasibility of a number of leprosy programmes in many countries. When it is remembered that about a third of leprosy patients receiving treatment are registered in programmes financed by Member-Organizations of ELEP, the responsibility of the Medical Commission in offering advice on these diverse schemes for leprosy treatment and control may be appreciated.

TROPICAL MEDICINE CONGRESS, ATHENS

At the Ninth International Congress of Tropical Medicine and Malaria, held in Athens from 14 to 20 October 1973, one of the concurrent sessions was devoted to leprosy.

Papers were read by B. Myrvang (Immunological evaluation of the spectral concept of leprosy), A. Bryceson (Leishmaniasis as a model for leprosy), E. Heid (Comparative skin testing), and A. Theodoridis (Cryoglobulins). Cultivation studies were presented by D. G. Jamison and J. Delville, and the preliminary

results in a controlled rifampicin trial were reported by S. R. Pattyn. S. G. Browne (who was the organizer of the Leprosy Session) examined leprosy programmes within the framework of endemic disease control.

The first and last topics particularly evoked lively discussion, and the unorthodox but careful work of Delville on the demonstration of non-acid fast "stages" in a possible complex life-cycle of *Myco. leprae* stimulated much thoughtful comment. The suggestion of Myrvang and his colleagues, working at the Armauer Hansen Research Institute, Addis Ababa, that prolonged exposure to leprosy induces demonstrable changes in lymphocytes and macrophages was received with great interest.

Despite the increasing tempo of research into diseases afflicting people in the medico-geographical tropics, the deeper knowledge of pathogens and vectors, and the development of curative and preventive agents, the actual delivery of services to those in dire need of them appears to make little progress. As in leprosy, so in schistosomiasis, trypanosomiasis, the helminthiases, the rickettsioses and the other major diseases, the gap between the research laboratory and the rural populations of the developing countries is no narrower today than it was 20 years ago. It became apparent during the Congress that *non*-medical factors such as the motivation and conscience of medical workers (including research workers, students and auxiliaries), the inertia and conservatism of village communities, and the self-centred allocation of resources play a greater rôle in community health and sickness than the level of medical knowledge available.

PAPUA NEW GUINEA MEDICAL JOURNAL—COMMEMORATIVE ISSUE

It was a happy thought to mark the Hansen Centenary by a Commemorative Issue of this *Journal* [16 (2)], and to invite well-known leprologists to add their contributions to those of local workers.

Clezy gives a useful historical study of "Hansen and his bacillus", Browne surveys the world scene in his "Leprosy today—a reappraisal". Local contributions come from Russell ("Leprosy in Papua New Guinea"), Clements and Ramsay ("Leprosy control: five years in the Southern Highlands"). Kerr writes on social factors and Kennedy on "Institutional care". Clezy follows with articles on Footdrop and Plantar ulcers, supplemented by a summary on Physiotherapy by Hamilton.

We are brought up to date with very useful contributions from Waters (Immunology), Shepard (Experimental chemotherapy), Ridley (Histopathology) and Rees (Experimental Leprosy). The rôle of voluntary agencies is emphasized by McKeown. Current medical practice in the specially difficult conditions obtaining in Papua New Guinea receives adequate mention.

Altogether, an excellent collection of articles that should stimulate interest in leprosy and raise the standards of care.

"KUSHT" OR "LEPROSY"?

The (Indian) State Branches of the Hind Kusht Nivaran Sangh—the lineal descendant of BELRA, the British Empire Leprosy Relief Association in India—are being requested by the National Headquarters to consider a suggestion made by Lieut-General S. N. Chatterjee (Director-General of the Armed Forces Medical Services), that the Hindi word "Kusht" be omitted from the full and

official title of the Sangh. It is felt that the term, which is commonly used for leprosy in Hindi-speaking circles, is rather "repugnant" and that a substitute should be sought. The Tamil Nadu Branch suggests that a non-Hindi name for the Association has much to commend it, and suggests that the title should be "Indian Leprosy Association" and that the State Branches should be free to use a name in the regional language.

HUMAN RIGHTS AND MEDICAL ADVANCES

A Round Table on the protection of human rights in the light of scientific and technological progress in biology and medicine was held in Geneva in November 1973, under the auspices of the Council for International Organizations of Medical Sciences (CIOMS). A panel of 32 distinguished scientists, theologians, philosophers and jurists opened the discussions on the chosen themes, and participation from the representatives of some of the 87 international scientific member-organizations was welcomed.

Some of the topics considered were only indirectly related to leprosy, such as the social implications of new genetic and medical techniques; the definition of death; euthanasia; abortion and sterilization; the use of food additives; and experiments in psychiatry. Others impinge upon leprosy in a very real way; for instance, the clinical testing of new drugs and procedures, and experimentation on human subjects. The ethical and moral implications of some of the new techniques, like amniocentesis and genetic engineering, were hotly discussed and debated.

The International Leprosy Association (which, incidentally, was elected to the Executive Committee of the CIOMS at the preceding business meeting) was represented at the Round Table by its Secretary-Treasurer, Dr S. G. Browne. He took the opportunity of putting in a plea for the rights of leprosy sufferers who in some countries are being by-passed by the medical and social services, and denied medical treatment, education, employment, privacy, and even freedom. When social, legal and sometimes ecclesiastical disabilities are hallowed by custom, enshrined in legislation and acquiesced in by the medical profession, groups of stigmatized individuals, obviously deformed or apparently healthy, are still suffering discrimination.

In the past, the Council of the Organization has convened Round Tables on such subjects as heart transplantation, drug abuse, and the training of research workers. It has developed into a kind of ethical watchdog or conscience for the medical sciences, and while retaining its links with WHO and UNESCO is able to maintain an independent and objective stance in regard to the moral aspects of medicine.

PERSONAL

Dr J. MacB. C. Bisset, and Dr E. W. Price, both of whom have given many devoted years to the service of sufferers from leprosy, have been awarded the O.B.E. in the New Year Honours; Dr Bisset for services to the advancement of Leprosy control in Thailand, and Dr Price for services to leprosy control in Ethiopia. We offer to both our very sincere congratulations and best wishes.

Lepr. Rev. (1974) 45, 78-82

Leprosy and the Community

LEPROSY CONTROL IN ETHIOPIA[a]

S. G. BROWNE

An account is given of the Government programme of leprosy treatment/control in Ethiopia, in which 48,352 patients out of an estimated total of 125,000 have been brought under treatment, mainly through clinics operating in small market towns. Reasons for the failure of premature attempts at integrating the leprosy service into the general health services are given. Tribute is paid to the co-operation of voluntary agencies, the work of ALERT, and the Armauer Hansen Research Institute.

The modern history of leprosy in Ethiopia really begins with the founding of the Princess Zenebework Memorial Hospital (near Addis Ababa) in 1932, although the Order of Malta had established an Institution for the study of leprosy in Tigre Province some two years previously. His Imperial Majesty, Haile Selassie I enlisted the co-operation of the Sudan Interior Mission, which built the hospital with a grant from the American Leprosy Missions, Inc. The World Health Organization and UNICEF showed interest in the leprosy problem in Ethiopia, and in 1958 welcomed an application from the government for assistance.

While the prevalence rates of leprosy in Ethiopia are not high by African standards, yet in a population of about 25 million a rate of 5 per 1000 means that some 125,000 persons are suffering from the disease. Higher rates than the overall are found in the Central Highlands (10 to 25 per 1000) and in the South East Highlands (10 to 15 per 1000). At present, some 48,352 patients are under treatment, about half of them by voluntary agencies working closely with the government and conforming to the official programme of leprosy treatment.

Given the scattered nature of the population, the poor communications, the low standards of hygiene, and the rudimentary rural health services, it is obvious that low-cost coverage is the only practical way forward. The "market saturation" principle has been adopted, by which treatment is made regularly available at all markets where people congregate on set days. By self-reporting and personal recommendation of registered patients, word gets around that leprosy can be treated. The need for this provision can be estimated from a consideration of the population density in the given area, together with an appraisal of the prevalence rate of leprosy as adjudged from small representative pilot surveys. Since it is suspected that about 15% of the 125,000 leprosy sufferers have some degree of disability and that 5% are totally disabled, the economic cost to the community of neglected leprosy becomes apparent.

[a] Based on a report by E. W. Price, Chief of the Leprosy Control Project, Imperial Ethiopian Ministry of Public Health, Addis Ababa.

Premature attempts at integrating the developing leprosy service into the general health services failed. Many reasons for this failure may be advanced; for example, the inadequate data of leprosy prevalence provided from inadequate surveys; the existence of static treatment centres, ill sited and ill suited for dealing with a chronic stigmatizing disease requiring prolonged treatment; the lack of central and peripheral control of drug despatch and distribution; and finally, poor supervision of the clinics and their standards of diagnosis and treatment. As a result of a bureaucratic decision to integrate, the regularity of attendance of patients fell to 10%, many of them failing to attend after the initial visit when they registered. It was the experience in many centres that medical auxiliaries, though responsible for treating everybody, neglected patients suffering from leprosy. If plans for combining treatment for leprosy with treatment for other endemic diseases can be developed locally–with full regard to local conditions and due deference to local sociological factors–then self-defeating, premature, attempts at integration would not be advocated.

Since 1964, mobile clinics have also been a feature of the anti-leprosy campaign. The main objects have been to provide treatment for as many patients as possible, as near their homes as is possible, and as early in the disease as possible. Hence, in addition to "market saturation", simple static clinics, "treatment posts", are provided every 10 km. It has been found that regularity of treatment depends on other factors than the sophistication of the service provided, but the low educational standards of the majority of medical orderlies militates against the raising of standards of treatment.

Cost/effectiveness enquiries have revealed that it is uneconomic to provide a treatment post for fewer than 20 patients. Where the prevalence rate/population density is high, then special facilities for leprosy treatment are necessary; but where this ratio is low, use should be made of existing health facilities.

The co-operation of voluntary agencies in the leprosy control programme is welcomed, and financial inducements are offered to those bodies conforming to official plans and recommendations to move into the rural areas with domiciliary treatment schemes. Tribute is paid to the valuable co-operation of voluntary agencies, who bring finance, experienced staff, and dedicated medical auxiliaries into the anti-leprosy campaign.

Although rehabilitation as such is only marginally the concern of the Report, appreciative comments are made on the work of ALERT in this field, and that of the Ethiopian Leprosy Relief Association. The influence of ALERT in raising standards of diagnosis and care, of laboratory cover and reconstructive surgery, and of teaching in an All-Africa context needs no emphasis, and the fundamental contributions made in the Armauer Hansen Research Institute, which is situated close to the Princess Zenebework Memorial Hospital, are being acclaimed the world over.

The anti-leprosy campaign in Ethiopia has much work to do and it has got off to a solid and promising start.

LEPROSY IN THE U.S.S.R.

Monsieur Marcel Farine, the President of *Emmaüs Suisse* (the Swiss Leprosy Relief Association) and this year's President of ELEP, paid a visit to the U.S.S.R. in September 1973.

At present, about 2000 leprosy patients are cared for in 16 leprosaria; some

70% of these are probably there for life, since they suffer from such gross deformities that they cannot be reintegrated into society. In addition, about 4000 are treated as outpatients. In 1972, 100 new cases were diagnosed in the whole of the country. Students from outside the U.S.S.R. account for 40 cases diagnosed during the past 20 years.

Leprosy research institutes in Moscow, Astakhan and Rostov-on-Don are interesting themselves in a wide range of problems appertaining to leprosy. Many doctors, besides those working in the institutes themselves, are concerned with leprosy in the U.S.S.R., and 176 leprosy specialists meet regularly for seminars and discussions on problems of research and treatment.

For the past 6 years, the activities of the Moscow Research Institute have been closely linked with the Leprosy Section of the WHO. *Emmaüs Suisse* has helped by providing chemical reagents difficult to come by in the U.S.S.R., as well as photographic supplies.

INAUGURATION OF GOVERNMENT SPONSORED LEPROSY CONTROL PROGRAMME IN SIERRA LEONE

Fifteen years of survey and rural leprosy control work by voluntary agencies in Sierra Leone received official recognition and support in January 1973, with the inception of a Government sponsored leprosy control programme designed to cover the whole country.

Sample surveys, undertaken by the late Dr C. M. Ross in 1957, revealed a prevalence of leprosy in Sierra Leone sufficient to demand specific control measures, especially in the Northern Province. LEPRA, which had sponsored the survey, appointed Mr Lowes, an experienced Leprosy Control Officer from Nigeria, to organize out-patient clinics in all the Districts of that Province in co-operation with the Ministry of Health, to which Mr Lowes was officially attached.

In 1963, Catholic Relief Services (CRS) began to assist leprosy work in Sierra Leone, following up the opening by the Catholic Mission, Makeni, of three general and leprosy clinics in the Bombali District. The whole programme, organized by Mr Lowes, LEPRA representative, and the Rev. Rocco Serra, then Director of CRS, was based on mobile units covering the whole of the Northern Province, with transport provided by OXFAM and LEPRA, and CRS providing food for patients. In a few months the new programme had an additional 6000 patients under treatment. Dr Leo Stocco, a missionary doctor with experience in leprosy work in China and East Pakistan (now Bangla Desh), joined the Catholic Mission, Makeni, in 1965 to participate in this programme.

In 1966 the German Leprosy Relief Association also began to participate, assisting generously with the building of a hospital centre at Makeni, comprising wards for about 30 patients, operating theatre, laboratory, physiotherapy and chiropody facilities, and an orthopaedic shoemaking centre, plus a general and leprosy outpatients' clinic. The same organization maintains the centre, and with expatriate help, five Sierra Leonians are being trained as cobblers.

LEPRA increased its assistance for the Sierra Leone Programme both by substantial grants-in-aid, and by providing three more Leprosy Supervisors to be attached to the Ministry of Health and be responsible for the Southern and Eastern Provinces.

With this substantial assistance, augmented by the interest and help of Cafod

known leprosy patients in all three groups received treatment throughout the trial period. After the 8th year, the incidence of leprosy in the villages that had received prophylaxis throughout was 0.43/1000; in the control villages, it was 1.31/1000; in the villages that had received prophylaxis for the first 4 years only, it was 1.46/1000.

Leprologist and an Administrative Director under the Deputy Chief Medical Officer, General Manager and Director of the Programme. (b) A Leprosarium at Masanga for special cases of leprosy and rehabilitation. (c) A Leprosy Hospital at Makeni for cases of reaction and temporary hospital treatment. (d) Shoemaking Centres at Makeni and Masanga to provide proper sandals and shoes for patients with foot ulcers. (e) A ward for leprosy patients attached to a number of hospitals in the country. (f) Sixteen Mobile Units to bring health education and treatment to the patients in their own villages. (g) Each Centre, attached to the local hospitals, has a Leprosy Control Officer as supervisor of the teams. Three Medical Doctors with special training in leprosy, residing in Makeni, Masanga and Bo, will be responsible for the medical aspects of the programme.

TEACHING FILMS ON LEPROSY

Science Service (Berlin 31 Sächsische Str. 26) announces that the long-awaited film entitled *Leprosy* is now available. This 30 minute colour film, with sound-track in English, French, German or Spanish, has been produced under the auspices of WHO and with the co-operation of leading leprologists from several countries. It was "shot" in Jerusalem, Ethiopia, Venezuela and Geneva, and concentrates on diagnosis, treatment, and rehabilitation, with some reference to the histopathological basis for the clinical findings. The price (excluding postage) is DM 2000 for a copy on 16 mm Eastman-colour Kodak, or DM 500 for the version on ½ in magnetic tape (Philips). Other sizes (35 mm and Super 8) are also available. Special prices will be quoted for medical institutions.

Two other films, 24 minute sound and colour, entitled *The Treatment of Leprosy* and *The Rehabilitation of Leprosy Patients*, are also on sale by the same organization at prices of DM 1500 on 16 mm Eastman-colour Kodak, or DM 500 on ½ in Philips magnetic tape.

When shown at the recent International Leprosy Congress at Bergen, *Leprosy* evoked appreciative comments. It should prove very useful in teaching medical students and physicians in countries of the Western world where clinical demonstrations are not generally possible. The quality of the presentation may be judged by the fact that, at the Berlin Film Festival in 1973, the film was awarded a Gold Medal.

(a) DAPSONE PROPHYLAXIS; (b) LEPROSY IN CHILD CONTACTS[a]

Dapsone prophylaxis confers an estimated 50% protection, according to an investigation in which the population in half the villages randomly selected, was given dapsone for 4 years, while the other half was used as a control. In the second 4-year period, the prophylactic drug was discontinued in half the villages that had previously received it, while in the other half it was continued. All

[a] Indian Council for Medical Research, Hind Kusht Nivaran Sangh, Annual Report, 1972, pp. 25-26.

(England), Fame Pereo (Canada), and Friends of Leprosy Patients in Italy and the U.S.A., the Ministry of Health in 1972 decided to sponsor a Leprosy Control Programme to cover the whole country, and this was inaugurated in January 1973.

Organization of the programme. (a) A central office in Freetown with a

The second investigation reported concerns a study made in Calcutta of the child contacts of leprosy patients. Out of 166 contacts of patients with contagious forms of leprosy, 72 had skin lesions, in 18 of which acid-fast bacilli could be demonstrated. Histological study showed epidermal changes in 22, subepidermal in 4, dermal in 25 and nerve pathology in 8. In the remaining 94 subjects (who had no visible skin lesions), acid-fast bacilli were found on histological examination in 4.

Among the 88 child contacts of patients with non-contagious forms of leprosy, 9 had skin lesions, in 8 of which no bacilli could be found on standard methods of examination; in one patient, scanty bacilli were found in a nerve.

Among the 79 children with no visible skin abnormality attributable to leprosy, only 1 showed acid-fast organisms in the smear.

Lepr. Rev. (1974) **45**, 83

Book Review

Historia de la Lepra en Espaňa, by Felix Contreras Dueñas and Ramon Miquel y Suarez de Inclan, 1973, Madrid. Graficas Hergon, S. L., Miguel Servet, 15. 207 pp. and Index.

This semi-popular history of leprosy in Spain traces the course of the disease from the earliest possible allusions in Egyptian papyri down to the 20th century. The authors refer to the various theories of the origin of leprosy before describing the more definite influx into Spain of the sufferers from a clinical entity resembling leprosy as the result of the wide-ranging voyages of sea-going Phoenician traders. It is probable that the spread of leprosy to the countries bordering the Mediterranean is to be explained more in these terms than in the overland caravans that criss-crossed the Roman Empire.

The Iberian peninsula suffered military incursions of the Arabs, which included the quieter invasion of *Myco. leprae* of the south and east of present-day Spain. Thereafter, the returning Crusaders brought more leprosy into the country. In their turn, Spanish conquistadores took leprosy with them into the Carribean and Central and South America and as far north as the lands that would later become the southern States of the United States of America. The vexed question of the pre-Columbian existence of leprosy in the Western hemisphere is bedevilled by nomenclature and by the dearth of accurate clinical descriptions in the ancient records, and also by the importation of *Myco. leprae* along with the slaves from the West Coast of Africa.

A valuable part of the book gives details, with dates, of the founding of hospitals for leprosy sufferers in South and Central America–Dominica, Mexico, Peru, Argentina, etc.–and further afield by Spanish priests in Japan.

The distribution of leprosy in modern Spain is described, province by province, and indications are given of the patchy nature of the endemic and the measures taken to alert doctors and the public of the signs of the disease. The wide influence of Spanish leprologists and of South American leprologists who have looked to Spain for inspiration and example, is shown in the contributions made at successive International Leprosy Congresses, particularly those held in Havanna (1948), Madrid (1953) and Rio de Janeiro (1963). By their training activities and research such centres as those at Fontilles (Alicante, Spain) and in Brazil, Argentina, Venezuela, and Mexico, continue to play a notable rôle in the struggle against leprosy.

Fitting tribute to Dr Contreras is paid by Raoul Follereau in a foreword.

S. G. Browne

Lepr. Rev (1974) **45**, 84

Letter to the Editor

May I draw the attention of your readers to a discrepancy in the published version of my paper entitled "The Nasal Mucus in Leprosy", which appeared in *Leprosy Review* (1973) **44**, 33-35?

In the 2nd paragraph, page 34, the phrase "(and unconfirmed histologically)" should be amended to read as follows:

"(and confirmed histologically in 7 representative patients out of 41)".

J. C. PEDLEY

Leprosy Review regrets that a misleading impression may have been given in the condensed version of Dr Pedley's paper.

Lepr. Rev. (1974) **45**, 85-93

Abstracts

1. LECHAT, M., MELARTIN PREHN, L., BLUMBERG, B. S. & MORIS, R. **Australia Antigen in Zaire. Studies in Leprosy.** *Ann. Soc. belge Méd. trop.*, 1973, v. 53, 173-178.(trs).

The authors studied the prevalence of Australia antigen in 936 patients in Zaire: 98 were pygmoid and the rest Bantu. Standard Ouchterlony double-diffusion methods were used.

The percentage of sera positive for Au antigen was 2.6. No differences were found between 286 patients with lepromatous leprosy, 361 with tuberculoid leprosy, and 191 healthy people.

S. G. Browne

2. BECHELLI, L. M., *ET AL.* **Some epidemiological data on leprosy collected in a mass survey in Burma,** *Bull. Wld Hlth Org.*, 1973, v. 48,(3), 335-344.(trs).

This paper should be studied in detail. It sets out objectively the most significant findings in the WHO survey in an area of Burma where prevalence rates of leprosy are high or very high.

The high lepromatous rates recorded were found in districts where the total prevalence rate and the annual incidence rate were both high. About 3% of such a population is prone to develop lepromatous leprosy if sufficiently exposed to infection.

The highest prevalence rates (48.11 per 1000) were found in the 30-39 years age group, in which the lepromatous rate was 12.5 per 1000. No child under 10 was found suffering from lepromatous leprosy. This observation was interpreted as an expression of the long silent period and the length of time generally noted before overt signs of lepromatous leprosy appear. Indeterminate leprosy was commonest in all age groups below 14, reaching its peak in the 10-14 group.

There was a true and significant male predominance: 40.4 cases per 1000 among males, and 24.0 among females. Under 10 years, the sex prevalence was approximately equal.

On the figures presented, multibacillary leprosy (that is the lepromatous and borderline forms combined) is only 3 times as contagious as tuberculoid leprosy, but it may be that contacts of patients with tuberculoid had also been exposed to persons suffering from the multibacillary forms.

It is noteworthy that on subsequent surveys, only indeterminate and tuberculoid leprosy was seen in the new cases. Initial lesions were found on thighs and buttocks; less frequently, on arms, forearms and legs.

Bacilli were demonstrated in skin smears of patients with tuberculoid leprosy, particularly if recourse was had to histopathological examination. Bacilli were also occasionally found in the nasal mucosa in such patients, and even in ear lobes of patients with clinically inactive tuberculoid leprosy or in the preclinical state.

It is considered that higher prevalence rates of tuberculoid leprosy are indicative of the spread of leprosy rather than of a higher level of resistance among the population. Leprosy can show itself at any age: the most important factor is exposure to infection. Given infectious index-cases, high prevalence rates may occur in any ethnic group, provided that the socio-economic and environmental factors are propitious. The early diagnosis and adequate treatment of patients suffering from indeterminate leprosy is probably a Utopian ideal, but one worth striving for.

S. G. Browne

3. NOORDEEN, S. K. **Epidemiology of (poly)neuritic type of leprosy.** *Leprosy in India,* 1972, v. 44, 90-96.

Accepting as criteria for the diagnosis of the neuritic type of leprosy, the presence of an area of cutaneous hypoesthesia and an enlargement of the corresponding nerve trunk, the author suggests that this type may account for about one-sixth of all cases of leprosy diagnosed in a rural area in South India. Clinical examinations of the population of about 8000 were made every year for 5 years. Among the 800-odd new cases of leprosy discovered, 106 were classed as neuritic.

In the majority of cases (56 out of 63) in one series, the lesion was confined to one limb, usually the lower. The lateral popliteal (44 cases) and ulnar (16 cases) were the nerves most commonly affected by far.

Males were affected more commonly than females in the proportion of 3:1, and the incidence increased definitely with age.

Spontaneous remission was the rule, though complete return of sensation did not usually occur. The 7 patients who had taken treatment were the only ones (out of 44 studied and followed up) in whom the nerve enlargement had not regressed.

The prognosis of the neuritic type of leprosy is considered to be similar to that of tuberculoid leprosy.

S. G. Browne

4. DELVILLE, J. P. **The differential diagnosis of *Mycobacterium leprae* based on its behaviour *in vitro* in human macrophages.** *Ann. Soc. belge Med. trop.*, 1973, v. 53, 195-199.

The author suggests that since the mouse footpad inoculation technique sometimes fails to differentiate between *Myco. leprae* and certain other mycobacterium (such as *Myco. abscessus*), his method of inoculating macrophage cultures with suspected *Myco. leprae* should serve as a differentiating procedure. He finds that the behaviour of *Myco. leprae* is different from that of other mycobacteria in certain objectively observable respects. *Myco. leprae* appears to be relatively non-toxic for the macrophages: whereas, ordinarily, most inoculated macrophages die within a few days, those that ingest *Myco. leprae* regularly survive for 3 to 4 weeks or even longer.

Again, formations resembling globi are sometimes seen in macrophages containing *Myco. leprae.* Whereas other mycobacteria may multiply outside the macrophages, *Myco. leprae* does not.

The number of macrophages taking up *Myco. leprae* in the inoculum is small. but the organisms disappear rapidly from the inoculum. The author interprets this finding as due to digestion of the organisms by the macrophages. He concludes that a mycobacterium that multiplies slowly in macrophages produces globi and does not cause the rapid destruction of the cell in which it is growing, has characteristics corresponding uniquely to *Myco. leprae.*

S. G. Browne

5. PRICE, E. W. & PITWELL, L. R. **The mineral content of inguinal nodes in barefoot people with and without elephantiasis of the legs.** *J. Trop. Med. Hyg.* 1973 v. 76, 236-238.

The study of oedema of the legs in patients suffering from long-standing lepromatous leprosy has led the senior author by a long and devious route to an investigation of the presence of trace elements (metals and silicon) in the inguinal lymph nodes of Ethiopian subjects.

Since in lymphatic tissues these elements may act as non-living physical irritants producing a sarcoid-like granulomatous response, with eventual disturbance of lymph flow and consequential blockage, the demonstration of the presence of silicon and aluminium in all cases and of beryllium in all but two, is worthy of note. No differences in metal content were discernible between subjects with elephantiasis of the legs and those without.

S. G. Browne

6. BROWNE, S. G. **Comment reconnaitre la lepre en Suisse. (How to recognize leprosy in Switzerland).** *Med. et Hyg.* 1973, v. 31, 1203-1204.

This practical article is intended primarily for general practitioners and dermatologists in Switzerland, and for any Swiss doctor who has medical dealings with people who have spent some time in countries where leprosy is endemic. With about 700,000 "guest workers" in Switzerland (not counting dependants), most of them from Southern Europe, the chance of leprosy being missed, or misdiagnosed, is quite considerable.

The author alerts doctors to the commoner modes of presentation of leprosy in the Western World, and discusses briefly the diagnostic criteria.

Author's Summary

7. GEIGER, J. **Behind the Bamboo Curtain.** *World Med.*, 1973, v. 9 (22), 15-23.

Although leprosy does not figure in this illuminating inquiry into the kind of medicine now being brought to the millions in mainland China, the reference to the use of barefoot doctors–their training, competence, deployment and activities–will be read with interest and profit by leprosy workers engaged in the preparation of medical auxiliaries for the leprosy programmes in different countries. The point is well made that for purposes of primary health care and the control of transmissible disease, such auxiliaries can be rapidly trained and widely (and wisely) deployed–at a small fraction of the cost of fully fledged Western style doctors, and the value of their work is apparent to all.

The curious admixture of traditional remedies and modern synthetic drugs, of "spot diagnosis" and the ready availability of facilities for major surgery, the rather naïve credulity and the sophisticated and pragmatic organization, should stimulate much radical thinking in countries where conventional medical services have made little impression on the leprosy problem.

S. G. Browne

8. VAUGHAN, J. P., MENU, J. P., LINDQUIST, K. J. & VENNEMA, A. **A trial with mixed BCG/Smallpox vaccine given intradermally.** *J. Trop. Med.* 1973, v. 76, 10.

Leprosy workers engaged in BCG vaccination programmes for tuberculosis/leprosy prophylaxis investigations will be interested to learn that the simultaneous administration of BCG vaccine and smallpox vaccine at the same site has no adverse effect on the efficacy of either vaccine. Whether the vaccines are delivered by a transcutaneous route (using the bifurcated needle) or intradermally, and whether the vaccines are actually mixed or not, apparently leads to interference, no loss of potency, and no increase in the rate of complications. As judged by the criteria of post-BCG allergy and reactions to vaccinia virus, the simultaneous administration of the two vaccines seemed, if anything, to have a mutually enhancing effect.

S. G. Browne

9. TOYOHO MUROHASHI & KONOSUKE YOSHIDA. **Stimulating effect of pyruvate on the growth of *Mycobacterium leprae* in cell-free, semisynthetic, soft agar medium.** *Bull. Wld Hlth Org.* 1973, v. 48, 571-579.

The authors report the growth of an organism resembling *Myco. leprae* in their semi-liquid, cell-free, soft agar medium, incubated at 37° C. The addition of pyruvate as a carbohydrate source seemed to stimulate multiplication to such a degree that after 50 weeks' incubation micro-colonies appeared in the primary culture. A bacterial suspension prepared from the first subculture of this strain elicited the same skin reactions in patients with lepromatous and

tuberculoid leprosy as did the standard Mitsuda antigen. On these grounds, the authors conclude that the organism isolated was indeed *Myco. leprae*.

S. G. Browne

10. **Third International Colloquium on the mycobacteria—"The Genus Mycobacterium"** *Ann. Soc. belge Méd. trop.*, 1973, v. 53, No. 4, 210-425.

This entire number of the Belgian *Annales* is devoted to papers presented at the Colloquium (held in Antwerp from 1 to 3 December 1972) and expertly edited and presented by S. R. Pattyn, who writes both the Foreword and the concluding chapter.

The papers (in English, French and German) give an excellent indication of the growing points of mycobacterial research, excluding *Myco. leprae* and *Myco. lepraemurium* (because of the imminence of the International Congresses in 1973).

Workers in microbiology will find in this volume a fascinating wealth of material, and research leprologists will appreciate the stimulating investigations now proceeding in many European laboratories. The identification of various mycobacteria has now reached a stage when Reference Laboratories can function. Many newly-indentified organisms are being discovered in the environment—especially in the tropics.

The direct and indirect bearing of these studies on the problems posed by leprosy will become increasingly apparent with the passing years.

S. G. Browne

The following abstracts are reprinted, with permission, from *Trop. Dis. Bull.* 1973, v. 70 and 1974, v. 71.

11. MOHYSEN, A. M. & ALEMAYEHU, W. **Application of Nyka's method for the staining of mycobacteria in leprous skin sections.** *Acta Path. Microbiol. Scand., Sect. A,* 1973, v. 81, No. 1, 71-4.

At the Armauer Hansen Research Institute in Addis Ababa a modification of Nyka's method was used to stain sections; this consisted firstly of removal of paraffin and rehydration, then the section was left in a trough of 5% periodic acid for 4 hours, then it was washed, and stained with carbolfuchsin—prepared from basic fuchsin, absolute alcohol, phenol and distilled water—for 30 min at 70° C. The section was decolorized with 2% lactic acid in 70% alcohol, and counterstained with haematoxylin, and "blued" in lithium carbonate. Adjacent sections from biopsy specimens from 10 patients with lepromatous, 8 with tuberculoid, and 2 with indeterminate leprosy were stained by the Ziehl-Neelsen (ZN) method and by the modified Nyka's method. In the lepromatous tissue Nyka's method "showed significantly greater number, of bacilli and a higher proportion tended to stain solidly" (the latter statement may seem surprising). Two photomicrographs support this statement. A table with the details of the other 10 biopsies shows that Nyka's method revealed from 3 to 5 times as many leprosy bacilli per section as the ZN method. Three sections from patients with "tuberculoid" leprosy showed by the ZN method 48 to 69 bacilli per section (!). It would seem that this modification of Nyka's method should replace the ZN method, but the authors advise against this because of the "relatively poor contrast" obtained (the illustrations do not support this statement).

C. S. Goodwin

12. GOTTLIEB, L. S. & SOUTHGATE, M. T. **Acute adenopathy in a young man.** *J. Am. Med. Ass.*, 1973, v. 224, No. 13, 1737-46.

This is the verbatim record of a case presentation and discussion. The patient, a young Portuguese man, had lived in Angola for 6 years until he entered the United States 9 months

before the onset of his illness. He was admitted to the Boston City Hospital 2 weeks after the sudden appearance of a tender mass in his groin for which he received penicillin treatment as an out-patient. On admission he was febrile and delirious, with enlargement and tenderness of the lymph glands, especially those in the inguinal and femoral regions. Out of a large number of investigations, only the tuberculin test was positive, with an induration of 20 mm, and treatment for tuberculosis was started, but without beneficial effect. It was noted at this time that lymph node aspiration produced abundant acid-fast material, but this was thought "possibly to be artifactual".

The discussion was led by Dr F. A. Neva who dealt with the many possibilities in the differential diagnosis and concluded that the patient was suffering from *erythema nodosum leprosum*—the diagnosis of acute lepromatous leprosy was subsequently confirmed, and "retrospective examination did indeed reveal the typical cutaneous and neurological lesions of lepromatous leprosy". This discussion, in which a number of experts in tropical medicine and pathology took part, makes interesting reading in the original, and provides details of further clinical and pathological investigations. There are 10 photomicrographs in colour which show the histology of the lymph glands and of skin and sural nerve preparations. A section of a gland showed "massive numbers" of acid-fast bacilli.

Twelve cases of leprosy have been seen in Boston "in the past year".

F. I. C. Apted

13. RAMANUJAM, K., RAMU, G., BALAKRISHNAN, S. & DESIKAN, K. V. **Nephrotic syndrome complicating lepromatous leprosy**. *Indian J. Med. Res.*, 1973, v. 61, No. 4, 548-56.

"The clinico-biochemical features of nephrotic syndrome developing as a terminal event in five cases of lepromatous leprosy who were subjects of recurrent lepra reaction along with the post-mortem findings in two of them are presented. The various aetiological factors that might have played a part in the causation of this condition in this group of cases are discussed. It is suggested that the recurrent episodes of lepra reaction, which in the acute phases were associated with abnormal urinary findings indicative of a focal glomerulo nephritis, could be due to the occurrence of lesions in the kidneys structurally similar to *erythema nodosum leprosum* or precipitation of antigen-antibody complexes in the glomeruli. Amyloidosis may be a more frequent accompaniment of recurrent lepra reaction than hitherto known. Properly designed studies for the assessment of renal functions supported by renal biopsies will serve to gauge the type of renal involvement."

14. FRIEDMANN, P. S. **Dapsone-resistant leprosy**. *Proc. R. Soc. Med.*, 1973, v. 66, No. 7, 623-4.

The patient, a woman aged 48 from Guyana, had been living in the U.K. for 15 years. Painless papules had developed on her face, arms and legs over the past 4–5 months. At first she denied having had any previous illness, but later admmitted that she had been treated for leprosy in Guyana at the age of 13 and had been taking dapsone (sent from Guyana), 50 mg twice weekly for at least 20 years. Acid-fast bacilli were present in "vast numbers" in the skin lesions.

In comment on this case presentation, Dr Stanley Browne said that the long history of self-medication with dapsone, perhaps irregular, and the recent subacute clinical exacerbation with a high proportion of morphologically normal leprosy occurring as the result of the emergence of drug-resistant organisms. The small fleshy papules, of no special distribution, were typical of clinical relapse. He also mentioned the value of the mouse footpad inoculation in confirming drug resistance (see *Trop. Dis. Bull.* 1968, v. 65, abstr. 2828; 1971, v. 68, abstr. 1013). All patients hitherto found with dapsone-resistant bacilli have responded to either clofazimine or rifampicin.

F. I. C. Apted

15. RUSSELL, S. L. & RUSSELL, D. W. **Isoniazid acetylator phenotyping of Amharas in Ethiopia.** *Afr. J. Med. Sci.,* 1973, v. 4, No. 1, 1-15.

Eighty-seven male Amharas in Gondar, Ethiopia, 19 Tigreans, and 14 Gallas were given 100 mg isoniazid at 07.00, 12.00 and 17.00 hr. On the next day at 07.00 hr urine was collected, and "acetylisoniazid: isoniazid ratios" (A:I) were determined. The "antimode" was at A:I 40 in the Gallas, A:I 10 in the Tigreans, and A:I 20 in the Amharas. Rapid acetylation was found in 5 Gallas, 9 Tigreans, but in only 15-17% of the Amharas. "The relevance of these findings to intermittent dapsone therapy of leprosy merits further study."

C. S. Goodwin

16. ROA, P. S. S., KARAT, A. B. A., KALIAPERUMAL, V. G. KARAT, S. **Prevalence of leprosy in Gudiyatham Taluk, South India. Part I. Specific rates with reference to age, sex, and type.** *Int. J. Lepr.,* 1972, v. 40, No. 2, 157-63. **Part II. Geographical variations.** *Ibid.,* 164-70.

In Gudiyatham Taluk in South India 276 568 people, 91% of the "rural population", were examined for leprosy. (The unexamined 9% may have contained many people with leprosy.) 7142 patients with leprosy were discovered. There were "only 731 female patients" for every 1000 male patients. The prevalence increased with age from 1.8% in children aged 5 to 9 years to 4.2% in adults aged 30 to 34 years. Geographically, the prevalence of leprosy per thousand population ranged from 12 to 126, with a mean of 26. The prevalence was higher in the hill areas. 16 tables and figures give the detailed results.

C. S. Goodwin

17. QUAGLIATO, R. Relatório sobre a Hanseníase no Alto Juruá (Estado do Acre). **(Leprosy in the Upper Juruá, Acre State, Brazil).** *Anais Bras. Derm.,* 1972, v. 47, No. 377-97.

This is a report on the incidence of leprosy in the Upper Juruá river area of Acre, Brazil's newest and most remote state; one of the two main towns, Cruzeiro do Sul, is situated 1400 km west of Manaus and only 180 km from the borders of Peru, and the capital, Rio Brancho, is 600 km to the east of Cruzeiro do Sul. Communications are very bad and as yet almost entirely dependent on the river (although the trans-Amazon highway is being built); information on the incidence of the disease is scanty but the author states that it is very high as, in 1970, of the total population of the state of 112,000, there were thought to be at least 1200 cases; this incidence is at least 16 times higher than that which WHO regards as high endemicity, and the upper Juruá river area seems to be particularly affected. The state has 2 leprosaria situated in the 2 main towns; there are also 2 dispensaries and 2 preventoria, also in the 2 main towns; the preventoria are now being renamed "Educatoria", and are where children living with an infective patient can be re-housed and given some education. According to the author, in 1970 not more than half the patients had had treatment in the past year and, as for ascertainment and prevention, since trained staff are almost non-existent, he suggests the use of 5th or 6th year students who, after some special instruction in the disease, could be sent to the area to carry out investigations and treatment; the provision of a fully equipped launch would also be of the greatest possible value.

(Although the author mentions both main towns it seems that the figures he gives relate almost entirely to the area under the aegis of Cruzeiro do Sul, but the distance of 600 km from there to the capital gives the reader some idea of the immense problems to be solved.)

W. K. Dunscombe

18. DRUTZ, D. J. & GUTMAN, R. A. **Renal manifestations of leprosy: glomerulonephritis, a complication of *erythema nodosum leprosum*.** *Am. J. Trop. Med. Hyg.*, 1973, v. 22, No. 4, 496-502.

In a study of 636 in-patients at Taiwan's national leprosarium, where the majority suffered from lepromatous leprosy, 11 were found to have urinary abnormalities consistent with glomerulonephritis, and there was a strong correlation with a history of *erythema nodosum leprosum* (ENL). In another (more detailed) study of 41 out-patients referred to the U.S. Naval Medical Research Unit No. 2, 21 of whom had lepromatous leprosy, 8 had active ENL and 7 of these reacting patients had urinary findings suggestive of glomerulonephritis, but such changes were absent in all the others. A total of 7 renal biopsies were carried out on patients with ENL (from both study groups) and 2 were found abnormal; these showed proliferative glomerulonephritis.

As ENL is considered to be an immune complex syndrome the authors suggest that immune complexes may be deposited in renal vasculature in some cases of ENL and give rise to glomerulonephritis.

W. H. Jopling

19. JOSHI, P. B., SHAH, A. H., AGASHE, P. K., BAFNA, R. G. & JOSHI, P. V. **Ocular manifestations of leprosy**. *Indian J. Med. Res.*, 1973, v. 61, No. 3, 435-41.

In Poona, India, the eyes and eyebrows of 654 patients with leprosy were examined, 84% of the patients were non-lepromatous. Posterior synechiae were found in 13 non-lepromatous and 3 lepromatous patients, and iritis in 9 of the former and 3 of the latter. Five tables give details of the lesions, but true ophthalmic lesions did not seem to have been frequent.

C. S. Goodwin

20. VERMA, K. C., SINGH, K. & CHOWDHARY, S. D. **Dapsone toxicity**. *J. Indian Med. Ass.*, 1973, v. 60, No. 7, 255.

This is a report of psychosis occurring in an Indian female aged 30 years after 1½ years of dapsone therapy for lepromatous leprosy. She had been treated as an out-patient and at no time received more than 300 mg a week. Dapsone was stopped and she was admitted to a psychiatric ward where she made a rapid recovery, but an attempt to re-introduce dapsone therapy, 50 mg daily, had to be abandoned when her mental symptoms recurred.

W. H. Jopling

21. KIRCHHIEMER, W. F., STORRS, E. E. & BINFORD, C. H., **Attempts to establish the armadillo (*Dasypus novemcinctus* Linn.) as a model for the study of leprosy. II. Histopathologic and bacteriologic post-mortem findings in lepromatoid leprosy in the armadillo.** *Int. J. Lepr.*, 1972, v. 40, No. 3, 229-42.

This paper presents an autopsy report on the first nine-banded armadillo to be infected with lepromatoid leprosy (see *Trop. Dis. Bull.* 1972, v. 69, abstr. 1692) which died of the infection 520 days after inoculation. As the histology is described in some detail and finely illustrated, interested workers are advised to consult the paper in the original. In general, the findings are those of an intense lepromatous (LL) infection with more widespread systemic dissemination than occurs in man. Some of the differences from the corresponding human infection may be due to the lower body temperature of the armadillo, but they are attributed also to a greater immunological susceptibility of this animal. The numbers of bacilli in the lesions were enormous and, in the ear lobe, were calculated to exceed by 200 times the numbers per gram of heavily infected human skin.

In the skin, tissue response was mainly in the deep lesions, although it did also extend up to the epidermis without any clear zone at the inoculation site. Nerves in the skin (and also the left peroneal nerve) showed invasion of bacilli in appreciable numbers, and the perineural tissue was similarly involved, but less so than in human lepromatous leprosy. Heavy lepromatoid lesions were found in the liver, spleen, lymph node, bone marrow (but not the muscle attached to the bone), lung, meninges and oesophagus. There was less severe involvement of testes, kidney, and some other viscera. Multiplication in the mouse footpad was obtained with *Myco. leprae* from the armadillo's skin, liver and inguinal lymph node. (The armadillo is obviously an interesting model from many points of view, and also a promising source of supply of *Myco. leprae*.)

D. S. Ridley

22. DI MARTINO, M., GUALDI, G. & MARRACINO, F. Attualtá sulla lebbra: aspetti epidemiologici e preventivi. **(The present position of leprosy: epidemiological and preventive aspects.)** *Nuovi Ann. Ig. Microbiol.*, 1972, v. 23, No. 5, 361-91. English summary (4 lines).

This is an extremely interesting report on the recent incidence of leprosy throughout the world. The authors point out that the true incidence is not known but give figures (Table 2) of registered and estimated cases by continents and countries; in 1965 these were 2.8 million and 10.8 m, and by 1970 it was not thought that they had altered greatly. However, the chronicity of the disease, the difficulty in the diagnosis of early cases and the costs of treatment and prevention multiply the problems. The authors discuss the diagnosis of stained films by the light microscope and the presumed difference in pathogenicity of fully stained, presumably live, bacilli and partly stained, possibly dead, bacilli; they feel that this subject is still obscure and are uncertain whether any prophylactic significance can be ascribed to this difference. The immunological state will have repercussions on the type of the disease and there may even be persons who are relatively resistant (see also *abstr.* 83 below). For treatment, thalidomide and B 663 (Lamprene, clofazimine) for leprotic reactions are mentioned, and also the various and numerous anti-leprosy drugs in current use, particularly rifampicin, although dapsone still seems the general maid-of-all-work. For prevention, the infectivity of the leprotic forms makes it especially important that children should be removed from such patients (but what of the indeterminate forms?) and the value of BCG vaccination of children is extensively discussed. Here the three great BCG campaigns in Uganda, New Guinea and Burma are mentioned, the success of the first being balanced by the failure in Burma, while the results in New Guinea are equivocal to say the least; so here also the position is still by no means clear.

The authors conclude that, in spite of all the efforts of those interested throughout the world, leprosy still retains some as yet undiscovered secrets.

(This paper is very well worth reading in the original for its extremely well balanced views).

W. K. Dunscombe

23. FIELDSTEEL, A. H. & McINTOSH, A. H. **Attempts to cultivate and determine the maximum period of viability of *Mycobacterium leprae* in tissue culture.** *Int. J. Lepr.*, 1973, v. 40, No. 3, 271-7.

"Repeated long-term attempts have been made to cultivate *Myco. leprae in vitro* in cultures derived from tissues of man, mouse and rat. These attempts were uniformly unsuccessful. However, it was possible to demonstrate that most of these tissues could be maintained from 110 to 413 days in a single passage with only minimal changes of nutrient fluids. When these tissues were infected with *Myco. leprae* and maintained at either 31°C or 34°C, phagocytosis was highly variable, ranging between 23% and 100%. In these experiments, cultures of murine origin appeared to be more favourable milieu than cultures of human tissue for maintaining viability of *Myco. leprae* over extended periods of time. Seven of the eight experiments in which *Myco. leprae* survived from 28 to 118 days were in murine tissue cultures."

24. MYRVANG, B., GODAL, T., FEEK, C. M., RIDLEY, D. S. & SAMUEL, D. R. **Immune response to *Mycobacterium leprae* in indeterminate leprosy patients.** *Acta Path. Microbiol. Scand., Sect. B,* 1973, v. 81, No. 5, 615-20.

"Immune responsiveness to *Mycobacterium leprae* was examined in 31 histologically classified indeterminate leprosy patients. Fourteen of the patients were also classified as indeterminate clinically (strictly indeterminate group), while the other seventeen patients were clinically classified as tuberculoid or borderline leprosy. The strictly indeterminate group appeared to be quite homogenous in their immune reactivity to *Myco. leprae.* All patients revealed a lymphocyte transformation of less than 3% (mean 0.57 ± 0.88) and only 1 out of 7 patients tested by the leucocyte migration technique revealed a migration index of less than 0.80 (mean 0.91 ± 0.16). Only one patient gave a positive early lepromin reaction. None of the patients revealed a positive reaction in gel precipitation to mycobacterial antigens. These findings are in agreement with the view that the immune response to *Myco. leprae* has not been triggered off in srtictly indeterminate leprosy. On the other hand, the clinically tuberculoid and borderline patients with an indeterminate histological picture responded on average more strongly to *Myco. leprae,* and by and large according to their clinical diagnosis. It is concluded that in classifying patients as indeterminate leprosy, the clinical picture may give more information than histopathology."

25. LOAIZA, W. O. Lepra en el Ecuador. **(Leprosy in Ecuador.)** *Medna Cutánea,* 1972, v. 6, No. 6, 447-50. English summary (6 lines).

The author mentions that the Andean Cordillera divides the country into 3 zones: (a) a coastal zone which has a hot and humid climate and where most of the cases of leprosy occur; (b) the sierra which is cold and dry; (c) the lower eastern zone consisting of tropical forest.

Historically, leprosy is thought to have arrived in the country with the Conquistadores but there are certain curious features as in the lower eastern zone and in the Galapagos islands where no autochthonous cases have been detected. The national anti-leprosy campaign began in 1963 although there had been no attempts at leprosaria before then. Between 1963 and June 1971 over 770,000 persons had been examined out of a total population of just over 6 million, and 1894 new cases detected. Of 1862 cases classified, the numbers were: lepromatous 765, tuberculoid 436, indeterminate 618 and dimorphic 43 (no details are given of the missing 32). Of the new cases 152 were in children under the age of 15 years, most of whom had the indeterminate form. In general, more males were affected than females and this was particularly the case in those over the age of 15 years. Over the 17 provinces of the country the incidence ranged from 0.02 to 1.21 per mille. The author stresses that there are important foci of the disease in 6 provinces, two of which border Peru, and he regards the degree of infection as of moderate intensity.

W. K. Dunscombe

CONTENTS

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