SESSION 3—12 MAY 1965

Dr. Binford. Dr. Robert C. Parlett, Professor of Microbiology at George Washington University, who was a very active participant in our committee for planning this meeting, will introduce the next speaker.

Dr. Parlett. It is my great pleasure this morning to introduce our next speaker, a man who has devoted much active research to mycobacteria. I enjoyed hearing him give a very interesting paper on *Mycobacterium ulcerans* infections at the last Leonard Wood Memorial Conference. He comes from Antwerp, Belgium, where, since 1950, he has been Director of the Prince Leopold Institute of Tropical Medicine. I take great pleasure in introducing Prof. P. G. Janssens to you.

Dr. Janssens. Mr. Chairman; members of the Conference: When I was invited to participate in this Conference I was so pleased that I agreed at once, but I quite misunderstood what I was asked to do. According to my personal interpretation I should have introduced the subject of leprosy research in an institute for tropical medicine during a round table discussion similar to the one we had at Johns Hopkins University four years ago. I was surprised and frightened when I learned from the preliminary program that I was scheduled for a formal lecture this morning. I would not have missed this meeting for all the copper of the Katanga, as we say, and so decided to think the subject over during the transatlantic flight and write my paper on arrival in Washington. The subject is a difficult one, and I realize that many participants here today may not understand how institutes for tropical medicine are kept alive in western Europe. So I shall say a few words on that subject first.

Leprosy Teaching and Research in Institutes of Tropical Medicine

P. G. Janssens, M.D.[1]

The majority of the institutes for tropical medicine are located in western Europe. This may give the impression that they are remnants of bygone colonial days, kept artificially and aimlessly alive. The fact is that even the World Health Organization insists on their maintenance, since they remain the principal depositors of the knowledge and experience accumulated during the past century in the field of tropical medicine. It is the duty of these institutes to keep that information available for the upcoming local generation of practitioners, teachers, and research personnel, and pass their experience on to them just as they provided it in the past to emigrant European doctors. The very reason for their foundation has been that a western type of medical training was unsuitable for efficient work in the tropics. This has not changed much, since while unfortunately curricula of the same type have been transplanted into the majority of the new universities overseas, a complementary training aimed at the medical work in tropical conditions is as necessary as ever, and not less so for the local doctors.

As a result of the changing pattern of geographic distribution of disease due to environmental factors, leprosy has become essentially a tropical disease. Although its teaching should be carried out at the medi-

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cal school, it is so neglected there that it has become a "must" for the institutes for tropical medicine.

From the recent literature on leprosy, one must agree with Muir's conclusion that "the easy time in leprosy has gone." Leprosy teaching and leprosy research programs must, therefore, be adapted thoroughly to this situation in all of the fields concerned. It may seem quite easy at first sight to fulfill these obligations, but on second thought several problems do appear.

If we take the clinical and therapeutic aspects first, it is obvious that leprosy must be diagnosed and treated in a clinical department attached to the institutes concerned. In this way we will provide the consulting patients with skillful help and be able to demonstrate the many puzzling clinical aspects of leprosy to our students. The clinical observation of a few selected cases will be of very high quality in a clinic equipped with all existing modern diagnostic aids. Although the clinicians in charge will endeavor to bring about useful improvements, their main concern will still be to confirm in a few patients the real value of the diagnostic and therapeutic trials as carried out in field conditions.

Teaching will not be restricted to this presentation of a few patients. It must transmit in a practical way the classic facts in the many fields concerned: pathology, bacteriology, immunology, epidemiology, diagnosis, evolution, treatment, and, of course, the current accepted classifications. Nobody would dare to suggest that this teaching is useless, because everyone does know that leprosy is the "parent pauvre" of medicine. Leprosy is not taught at all in the majority of medical schools, where many hours are happily devoted to curiosities without real value for basic medical training. Leprosy is systematically and intentionally ignored, even by practitioners in countries where the disease may be found at every street corner. Leprosy patients may even not be accepted in the skin clinics of some countries.

In the teaching process it should not be forgotten that in rural areas many general practitioners will have to devote themselves to the well-being of leprosy patients. They will end up as so-called "leprologists," who are in fact good-will amateurs, without serious technical training in the many disciplines involved. For this reason it is advisable to cover, during the training period as far as possible, the whole field, including epidemiologic surveys, histopathologic diagnosis, therapeutic evaluation, health education, rehabilitation, and physiotherapy. It is important, in planning the training, to supplement lectures on what we do know by information on what we ignore. The reason for this is that research will have to rely heavily on a comprehensive collaboration with workers in the field.

The clinical approach to leprosy would benefit to a great extent by more accurate information on several matters. A major item is the recognition and the significance of very early signs, the "hazy spots," latent leprosy, the cyclic evolution, and the spontaneous healing of leprosy. As Dr. Cochrane suggested, it would be fortunate if we could, in analogy with what has been done for the precancerous state, find a new terminology to designate the very mild and beginning lesions. Actually one may hesitite to diagnose "leprosy" as such since it is a "major disease" in many countries and involves many social implications.

A better record of the onset, morphologic appearance, localization, and evolution of most leprosy lesions is still commendable. We should know the "porte d'entre," the nature of monomacular lesions, the degree of depigmentation, cutaneous nerve involvement, the sweating process, the exact temperature of the lesions and the body, the anesthesia, the cyclical evolution, and the self-healing tendency. The evolution of skin lesions will be ascertained in suitable fashion by color photography, provided pictures are made under identical conditions and at regular intervals. Some patients see their macules disappear quickly; in others they may remain stationary; in a few there will be dangerous exacerbations. This is true also for nerve involvement. Some patients never proceed toward nerve or atrophic complications, while others will develop

very serious nerve involvement, although they may never show more than one macular lesion.

The study of symptomatology should never be restricted to a dermatologic, ophthalmologic, radiologic, endocrinologic or any other special medical examination. Leprosy must be integrated in the total picture and context. By extending our diagnostic procedures and clinical observations we will provide the medical profession with a good possibility for first-hand knowledge of leprosy, and thereby ease up the systematic opposition to admission of leprosy patients in hospitals and clinics. Many consultants will thus not only become interested in leprosy, but will be surprised to learn that among leprosy patients numerous cases of otherwise rare disturbances (gynecomastia, nipple hypertrophy, amyloidosis, etc.) may be found. Furthermore, it might happen that through this contact with a large variety of leprosy problems, some of the difficulties encountered in recruiting leprologists may be overcome.

By insisting in our teaching on our lack of knowledge in many fields, the way will be opened for a comprehensive and factual programing of research, and a powerful indirect stimulation to research at the highest level will be provided.

A good example is the bacteriologic approach to leprosy. The presumptive organism, *M. leprae*, was almost the first bacterium identified as causing a human disease. But about all we do actually know about this mycobacterium is its rod shape and its acid-fast staining, facts somewhat complicated by the possible existence of morphologically totally different forms. Our failure to cultivate this germ and to infect the ordinary laboratory animals with it will be stressed. The bacteriologist will, of course, insist that our failure is due to *M. leprae's* own faulty behavior, which does not conform to ordinary bacteriologic ways and means. For more than 90 years *M. leprae* has remained the only impossible customer for the bacteriologists.

A new generation of microbe hunters is currently hotly engaged in breaking through this "barrier" by new approaches and modern technics. Thus far they have been at least partially successful. But much simpler and faster methods will have to be found if this new effort is to lead to practical routine applications. Although valuable contributions have been made recently, there is still need for a reliable, easy test by which the viability, the multiplication and the infectivity of *M. leprae* can be demonstrated. Generally *M. leprae* do not disappear from the skin and the nasal secretions after years of treatment. In other patients, however, they are gone after a few weeks of treatment, or may even disappear without treatment. In still others they may all of a sudden be present in huge numbers. We know nothing about the significance of these variations from the point of view of infectivity. The excellent general health of so many lepromatous patients harboring billions of mycobacteria is the more surprising when we realize in what a severe way the same amount of *M. tuberculosis* would undermine the patient.

Since no one so far has been able to reproduce a typical histologic lesion in an experimental animal, *M. leprae* falls short of fulfilling "Koch's postulates." Acid-fast organisms have been isolated by the dozens, over and over again, since the time of Bordoni. Uffreduzzi initiated the cultivation of such germs out of lepromatous tissue in 1887. Although none of those cultivable mycobacteria is *M. leprae*, they may well play an important role in the pathogenesis of leprosy and give us some new clues to solve this difficult problem.

The teaching of immunology usually does not go much farther than discussion of the lepromin test and its two types of reaction, the Fernández and the Mitsuda varieties, and of the complex problems of BCG vaccination and its possible value. But every leprologist really needs one or more classic or modern serologic tests to be able to take care of difficult diagnostic problems like the detection of healthy carriers, latent infections, very early infections and information to be used as a criterion of healing.

The epidemiology of leprosy is a sequence of aphorisms, poor statistics and

queries. Many a leprologist's room resembles an administrative rather than a medical office, with its walls covered with colored charts, graphs, and maps. All of this accumulated information represents endless, but also always more or less identical surveys, characterized by poor selection, ill-planned collection, superficial recording, and uselessness for further analysis.

The special aims and the well-known sampling technic of this particular discipline must provide us with better knowledge of leprosy, its distribution throughout the world, the incidence of its basic forms, and an overall picture of factors involved in the presence and transmission of, infection by, and resistance to *M. leprae*.

What do we really know, for instance, about contamination? The reservoir of the pathogenic organism is constituted by the lepromatous, borderline and reacting tuberculoid patient, and *M. leprae* originates from "overt" skin or mucous lesions. But can *M. leprae* remain alive in the outside world? Does a soil-borne or filth-borne transmission occur? Or is a "skin to skin" transmission the only way for infection? Some good arguments may be brought up in favor of this latter possibility, e.g., the forehead lesion of babies living on their mothers' backs, but many other possible contact places remain healthy and some first lesions also appear on places where skin to skin contact seems next to impossible. What do we know about the role of microtraumatisms, skin temperature, skin physiology, not only in general, but also during infancy, puberty and particularly adult years.

The widely advertised higher susceptibility during childhood is accepted by many and denied by others. Assessments are based often on so-called "clinical experience," which is, of course, a solid ground if the opinion-maker has really studied a fair number of leprosy patients thoroughly. What do we know of the skin, or body, resistance to *M. leprae*? The contamination might be either (1) a generalized invasion by the infecting organisms, whatever their infective form might be, i.e., rods, L-forms or some other form, followed by localization in a so-called primary lesion with the possibility of secondary dissemination from this clinical lesion, or (2) localized infection of some sort of "porte d'entre" type, and only later on an eventual systemic dissemination. Arguments may be produced in favor of both possibilities. Excision of a monomacular lesion sometimes results in definitive healing, but the tuberculoid first lesion is not always a typical macule, healing in its center while extending peripherally; it may be a circular, or a succession of papules without any central origin. Nerve invasion is another matter for thought, since nerve lesions develop progressively in the mycobacteria-poor tuberculoid type, but do appear only much later in the massively infected lepromatous type.

The predilection zones of the primary localizations are known, but more comparative studies on a geographic basis are needed. These should be supplemented by the study of nonselected biopsies and of the lymph node contents in early leprosy and their contacts. It is already known that predilection zones appear not to be identical in India and Central Africa.

The problem of host susceptibility or resistance may be clarified by the genetic research now under way. But again, if accurate information is to be collected on a world-wide basis, under different environmental conditions, and according to the different leprosy types, with or without reaction, it will be done more successfully, and in a shorter time, by a study of the genetic polymorphism in "isolates"—tropical forests, islands, social outcasts, displaced persons—than by a survey of known genetic markers in thousands of patients haphazardly collected.

A valuable survey will never be made under best conditions by a single institution. One of the major problems will be to direct the collection of material and information by centers where the diagnosis of the different types of leprosy is made with accuracy, and where a suitable record of case histories is kept. This selection of cooperative and trustworthy leprosy centers will be made more easily by the institutes of tropical medicine, which have

been working in close contact with the outstanding centers for many decades. The evaluation of the positive or negative role of genetic information in leprosy needs not only a good geographic selection of collecting centers, but also agreement on the technics to be used and restriction to a few departments highly specialized in the performance of certain delicate, sophisticated technics, and agreement also on the regular exchange of control material to ascertain the comparability of the figures obtained in different laboratories, and finally on a centralization of all the records prepared on an identical pattern in one single center where the statistical interpretation could be made. Such a comprehensive program can be worked out only by a large integrated research group, with interinstitutional or, even better, international approach. Emphasis on this suggestion has been made by several authorities in the field, e.g., Dr. R. G. Cochrane, Dr. Stanhope Bayne-Jones, and others here.

The therapy of leprosy is now established on solid ground and trustworthy treatment schemes are well known, including the prevention and handling of the therapeutically troublesome reactions. The chief regret is that the available drugs are not yet good enough. The lack of good criteria for correct estimation of the results of the treatment is often disturbing. It is possible that a study of the lysosome content of a leprosy lesion may be a new avenue to success, but meanwhile many a patient, told by an expert that his disease is by now stabilized or even cured, returns before long in full reaction. This warns the leprologists against overenthusiastic declarations. More usable "screening systems" for trials with new chemotherapeutic compounds are necessary if we wish to keep the pharmaceutical industry interested in leprosy.

It should never be forgotten that reconstructive and plastic surgery transform the future outlook for many invalids completely, provided the successful surgical and restorative measures are complemented by rational physiotherapy.

In discussing therapy, one should include the organization of medical care for inpatients in the all too well-known institutions aiming at a compulsory or voluntary isolation. Isolation should be restricted to the shortest possible time and patients should be transferred for treatment as soon as possible to outpatient sections in dermatologic clinics, health centers, rural clinics, and even home, by competent staff members or by mobile teams. Irregularity in attendance by leprosy outpatients, inherent to the long duration of the disease, is well known; therefore the necessity should be stressed of thorough investigation of the reasons and the excuses. This can be done by careful follow-up of the patients, and analysis of their periods of poor attendance and alleged reasons for nonattendance. The causes may vary from region to region. Scientific approach to the problem is needed, but common sense may be even more useful. For example, in some communities the rhythm of convocation of the population for all kinds of good reasons, such as malaria eradication, tuberculosis control, BCG vaccination, health education, agricultural programing, tax collecting, etc., may be so heavy that everybody becomes fed-up with so much good-will, and as a result leprosy patients ignore the leprosy teams. This defect can be overcome to some extent by integrating in one team the majority of the health promotion activities. The need for including leprosy teaching in the regular curriculum of institutes of tropical medicine will be easily accepted. But if its scope is widened from informative lectures on accepted knowledge to the underlining of the numerous questions requiring or awaiting solution, this teaching will be helpful in rehabilitating the disease among members of the medical profession and might become a powerful stimulus for research. Candidate-leprologists should, however, be given a comprehensive digest of subjects such as those on the program of this conference.

Education of a leprologist does not mean a certain scientific and technical baggage provided once and for all. He will, of course, improve in acquiring experience in this particular field, but he will badly need also current information in the different fields connected with leprosy. The

leprosy journals are well edited, very useful and very stimulating, but in some ways too specialized to cover all the needs of the common practitioner engaged in leprosy detection, treatment, rehabilitation, and protection. A journal is needed also giving general information on recent advances in allergy, skin physiology, comparative pathology, endocrinology, neuromuscular pathology, health education, improved treatment, and rehabilitation technic. Possibly there should be provision for "questions and answers," as well as news about general activities in the leprosy field and the location of leprologists. The publication *Leprosy Briefs* made a tentative start in that direction, but unfortunately has been discontinued. There is need for a substitute publication or reshaped bulletin, enjoyable and practical for the leprologist and his auxiliary personnel. The institutes of tropical medicine should at least collaborate in the production of such a publication.

Research in leprosy is a must for the institutes of tropical medicine and for several obvious reasons, so that good teaching and research may never be disconnected for too long a time. Only a very few, however, are active in this particular field. Apart from teaching, their natural role should be a reliable connection between the field operators and fundamental research.

At the Prince Leopold Institute in Antwerp, Belgium, experimental work on animal inoculation and the multiplication of *M. leprae* in several tissue culture systems has been in progress for several years. S. R. Pattyn will present, at this conference, some of his observations on the thermoresistance of *M. leprae*. Jadin and Wery (see page 600) made successful use of the puncture of lymph nodes of leprosy patients as basic material for the intracellular multiplication of the mycobacteria in cells of human origin in an enriched Hanks medium. Mycobacteria thus obtained are transferable to fibroblasts of trypsinized human skin. This *M. leprae*-intracellular-multiplication-system is under assay for study of the effect of several antileprosy drugs on mycobacteria from different sources and countries. The histopathology of leprosy has always been studied at the Institute. It still goes on, and has been extended recently to histopathology of the bones of leprosy patients and inoculated foot pads of mice. Coutelier works on this particular problem in the widely known department of Prof. Lacroix at the Catholic University of Louvain.

Problems that should be investigated will be brought to the attention of the members of this conference by several participants, and the choice of subjects offered will be more extensive than the existing potentiality in men and research grants. The need for more leprosy research will become more apparent, now that things are really on the move. But it cannot be overemphasized that future research should be on the highest possible level of fundamental studies in biochemistry, microbiology, cellular physiology, genetics, histopathology, and clinical observation. This research should, if possible, be planned on a basis of international coordination and cooperation.

The aim of all institutes of tropical medicine must be to pass on their experience and knowledge, to stimulate research in every possible field, and in every way at their disposal, accept their share of the research burdens, and furnish liaison, wherever necessary, between the field and the research institute. Leprosy should become one of their major objectives.

Dr. Parlett. Thank you, Dr. Janssens, for another very interesting talk. It is now my pleasure to turn the chairmanship of the meeting over to a very good friend of yours and mine, Dr. Russell S. Weiser, Professor of Immunology in the Department of Microbiology, University of Washington, who is a long-time expert in the fields in which we are concerned, which have to do, as yesterday, with the cultivation problem.