# The Need for Bringing Leprosy Research Into Universities[1]

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When Dr. Chapman Binford suggested that I speak at this conference on the above topic my first reaction was "That is just up my street," but when I sat down to prepare this paper I began to realize how difficult a subject I had been given. Nevertheless, I am fully aware of the great importance of bringing leprosy into university research departments, for I have continually emphasized the need for integrating leprosy into the total picture of medical research. Therefore, while I do not feel adequate or familiar enough with research at the university level, nevertheless I welcome an opportunity to introduce this topic at what I believe will be one of the most significant conferences that has ever been held on leprosy, a disease that is attracting an increased amount of attention throughout the world.

I do not claim to be a research worker. I have always insisted on the fact that I am a clinician who is interested in research. I give complete assent to the statement that significant progress in clinical medicine and therapy is absolutely dependent on the fundamental research worker. I have acted on this principle for well over 30 years and, having been privileged to travel widely, and having also met a large number of outstanding research workers in various fields of medicine, I think I can claim that I have had, thanks to the friendship and cooperation of these workers, some little success in integrating leprosy into medicine in general and medical research in particular. I shall, of course, not be able to cover ade-

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quately the large sweep of the subject allotted to me, but I will endeavor to present my subject in such a way that the significance of recent work will be viewed against the whole context of medicine.

In order, therefore, to indicate the importance of leprosy research in connection with the schools and universities of higher learning, I think the best way is to take certain important branches and outline the general approach that universities could make toward a particular problem in leprosy and see just where this would lead one. In this connection I do not intend to deal with the research programs in relation to the *M. lepraemurium,* for scientific and university research in regard to rat leprosy is adequately cared for, and it is because scientific research in connection with the *M. leprae* was so difficult to organize that the attention of bacteriologists and others was turned toward the rat leprosy bacillus.

It was much easier to study the various bacteriologic and biochemical factors in the metabolism of *M. lepraemurium* than to pursue a similar study of *M. leprae.* Now that Shepard (15) and Rees (14) have shown that it is possible to grow *M. leprae* in the foot pads of mice, the way is open for a much more detailed study of this bacillus. I would suggest that the investigation of this mycobacterium should be extended to other animals, for the animals that have been used so far have been the smaller ones with a span of life of approximately two years. Furthermore, the size of the animal itself is a handicap to the harvesting of a reasonable number of acid-fast bacilli and, therefore, it would seem to me more appropriate to use an animal with a longer life, such as a dog or a cat. It may be that the temperature of the foot pads of these larger animals is not suitable to the growth of *M. leprae.* Nevertheless, it would seem worthwhile to set up similar experiments using larger animals for the purpose; if successful, then it will be possible to harvest larger quantities of *M. leprae* and so give the research worker greater scope for his researches in this direction. In view of the interest that is being taken in the whole question of fundamental research in relation to leprosy, it would seem worthwhile to appoint an official committee to coordinate leprosy research work undertaken by quite a number of universities and other bodies interested in leprosy. This committee could be either convened by the Leonard Wood Memorial or else set up as a subcommittee of one of the committees of the National Institutes of Health. In this manner the overlapping of research work would be avoided. The limited availability of *M. leprae* from human sources would be conserved. The total research program would be reviewed so that a fair distribution of the funds to various research workers could be made, and an exchange of opinions mustered so that the total leprosy research program in the United States might be a cooperative, meaningful research program adequately and fully integrated into fundamental research in general and medical research in particular. In this way the whole potentiality of the country for leprosy research would be mobilized.

As a result of the revival of the study of genetics in leprosy,. largely through the work of Spickett (18), a completely new avenue for research has been opened, but this type of investigation can be undertaken only at university level and in association and cooperation with epidemiologists and those well versed in the science of statistics. University departments with their resources and their equipment are capable of setting up a detailed research project in genetics and, as I have already indicated, such a project would have to be undertaken with the departments of human statistics and biophysics, and with the assistance of clinicians well versed in the protean manifestations of the disease, and with a wide experience in the international variations manifested in individuals of different races. It is well known that the clinical manifestations of leprosy in the Caucasian and Mongolian races are very different from the clinical manifestations of leprosy in the Indians and Africans.

A detailed research project from the genetic aspect of leprosy must be based on the assumption that it will involve a considerable amount of time and relatively large funds if it is not going to become, as so many research projects have, of limited

value and conclusions at the end, not adapted to detailed analysis. Therefore three prerequisites are necessary before it would be possible to investigate thoroughly the genetic aspects of leprosy and come to conclusions that would be really valid. The first prerequisite is that the leader of the team must be well versed in the planning of such a project and, preferably, should be an epidemiologist with a wide knowledge and a thorough grasp of the statistical aspects of such an investigation. Associated with the leader of such a team should be a human geneticist, who would be able to direct the genetic aspects of the project, and a clinician with a wide experience in world leprosy, an experience that would enable him to indicate the choice of a main area where the team should work, bearing in mind the variegated patterns of world leprosy. It would be relatively profitless to launch out on sporadic attempts to organize genetic research in leprosy; it must be organized on the highest university level and in cooperation with other fundamental research workers, if valid results are to be obtained. In this connection it is worthwhile repeating a statement which Spickett [18] made to me concerning advanced research in leprosy; viz., "the most hopeful approach to leprosy in terms of the use of time and money for research would be the formation of large integrated research groups; such groups must represent a variety of disciplines, for the pattern of the epidemiology of leprosy is so diverse over the world that groups should be international in their approach. It seems that university centers must have a very clear understanding not only of the need for leprosy research, but of its importance to other scientific disciplines. At the present time leprosy research is, generally speaking, ill-designed and uncoordinated, because communications between research groups and research workers are so poor, because relatively few persons in leprosy research have adequate training in scientific methods. On the other hand, research workers trained in rigorous scientific disciplines often become involved in peripheral matters, because their lack of knowledge of leprosy precludes their recognizing the relevant questions. It is therefore necessary to convene an advisory group to define objectives of leprosy research and to recommend how such objectives may be realized."

Such remarks may be thought uncalled for in a group such as has been called together to discuss research in leprosy, but, nevertheless, when one investigates the place of leprosy research in the scheme of research programs in the universities, one finds that there is either unwillingness or lack of appreciation of the importance of setting up a research project, for as Spickett [18] has rightly said, "leprosy research suffers on two counts; those who are doing what might be called pure research in leprosy tend not to have a vast clinical experience, and those who have clinical experience are out of touch with potential research workers."

In all the great research potentialities that are seen in leprosy there is one factor which still baffles the scientific worker. That is the possibility of growing *M. leprae* in artificial media. Not until we are able to do this and produce regular growth of the organism with the possibility of subculturing *M. leprae* through an indefinite number of generations will we really be able to study the life history of the bacillus, its metabolic requirements, the by-products of its growth, and, what I believe is more important, the break-down products of its death. Such research raises the whole question of suitable media in which to cultivate *M. leprae*. Innumerable attempts have been made over the past century to cultivate *M. leprae*, but none has been substantiated. In this connection one must mention the work of Duval [3, 4], Kedrowski [5], Reenstierna [12, 13], Soule [16], McKinley [6], Soule and McKinley [17], and the more recent investigations of Sister Marie Suzanne [8] and Sister Marie de la Trinite [7]. I am of the opinion that the work of Ranadive, Nerurkar, and Khanolkar [11] should receive more attention. In the first place their approach to the problem appeared to be logical, for they started with posterior root ganglia and found that after a period this organism grew in a medium for *M. tuberculosis*. I made a state-

ment in this connection in the second edition of *Modern Trends in Dermatology* (R. M. B. McKenna, 1954): (1)

> "The work, particularly that of Khanolkar (1951) which demonstrates that *Myco. leprae* first appears in the small superficial nerve plexuses of the skin, suggests that the skin is probably the mode of entrance of the organism, and that this predilection for nerves in the early initial phases points to the possibility that *Myco. leprae* can only become pathogenic in man after passing through the superficial nerve plexuses of the skin. This suggested "passage" through the nerve tissues opens up intriguing possibilities in relation to fresh approaches in the attempt to cultivate the *Myco. leprae*." (1)

In a recent conference I had with Dr. Ranadive and her colleagues certain conditions were laid down for the continuance of these studies. Among these were (a) study of the behavior of the ICRC bacillus in relation to the foot pads of mice, and (b) study of the results of the lepromin reaction, comparing lepromin made from this bacillus and the standard Mitsuda lepromin. I believe that all those who are in any way dealing with leprosy should test their organisms against their behavior in the foot pads of mice, and, further, I am of the opinion that lepromin should be made from the organism and compared with the standard histopathologic picture after use of Mitsuda lepromin. If these two pictures tally, then there is additional circumstantial evidence that the bacillus so isolated, if not *M. leprae,* has a close affinity to it. One must always remember, in the study of *M. leprae,* either in animals or in artificial media, that a change of environment may produce mutants of the organism, and, therefore, that what we are really studying is a different strain and variety of *M. leprae* that has undergone genetic variation. Nevertheless, I think the work on the ICRC bacillus is worth repeating. I do not think that the work of the Cancer Research Centre on the growth of *M. leprae* can be put aside; it needs further, rather close investigation.

In connection with the growth of Schwann cells, an important advance has been made by Margaret Murray (9) of New York University who has succeeded in subculturing Schwann cells. Therefore those who are working in leprosy in relationship to the Schwann cell, should study under Margaret Murray (9), so that the technic of the growth of these cells can be mastered. This, I believe, is of very high priority. As I have already mentioned, the work of Shepard (15) and of Rees (14), is of very great significance, but we will not succeed completely in our quest until *M. leprae* is grown in artificial media, and this again means research at the university level.

It is impossible to review research in leprosy at the university level adequately in the time at my disposal, but the discovery of lysosomes by de Duve (2) and Novikoff (10) is of very great significance in relationship to leprosy research. The presence of the hydrolytic enzymes in these bodies explains why relatively so few persons develop leprosy even after most intimate and prolonged contact. For instance, even in children who are constantly exposed to infection with *M. leprae* under conditions greatly favorable to the organisms, 70 per cent escape infection. In this connection I have been told that Schwann cells are rich in lysosomes. Therefore I make bold to suggest that natural immunity rests in the Schwann cells, and that the great majority of Schwann cells, genetically, have sufficient lysosomal activity to deal with any bacteria that may be introduced into their cytoplasm. I am beginning to form the opinion that in the study of lysosomes in leprosy, we may have the answer not only to those cases that do not improve adequately under therapy and go from one reactive stage to another, but also to those cases that apparently recover and relapse. In order to introduce a conception that may be difficult to accept, which has a direct bearing, I believe, on research at the university level, I must relate events that led me to form the opinion that the reason why certain cases do not respond to therapy adequately, or relapse, lies in the fact that under certain circumstances the cells are

deficient in lysosomes, or else lysosomal activity is inhibited, or weakened, in some way or other.

When I was discussing the question of electron microscopic appearances in tissue sections with Dr. Brieger, I pointed to certain structures within the cells and asked him what they were. He told me that probably they were lysosomes. I asked him what were the functions of lysosomes, and he mentioned that they had the property of destroying bacilli and bacillary debris. It came to me that in these bodies may lie the answer to the whole question of therapy and relapse in leprosy, and I said to him, "Brieger, you have started an idea in my mind which I must investigate to see whether there is any possibility of proving what I am thinking." A few weeks later we had a case of leprosy which had a very serious relapse, and I telephoned Brieger and said, "If my theory is correct, please come and take a biopsy from this patient and tell me whether there is lysosomal activity or not." Shortly thereafter I rang him up again and was told that there was no evidence of lysosomal activity. I went on to make further inquiries and in a conversation with Dame Honor Fell, Director of the Strangeways Laboratories at Cambridge, I was discussing this question of lysosomes and I made two statements, one that the general consensus was that DDS was better given in small dosages rather than in large, and that the general tendency was to reduce our dose of DDS considerably. The second statement I made was that "it seemed that persons who were given corticosteroids were very much worse from the therapeutic point of view than before they were given such drugs." Dr. Fell pointed out that this was a very interesting observation, because it is known that certain drugs in small doses activate lysosomes and in large doses inhibit lysosomal action. Furthermore, the drugs that are the most powerful agents in inhibiting lysosomal action are the corticosteroids. I came to the conclusion therefore that if this were true our dosage of DDS was far too high and that we should reduce it considerably. When I returned to London from Carville last December, I put certain lepromatous cases that had been extremely difficult to treat, on very small doses of DDS, starting with 10 mgm. a week and not exceeding 30 mgm. At the recent All-India Leprosy Workers' Conference, and the Conference of the Association of Leprologists of India, Dr. Stanley Browne from Africa and myself from the West both advocated very much smaller dosages of DDS than had hitherto been given.

On my return from India on March 24, I saw three cases that had been given not more than 30 mgm. DDS a week—one was actually taking 20 mgm. While I have not yet had the opportunity to perform a biopsy on this case, I know that she showed considerable improvement. This was in spite of the fact that, up to then, she had been going in and out of reaction; her history was one of improvement and then relapse, with periodic bouts of erythema nodosum. I began to despair of ever getting her improved clinically; all I could say was that she had not become disfigured or deformed. Three months after she had taken the small doses of DDS the clinical improvement—I must be careful not to overstress the improvement—was at least very much better than it had ever been before.

The second case was one in which relapse had occurred after ten years. Acid-fast bacilli were very numerous throughout the section, and were solid acid-fast rods. I have not had time to rebiopsy this patient, but on clinical examinations the macular lepromatous lesions that had covered the front and back of the chest and were scattered pretty well over the body, had completely disappeared and the patient had a clear skin.

The third case is in the Homes of St. Giles. The patient has had leprosy for at least 30 years. Six months ago he went through an extremely serious bout of reaction; his skin ulcerated and he was in a very distressing state. We gave him a course of streptomycin and isoniazid because there was some question as to whether he had a tuberculous infection. This was subsequently disproved. The patient improved somewhat and was then placed

on long-acting sulfonamides. The improvement, as far as the ulceration of the lesions was concerned, was maintained, but he still had gross signs of the disease. The patient was then placed on 30 mgm. DDS a week and became very much better. His skin was smoother and his lesions had improved definitely. In each of these cases there was no further evidence of any reactive phase setting in.

I am fully aware, as the result of 40 years' experience in the therapy of leprosy, that it is very dangerous to draw any conclusions on such little evidence. Nevertheless, the fact of clinical improvement in cases in which I had pretty well made up my mind that the chance of any improvement was unexpected, seemed of some significance. I suggest to you, therefore, that we have probably been treating our cases of leprosy on entirely wrong lines, and if it is found that DDS in small doses is able to stimulate lysosomal activity in leprosy, that this would account for these interesting results. I suggest, therefore, that when a case relapses it is not a true relapse, but that the continuous administration of large doses of DDS so inhibits lysosomal activity that it enables the *Mycobacterium leprae* to multiply within the macrophage cells. When the dose is reduced to almost a homeopathic level, the drugs begin to act in the opposite way and activate lysosomal action and enable the enzymes, presumably of a lysosomal nature, to destroy the bacilli, and when they are broken up into granules to dispose of the granular remnants.

In a meeting of the Acid-Fast Club in London some three years ago I put forward the suggestion that DDS does not act directly on the bacillus but alters the cellular environment of the macrophage so that the cell itself is more capable of destroying the bacilli and thus the patient recovers.

I am fully aware that those working in Africa and India, and those who have had experience with large numbers of patients who have become negative on standard doses of dapsone will doubt the validity of my remarks, but we do know this, that the Caucasian and Mongolian races are much more difficult to treat and are much more prone to reactive phases than the Indian and African. These observations, therefore, open up a wide field of investigation as to the lysosomal content of the cells in these races, and it may be that there are biochemical or biophysical factors in the cellular structure of the African or Indian race that result in more powerful lysosomal activity. In this connection it is known that the darker races are, generally speaking, less prone to severe reactions and easier to treat than the lighter colored races. Herein lies a field of investigation of pigment cells in relation to lysosomal activity. I am fully aware that all this is speculation, but speculation has its value; therefore I express these thoughts for I believe they will lead to a greater interest in leprosy at the university level and be helpful in the solution of related disease problems.

I must now refer to leprosy as an autoimmune disease. It is generally accepted that the *M. leprae* is the causative organism of the disease, but because of the fact that it is a very lowly pathogen, probably having to pass through neural tissue (Schwann cells) before it becomes pathogenic, certain questions have arisen in the minds of many investigators during the past fifty or more years as to just what part *M. leprae* plays in the total picture of the disease.

The fact that certain early workers expressed doubts as to the *M. leprae* being the cause of leprosy is explained, if, while not denying the presence of *M. leprae* as the initial cause of leprosy, we assume that this organism itself is a relatively harmless parasite first invading neural tissues, particularly Schwann cells, and then the dermal tissues, and finally parasitizing the whole of the reticulo-endothelial system. Its very presence seems to trigger off certain disease processes that precipitate the more serious manifestations and complications of leprosy. For instance, there are serum changes; for example, the presence of cryoprotein and the absence of alpha globulin link leprosy with the autoimmune diseases and collagen disorders, e.g., disseminated lupus erythematosis and rheumatoid arthritis. In a recent paper Trautman and Matthews [19] have shown this link in leprosy with autoimmune pheonmena.

The conclusion, therefore, to which one is forced is that while *M. leprae* is the causative organism of the disease, it appears to set up side reactions that make this mycobacterial invader merely an onlooker quite unable to intervene in the disturbances that have been set up. It is rather like the person who throws a match on dry and arid ground and sets a forest fire going. The match is the original cause, but the forest fire is the effect.

In other words, the presence of *M. leprae* merely serves to trigger a whole series of chain reactions, which render it rather a passive onlooker in a series of malignant processes for which the organism has been initially responsible. The study of leprosy should be linked closely with the general dermatologic approach to disease, and particular attention should be paid to its relationship with disorders of collagen, autoimmune processes, particularly in relation to disseminated lupus erythematosis, and disorders of pigment, such as pigmented nevi. Diseases related to nonspecific clinical manifestations should not be overlooked.

Finally, many will be thinking that the paper I have presented thus far deals with the advanced stage of leprosy, and that I have not added in any way to the question of early diagnosis. I come now to this very important question and open this aspect of my paper by saying that "the first presenting sign of leprosy, in well over 90 per cent of all cases, is anesthesia or an area of numbness, and if leprosy is diagnosed at this stage, then it is only a passing incident in life and causes no trouble whatever." I wish very briefly to enlarge on this statement. In my investigation of case histories at Carville, and more recently in Bombay, in over 90 per cent of all those who were interrogated carefully, the first presenting sign or symptom of this disease was anesthesia. I am convinced that if very careful histories were taken, without prompting the patient to admit that he has had anesthesia, one would be surprised at the very large numbers who voluntarily bring forth information that anesthesia was the first sign. For instance, at Carville, when I was going over many of the cases, we could not get a history of anesthesia out of a certain individual, but when we undressed him we found a large scar on his thigh. I said "How did you get that?" The patient replied "Oh I got that many years ago when I was cut by a jagged piece of wire." I then said "Did you feel it?" The patient replied "No, not much." In another instance, a patient who presented himself at the Tropical Diseases Hospital in London said that he had had the disease only for a matter of a few months. When he was undressed, again I noticed a scar on his thigh which had the typical appearance of an old dimorphous lesion. I said to him "What is that?" He replied, "Oh, 15 years ago I had a patch there and when I went to the doctor he diagnosed it as urticaria." I am of the opinion, therefore, that the most important step to take in the campaign against leprosy is to set up diagnostic clinics, so that attention may be attracted to these very early signs. Just as diagnostic clinics are being set up in relation to cancer in women, there should be organized similar clinics in relation to leprosy, for I believe that if leprosy is diagnosed at the very earliest stage it will be only a passing incident in life. We have had several remarkable cases in which the disease was diagnosed at the stage when bacilli were in nerves only and the treatment was entirely successful. In one instance a child of nine was so diagnosed and the biopsy showed bacilli in nerves arranged as lepromatous leprosy. The child is now 22 or 23, has two bonny children and may now forget that she ever was infected with Hansen's bacillus.

I am much concerned about this matter of early diagnosis. If squamous carcinoma of the skin is diagnosed in the pre-cancerous stage, the disease is completely curable in its very early stages. When a patient goes to a clinic with a chronic keratotic condition of the skin the medical man does not say that the patient has cancer; he says "That had better be taken away because it may be dangerous." Similarly, when these very early evidences of leprosy are diagnosed, one should not say to a person "This

is leprosy," but should say, "This is a condition that may be dangerous and must be treated." If the patient says "Is it leprosy?" the reply is "No, but if not treated it will become leprosy."

In this early stage of the disease, it would be well if we endeavored to find another name for leprosy. Recently, on making inquiries in Bombay, I was told that of 2,000 patients who presented themselves for diagnosis, over 50 per cent never returned. They heard the diagnosis of leprosy, saw the damage that leprosy did to the body in waiting patients, were frightened, and did not return. Some would go to leprosy clinics miles away in order to hide the fact that they had this disease. If the physician had only called leprosy at this stage by an entirely different name and not sent the patient to a leprosy clinic but to a neurologist or dermatologist, the patient's whole outlook on the disease would have been changed and he would have been more ready to continue treatment. Therefore, if anyone can think of a name for these very early lesions, it would be of great benefit to our total program in the campaign against leprosy. It is no use naming the more advanced cases by another name, for it does not matter what name you give such a case; the stigma of leprosy will very speedily attach itself to the new name.

In closing, therefore, I would make a plea that, while we continue all the present splendid efforts to rehabilitate the leprosy patient with reconstructive surgery, we give some attention to the research problems that I have indicated in this paper. I believe they represent a type of research that should appeal to those in universities. Much of our efforts in leprosy can be likened to an ambulance service dealing with the casualties at the bottom of the precipice; there is often very little attempt to build a fence at the top. We are so busy dealing with casualties that we have no time to erect the fence that would ultimately bring this age-old disease under control. This fence consists of studies in lysosomal activity, autoimmune processes, and methods of diagnosis at a stage when the average physician, neurologist or dermatologist is not aware that the presenting signs are indicative of leprosy.

Leprosy is a thrilling research disease, and I trust that I have convinced all here that to investigate leprosy along lines of fundamental medicine would bring dividends of very great value and result in added prestige for this ancient disease. The number of physicians and research workers interested in leprosy would automatically increase. It is difficult to recruit physicians for the study of leprosy because, at the present moment, there is neither finance nor prestige in taking up this disease as a specialty. We cannot promise great monetary rewards in the study of leprosy, but we can promise a life of intense interest and a contribution to scientific medicine which is second to none.

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**Dr. Binford.** Dr. Cochrane, we deeply appreciate your giving us this address and bringing to us ideas which we hope will germinate in university circles.

Before beginning the task of finding why microbiologists have not cultivated *M. leprae*, it would be worthwhile to have a look at the man who first saw the rods that were later stained and identified as the causative organism of leprosy. Dr. William H. Feldman, whom all of you know, has agreed to present this subject. Like our previous speaker Dr. Feldman was originally a Scotsman. He came to the United States some years ago. From 1927 to 1957, he was on the research staff of the Mayo Clinic. He, with co-workers, reported the effectiveness of Promin, a sulfone drug, in experimental tuberculosis. As a result of this work Dr. G. H. Faget and his staff at Carville were stimulated to try this drug in leprosy patients (The Promin treatment of leprosy; progress report. *Publ. Hlth. Rep.* **58** (1943) 1729-1941). Dr. Feldman will present the story of Hansen's discovery of the leprosy bacillus.