

Leprosy Research in India

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It is indeed very encouraging and gratifying to see leprosy research being carried out at present at a fairly large number of centres in various countries, including some where the disease does not create any special problem. It is all the more heartening to see that leprosy research is no longer confined to leprologists, and that workers in various other disciplines in science are taking increasing interest and lending their support in the search for the solution of many of the unresolved problems with respect to the causative organism and the disease it causes.

Under such circumstances one is apt to

lose sight of the importance of some early work, done by a small number of workers under conditions much less favorable than those available at present and under various handicaps. It may be advantageous, therefore, to have a retrospective look in the field of leprosy research. That is the author's excuse for beginning this paper with reference to early research work in India.

THE FIRST FULL-TIME LEPROSY RESEARCH CENTER IN THE WORLD

Establishment of the Centre. India is responsible for about one-fifth of the total leprosy of the world. It has, therefore, been in the fitness of things that it has also

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shouldered its due, possibly more than due, share in leprosy research, especially in its early phases. It was the first country in the world to establish a full time Leprosy Research Centre. This was done in 1925 at the Calcutta School of Tropical Medicine. That Centre gave lead to leprosy research in many directions.

The Centre was organized as the Leprosy Department of the Calcutta School of Tropical Medicine through the enthusiasm and foresight of late Sir Leonard Rogers, and under the auspices of the then existing Indian Council of the British Empire Leprosy Relief Association (now the Indian Leprosy Association). The veteran and world-renowned Dr. E. Muir was the first Head of the Centre. He was followed by the late Dr. John Lowe, and the author had the privilege of taking Dr. Lowe's place, to be followed by other workers. The well known leprosy worker Dr. S. N. Chatterjee has been a product of this Centre. The Centre was run by the Leprosy Relief Association in collaboration with the Endowment Fund of the Calcutta School of Tropical Medicine, and the Indian Research Fund Association (now known as the Indian Council of Medical Research).

Activities of the Centre. Since it was the only leprosy research centre at the time of its establishment, the small number of workers there had to deal with all of the various aspects of the disease, i.e., clinical medicine, therapy, bacteriology, histopathology, and epidemiology. Brief reference will now be made to these activities.

Clinico-bacteriologic and histologic studies. The clinico-bacteriologic and histopathologic studies at the Centre threw considerable light on the nature of lesions of the various kinds in leprosy. Long continued follow-up studies, correlating such factors with the progress of the disease in individual cases, were of special value in this respect.

A special study was made of thickened nerves, both clinically and histologically, in relation to lesions of leprosy, and this provided one of the present three cardinal diagnostic signs of leprosy (the other two being loss of sensation and presence of lep-

rosy bacilli). The credit for this belongs mostly to Dr. S. N. Chatterjee.

Therapeutic studies. At that time, and for the following two decades, hydnocarpus (*chaulmoogra*) oil was the mainstay in the treatment of leprosy. The Calcutta Centre, therefore, put special efforts in working on the chemistry of the oil, improving methods of treatment with it and its esters, separating the active principles of the oil (hydnocarpic and chaulmoogric acids), and preparing the sodium salt of the hydnocarpic acid (sodium hydnocarpate) for intravenous use. Later, when the sulfone drugs were introduced in the treatment of leprosy, the Centre contributed its share in investigations of the various sulfone drugs from various points of view. The studies at the Centre played an important role in evolving the low dose schedule of the parent sulfone (DDS) in common use at present.

Immunologic studies. A detailed study was made at the Centre on the preparation of antigen for the lepromin test and the interpretation of results in cases of leprosy and their healthy contacts. The prophylactic significance of a positive lepromin reaction in healthy contacts was demonstrated. It was shown that lepromin-positive healthy contacts do not acquire the lepromatous form of the disease, and that the incidence of the nonlepromatous form is much less than in the lepromin-negative contacts.

Cultivation and animal inoculation. Various attempts were made at cultivation of the leprosy bacillus, including trial of the method of McKinley and Soule, and tissue culture, and at transmission of the disease to laboratory animals, including monkeys and hamsters, with negative results.

Epidemiology. A considerable amount of study was devoted to the epidemiology of the disease. In addition to other activities in this direction, a rural investigation centre was established in 1935 in an endemic district (Bankura) in Bengal for epidemiologic studies, and valuable information was collected over a number of years.

Training in leprosy. Besides the various research activities, a very important activ-

ity of the Centre, from its very inception, has been the training of medical men in leprosy, including both medical graduates and undergraduates. The facilities for training at this Centre were utilized not only by medical men in India, but also by those from outside countries.

The training program served a double purpose. First, it made medical persons available for leprosy work; and, second, it helped in changing the attitude toward leprosy of the medical profession in general. Now that training is available at a large number of places, and the attitude of the medical profession has undergone a considerable change for the better, it is difficult to visualize the importance of this pioneer activity of the Calcutta Centre in this direction.

Activities still continued. This Centre at the School of Tropical Medicine, Calcutta, is still carrying out its activities. However, the Indian Leprosy Association is no longer financing the Centre; it is now the combined responsibility of the School of Tropical Medicine and the Indian Council of Medical Research.

OTHER LEPROSY CENTERS IN INDIA

For some time the Leprosy Department of the Calcutta School of Tropical Medicine remained the only research centre in India, although antileprosy work in the country gradually expanded to a considerable extent as a result of the all-India activities of the Calcutta Centre. Later several centres of leprosy research in the country have gradually come into existence. In this expansion of leprosy research in India the Indian Council of Medical Research has played a very important role, by supporting investigations on various aspects of leprosy work in several centres. The Government of India also has stimulated leprosy research to a considerable extent, indirectly through the Indian Council of Medical Research, which derives its funds from the Government, and now directly by establishing the Central Leprosy Teaching and Research Institute. Of late some other organizations also have been sponsoring leprosy research in India.

In the expanded leprosy research program, the first centre, after Calcutta, to take it up was the Lady Willingdon Leprosy Sanatorium at Chingleput, which has now formed the nucleus for the establishment of the Central Leprosy Teaching and Research Institute at the same place. Later the Acworth Leprosy Home and the Tata Institute for Cancer took up research investigations in leprosy. The other important centres of leprosy research have been the Christian Medical College at Vellore, and the Schieffelin Leprosy Research Sanatorium at Karigiri, near Vellore. Besides these regular centres of leprosy research, this activity as a part time work is undertaken at several places in India where antileprosy work is in progress, and an attempt is now being made to interest universities and medical colleges in the field of leprosy research.

The salient features of work at the various leprosy research centres listed above are described briefly below. The activities of the Centre at the School of Tropical Medicine, Calcutta, have already been considered, and those of the Central Leprosy Institute, Chingleput, will be considered separately.

The Lady Willingdon Leprosy Sanatorium, Chingleput. Leprosy research at this centre was developed by the now world renowned leprologist Dr. R. G. Cochrane. Besides clinical, therapeutic, pathologic and other studies, the special feature of work at this centre was the study of childhood leprosy. For this purpose a special centre, known as the Silver Jubilee Children's Clinic, was established at Saidapet in Madras City, about 35 miles from Chingleput. The most important finding at this centre has been that in a very large percentage of cases of benign, i.e., nonlepromatous or tuberculoid leprosy, the disease is self-arresting. This conclusion was reached after keeping children with leprosy under observation for a large number of years without any antileprosy treatment. In this work Dr. Cochrane was ably assisted by Dr. K. Ramanujam, a leprologist of long experience and great clinical acumen.

In 1955 the Lady Willingdon Leprosy Sanatorium, along with the Silver Jubilee

Children's Clinic, was taken over by the Government of India to form the nucleus of the present Central Leprosy Teaching and Research Institute, Chingleput.

The Tata Cancer Institute and the Acworth Leprosy Home, Bombay. The investigations at these two centres are considered together, as their work has been mostly of a collaborative nature. The guiding forces of the work here have been the renowned Prof. V. R. Khanolkar of the Cancer Institute, and Dr. N. Figueredo of the Acworth Home. The investigations at these two centres have been concerned with the following aspects.

1. *Histopathology.* Detailed histopathologic studies were carried out on lesions of various kinds of leprosy. The studies were especially helpful in giving a clear histologic picture of leprosy lesions, as they were carried out by a veteran pathologist, Prof. V. R. Khanolkar.

2. *Role of nerves in disseminating the disease in the body.* One of the special features of the histopathologic studies was the revival of interest in the spread of leprosy infection up the cutaneous nerves. Although Prof. Khanolkar's views on the upward travel of the leprosy bacillus inside the axon itself have not been confirmed, the importance of nerves in the spread of leprosy infection, after its entry in the body, is amply borne out by recent work indicating the important role of the Schwann cells in this respect.

3. *Acid-fast bacilli in the skin of healthy contacts.* Another important feature of the histologic studies was the finding of acid-fast bacilli in skin biopsies from a large percentage of apparently healthy contacts of leprosy cases. The presence of the acid-fast bacilli was correlated with a positive lepromin reaction in the contacts, and the acid-fast bacillus found in the contacts was presumed to be the leprosy bacillus. This presumption still lacks confirmation. While in some instances the acid-fast bacilli found in the skin of healthy contacts may be leprosy bacilli, the possibility of their being other acid-fast bacilli in some of the persons examined cannot be ruled out.

4. *Cultivation of the leprosy bacillus.* An acid-fast bacillus, designated the ICRC ba-

cillus, was cultivated from leprosy material, initially in culture of spinal ganglion cells and fibroblasts derived from them. Later there has been luxuriant growth in ordinary laboratory media, both solid and liquid. This bacillus is presumed by the Bombay workers to be the leprosy bacillus. A detailed study with it was reported in a recent issue of the *INTERNATIONAL JOURNAL OF LEPROSY*. However, there is still no definite evidence as to the genuineness of the cultivated organism as the leprosy bacillus. As a matter of fact this difficulty will arise in the case of any supposed culture of an acid-fast organism, since no dependable criteria exist at present to prove the genuineness of a supposed culture of the leprosy bacillus, other than the results of skin reactions in the two polar types of the disease with an antigen prepared from the organism.

5. *Biochemical and enzymic properties of the leprosy bacillus.* Dr. Braganca's work in this direction has yielded very interesting and useful results. Her studies have shown that the leprosy bacillus specifically possesses three enzymes, not shared by the other acid-fast bacilli included in her studies. These enzymes include one for decarboxylation of glutamic acid, converting it into glutaminobutyric acid (GABA); an enzyme for oxidation of tyrosine, breaking it up into various derivatives; and an enzyme to oxidize dihydroxyphenylalanine (DOPA). Special importance of these studies lies in the fact that the presence of these enzymes may serve as additional criteria for determining the genuineness of a supposed culture of the leprosy bacillus.

6. *Prophylactic value of DDS in healthy contacts of leprosy cases.* The studies of Dr. N. Figueredo and coworkers indicated that prophylactic treatment of healthy contacts of leprosy cases with DDS protected them from acquiring leprosy. Until recently there was no conclusive evidence regarding the value of this preventive measure, and this view was expressed in the Report of the Panel on Epidemiology and Control of the VIIIth International Congress of Leprology at Rio de Janeiro in 1963. However, the studies on the matter

currently in progress at the Central Leprosy Institute, Chingleput, appear to provide such evidence. This matter will again be referred to later, in further consideration of the activities of this Institute.

The Christian Medical College, Vellore, and the Schieffelin Leprosy Research Sanatorium, Karigiri. Work at these two sister institutions originated mainly from the outstanding achievements of the now world-renowned Dr. Paul Brand and his co-workers in the use of physical and surgical methods in the prevention and management of deformities in leprosy. The Karigiri Centre is, however, now engaged in all the various aspects of leprosy research.

Although the use of physiotherapeutic measures, such as massage, exercises, diathermy, and splinting of affected parts, had long been advocated, and some surgical measures, such as removal of affected bone, amputation, trimming, and decapsulation of nerves, had long been used in the treatment of leprosy, the pioneer and outstanding work of Dr. Brand provided a fresh stimulus, and clearly brought out the value of physiotherapy and reconstructive surgery in the treatment and prevention of deformity, and in the rehabilitation of leprosy patients.

Dr. Brand's work has not only focused attention on the importance of these measures, but has also greatly widened their scope by applying the principles of orthopedic and plastic surgery in general for the correction of deformities in leprosy patients. Furthermore, it has brought out the importance of the role of protective footwear in the prevention and treatment of trophic ulcers of the feet. Following his lead, reconstructive surgery in leprosy is being developed at several centres in India, and physiotherapeutic measures have become a part of routine treatment of the disease.

CENTRAL LEPROSY TEACHING AND RESEARCH INSTITUTE, CHINGLEPUT

As previously stated, the Central Leprosy Teaching and Research Institute was established by taking over as a nucleus the

already existing Lady Willingdon Leprosy Sanatorium at Chingleput, and the Silver Jubilee Children's Clinic at Saidapet in Madras City. The Institute has been developed by providing additional buildings, staff, and equipment. It is ideally situated in the midst of a large belt of high endemicity of leprosy, the prevalence rate varying from 20 per thousand upward. The Institute is now well provided with necessary equipment and staff for research work in all the various aspects of leprosy. There are three full fledged Divisions: Clinical, including reconstructive surgery; Laboratories; and Epidemiology. There is also a Welfare Section and a section for training patients for rehabilitation.

All the various Divisions collaborate in carrying out investigations on different aspects of the disease. In addition to research and treatment of patients, an important aspect of the work of the Institute is the training of medical and paramedical workers to meet the growing needs of personnel in handling the rapidly expanding National Leprosy Control Program.

The Clinical Division. The Sanatorium attached to the Institute has accommodation for about 1000 inpatients, and affords abundant facilities for clinical, therapeutic and laboratory investigations, many of which are in progress. In addition, over 5000 patients are treated annually in the surrounding areas by the Mobile Treatment Unit, and in Madras City at the Silver Jubilee Children's Clinic, Saidapet. These cases afford additional facilities for investigations of various kinds.

There is an Orthopedic Section with a well equipped operation theater, an x-ray unit, and physiotherapy. This section is to be expanded shortly into a full fledged Division of Rehabilitation and Reconstructive Surgery with a splint workshop and an orthopedic gymnasium.

The Welfare Section looks after the welfare of the patients. There are arrangements for training inpatients in various crafts.

The Division of Laboratories. This Division has well equipped sections for histopathologic, bacteriologic, biochemical, and other investigations. A considerable

amount of work has been done in studying histopathologic pictures in various kinds of leprosy lesions, including borderline and reactional lesions, with a view to correlating the histopathologic picture with the type of disease and phase of activity. Biochemical studies also are in progress, to elucidate the underlying cause or causes of reactional states. Work is expected to be started shortly on experimental transmission of the disease to animals, including the Shepard method of inoculation of leprosy bacilli in the mouse foot pad, and on attempted cultivation of the bacillus in tissue culture. It is also expected that work on standardization of lepromin and other problems will be taken up.

The Epidemiologic Division. This Division has ample material and facilities for carrying out field studies on various epidemiologic problems in leprosy, and several of them are in progress. The epidemiologic studies are not to be confined to the areas surrounding the Institute, but are to be carried out in different parts of the country. For this purpose mobile epidemiologic units are being established. A study is in progress on the role of genetic factors in the production of leprosy and its types. An outstanding piece of work in progress at present, and about which I would like to give some details, is investigation on the prophylactic value of DDS in healthy contacts of leprosy patients.

Investigation of the prophylactic value of DDS. A properly planned investigation on the subject, on a scale capable of producing statistically significant results, is in progress at the Institute. Because of the importance of the investigation, and because some suggestive results are already available, a brief account of the investigation and the results obtained thus far is given.

The investigation was properly planned with the help of statisticians, and is being carried out in a rural area around the Institute, where there is a prevalence rate of 21 per thousand, and a lepromatous rate of about 15 per cent. The project covers a population of nearly 215,000 persons living in an area of about 325 square miles. A preliminary census leprosy survey was

carried out with a view to examining every man, woman, and child in the area. The preliminary survey took about a year, and 96 per cent of the population was actually examined. The total number of cases detected was 4,370, of which 624 were of the lepromatous type. Of the remaining 3,746 cases of the nonlepromatous type, 52 were found to be bacteriologically positive. All the lepromatous cases and the 52 bacteriologically positive cases were considered as "sources" of infection for the purpose of the study. The total number of "source cases" was thus 676. The study has been concentrated on the intrafamilial contacts of these "source cases," below the age of 15 years.

Of the 676 "source cases," 314 had no child contacts. Only 362 had healthy child contacts in the family, and the number of such contacts was 732. With the help of a statistician these 732 contacts were divided into two comparable groups, viz., a "prophylaxis" and a "control" group.

DDS in doses established in a previously agreed schedule is being given to the contacts in the "prophylaxis" group, and placebo tablets of similar appearance are given to those in the "control" group. The experiment is being carried out according to the "double blind method." Neither the workers who administer the tablets, nor the medical officers who examine the contacts periodically, know which of the contacts are receiving DDS, and which the placebo, nor do the contacts or their relations.

All the contacts are being examined periodically by experienced leprologists, and those reported to have developed suspected or definite signs of leprosy are examined by another set of experienced leprologists in order to confirm or exclude the diagnosis. Strict supervision is maintained on the work at all stages. Examination of specimens of urine from the contacts is also being carried out for the presence of DDS.

As previously stated, the first year was taken up in completing the survey of the population of about 215,000, in finding the infective patients, in listing their household contacts up to the age of 15 years, and in making two comparable groups of the con-

tacts, i.e., the "prophylaxis" and the "control" groups. The investigation proper has now been in progress for 18 months, during which prophylactic treatment with DDS, or treatment with placebo tablets, has been given to the contacts in the two respective groups. All the "source cases" are also being treated with DDS. During this period 38 cases of leprosy have been detected among the contacts. The distribution of these cases in the two groups according to the period that elapsed between the start of the treatment and detection of signs of the disease, is given in Table 1.

TABLE 1. *Distribution of cases of leprosy according to duration of treatment and detection of cases.*

Duration of treatment	Number of leprosy cases detected	
	Prophylaxis group	Control group
Up to 6 months	8	9
7 to 9 months	3	3
10 to 12 months	1	5
13 to 18 months	—	9
Total	12	26

Table 1 brings out the following points:

1. The total number of cases in the contacts during the 18 months of the study has been 38, viz., 12 in the "prophylaxis" group, and 26 in the "control" group. The differences observed in the two groups are found to be significant at the 5 per cent level.

2. In the first nine months of the study there was no difference in the occurrence of new cases in the "prophylaxis" and the "control" groups; 11 cases were found in the "prophylaxis" and 12 in the "control" group.

3. During the next nine months, however, there has been a definite difference in the occurrence of cases in the two groups; only one case occurred in the "prophylaxis" group, as against 14 in the "control" group.

From this observation it could be concluded tentatively that prophylactic treatment for the first nine months is not effective,

but that, after nine months, it appears to begin to have a protective effect. The study will be continued, however, and the results will be analyzed properly from all points of view, before any definite conclusion is reached. It appears likely, however, that for a definite answer one need not wait for five years.

SCOPE FOR COLLABORATIVE STUDIES

The above account of leprosy research activities in India should make it apparent that in that country ample scope of collaborative studies exists on an international basis. Such collaboration is already in existence to some extent, but there is scope for further developments in this direction. Being directly connected with the Institute, the author of this paper can say that the Central Leprosy Teaching and Research Institute, Chingleput, offers excellent scope for such collaborative studies.

The location of the Institute in the midst of a large belt of high endemicity of leprosy, the availability of a large number of inpatients and outpatients, and fairly well equipped laboratories, provide excellent facilities for clinical, therapeutic, epidemiologic, and laboratory investigations. In addition to the availability of plenty of material and facilities for work, there are present at the Institute a band of able and trained workers for undertaking research investigations in the various directions. As in most centres of leprosy research in India, all of them are full time workers engaged exclusively in leprosy work.

The Institute provides scope not only for collaborative research work in leprosy, but also for collaboration in training of medical men in leprosy. The training in leprosy cannot be considered complete unless the trainee has seen the earliest manifestations of the disease so that he can make a diagnosis of the disease at a very early stage, which is essential for curing the patient without deformity. In India there are ample opportunities for this purpose. One could visualize the Central Leprosy Teaching and Research Institute being utilized as an international training centre for leprosy.