

LEPROSY: FIFTY YEARS OF PROGRESS¹

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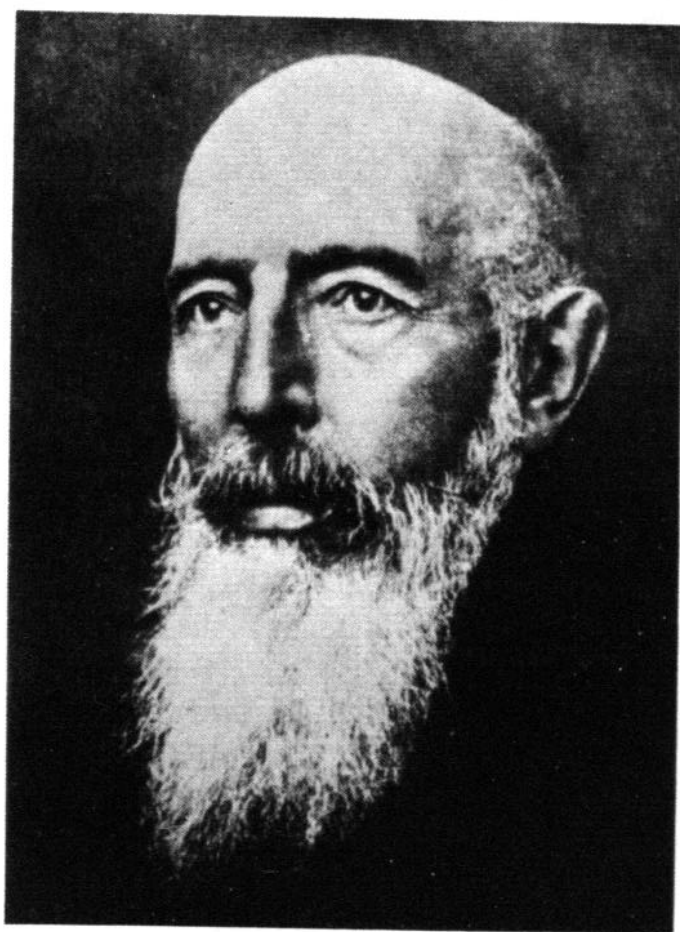
The first technical issue of the Boletín de la Oficina Sanitaria Panamericana, published in 1922, was dedicated to leprosy. During the intervening 50 years considerable progress has been made in understanding the disease, leading to benefit for the patient and more effective control. Movement away from institutionalization and toward ambulatory care for patients, plus new and effective treatment methods, has changed the picture from one of hopeless despair to one where cure is expected when the disease is diagnosed and treated early. Such treatment also reduces infectiousness of the patient and the general reservoir of infection. In short, administrative methods and procedures are now available which, if properly applied, will control and could ultimately eradicate leprosy.

Introduction

The year 1973 marks the 100th anniversary of Dr. G. Armauer Hansen's observation of the bacillus which causes leprosy. Nevertheless, *Mycobacterium leprae*—the first bacteria described as the etiologic agent of a specific disease—has still not been shown to fulfill Koch's postulates, because it has not been cultivated on laboratory media. It is thus appropriate that the *Boletín de la Oficina Sanitaria Panamericana*, now in its 50th year, should present a review of progress made in leprosy during the time elapsed since one of its first issues was devoted entirely to that subject in June 1922 (1).

Perusal of the contents of that early issue reveals several practices that are not in accepted use today. One of these was extensive use of the term "leper," a word which has since been dropped by international agreement because it conjured up a vast and variable array of concepts, biases, and misconceptions about the disease leprosy and those who suffered from it.

Since many diseases and afflictions of man were erroneously called leprosy, the "leper" of



Dr. G. Armauer Hansen (1841-1912) of Norway, discoverer of the leprosy bacillus *Mycobacterium leprae*.

¹Also appearing in Spanish in *Boletín de la Oficina Sanitaria Panamericana*, Vol. LXXIV.

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history often had a physical or social malady in no way related to the actual disease. For this reason "leper" has been relegated to the his-



A branch of the Chaulmoogra tree (*Taraktogenos Kurzii*), with leaves and fruit, growing out of the trunk. (Photo from *Boletín de la Oficina Sanitaria Panamericana*, July 1922.)



Fruits of the Chaulmoogra tree, with one cut open to expose the seeds from which Chaulmoogra oil is extracted. (Photo from *Boletín de la Oficina Sanitaria Panamericana*, July 1922.)

torical wastebasket—along with words like “nut,” “lunatic,” “consumptive,” etc.—and there are those who would discard the word “leprosy” as well, replacing it with “Hansen’s disease” or some other term better suited to the disease as it is known today. This possibility has become reality in the Brazilian State of São Paulo, where the term “leprosy” has officially been replaced by the name “*hanseniasis*” and a coterie of related terms (2).

The June 1922 *Boletín* also reflected subdued but hopeful enthusiasm about a new ester of Chaulmoogra (*hydnocarpus*) oil, which seemed to offer a new ray of hope for the treatment of leprosy (1). The use of Chaulmoogra oil for leprosy dates back an undetermined period of time, and according to Cochrane (3) can be traced to Burmese folklore. It was a British surgeon of the Indian Medical Service, Mourat, who in 1854 appears

to have introduced the oil as a treatment for leprosy. However, according to Tomb (4), an Egyptian leprologist, Tortoulis Bey, first used the drug via injection in 1894. Binford (5) reports that in 1907 another Egyptian, Engel Bey, had two German chemists (Hoffman and Taube) prepare ethyl esters of Chaulmoogric acid, which he used in treating leprosy—and on which he reported favorably in 1909. In 1915 the U.S. Public Health Service reported injection of Chaulmoogra oil to be useful in some cases. Other studies by the Public Health Service were later reported to show that the esters of Chaulmoogric acid were of no specific value. Binford, writing in 1936, said that this emphasis on treatment, induced by the Chaulmoogra “cure,” had undoubtedly delayed fundamental research.

Equally notable in the early *Boletín* articles was the thought that isolation of “lepers” was

necessary for control. Heiser (6) made it very clear that control would only come through careful and complete isolation of people with leprosy. In support of this belief, he stated that in Europe, where isolation had been practiced, the disease had disappeared, while in South America there were 150,000 "lepers," or 1 for every 533 inhabitants. (This was reported to be 150 times the leprosy rate in the United States of America).

Mr. Danner, Secretary General of the American Mission to Lepers,³ pleaded for laws adequate to enforce isolation for disease control, and for health education to "prevent lepers from walking around in public." He said that several countries (Brazil, Colombia, Ecuador, and Venezuela) had adequate laws, though enforcement was sometimes insufficient for control, and that segregation had to be insisted upon to achieve leprosy "eradication" (7). Supporting this sentiment, Dr. Heiser voiced the hope that proper treatment would eventually obviate the need for isolation (6).

Modern treatment methods have made Dr. Heiser's hope come true, but segregation in no way accounted for this development. Indeed, segregation failed to satisfy the most fundamental requirement of disease control—patient acceptance and cooperation. The attempt to isolate and institutionalize leprosy patients drove them into hiding in the early stages of the disease, at a time when they were most infectious. Only when the disease became grossly manifest—usually due to disfigurement and disability—were they forced into leprosaria. At that stage they were often no more infectious than disabled poliomyelitis victims, bearing only the results of earlier disease.

Today, especially in the Americas, large health budget allotments are drained away by costly institutional care which detracts from effective disease control rather than contributing toward it. Much has changed in this regard in the past 50 years, but much is yet to be gained by thoughtfully removing scarce funds from unnecessary, unproductive institu-

tions and putting them into effective control programs. Through such action, patients can be made willing to accept treatment, leprosy can be brought into the mainstream of medicine, and early diagnosis and treatment can prevent both disfigurement and disability while at the same time reducing the reservoir of infection.

Leprosy in the Western Hemisphere

The exact origins of leprosy are obscure, but there is no evidence that it existed in the Western Hemisphere before the time of Columbus. Leprosy in the Americas was therefore an introduced disease, and its pattern of spread for the most part followed the movements of the explorers and colonizers who brought it with them. The Portuguese introduced leprosy in Brazil, while the Spanish were largely responsible for its introduction elsewhere in South America—as well as in Central America, Mexico, the Caribbean, and southwestern and southeastern portions of the United States. Since the indigenous peoples were generally not susceptible to the disease, leprosy in the Americas was seeded among other non-indigenous peoples.

Later, African slaves brought both the disease and a susceptible population to the new world, contributing to the growing leprosy problem. Additional pockets of disease developed as colonization continued and population movements increased. The infection was brought by Chinese laborers to the west coasts of North and Central America, by Scandinavians settling the upper Mississippi Valley, and by German and Czech immigrants who settled in Texas. The romantic story of Evangeline, heroine of Longfellow's long and arduous poem, tells of the Acadians, French settlers who were forced to leave Canada and migrate to Louisiana. The poem depicts a tale of love and hardship but does not mention leprosy. However, the progeny of these people (now called "Cajuns" in Louisiana) for many years constituted the largest reservoir of infection in that state.

Over the past 50 years much has been

³Now the American Leprosy Mission, Inc.

learned about the psychosocial implications and complications of leprosy and its cost—both personal and public. Of course, as is true of other diseases, much remains to be discovered. And yet, enough is known today to control and ultimately eradicate the disease if only a concerted effort were undertaken to apply it. Too often we succumb to inaction, bemoaning the lack of a vaccine or other more effective ways to control or eradicate leprosy. In fact, with a few notable exceptions, we are not witnessing effective use of the knowledge and tools now available. There is thus an urgent need to demonstrate the success that concerted effort can produce.

Leprosy Research

From a historical point of view, the most important contribution to the field of leprosy treatment and control was introduction of the sulfones. In 1943 Dr. Guy Faget (8) and his workers at the U.S. Public Health Service Hospital in Carville, Louisiana, cautiously reported the results of using Promin, a form of sulfone, in leprosy treatment; after one year of treatment, 15 out of 22 patients had improved.

In January 1954, members of a U.S. Public Health Service Sub-Committee on Leprosy Research meeting in Washington, D.C., listed among other important needs the cultivation of the etiological agent of leprosy. Eleven years later, the Leprosy Panel of the U.S./Japan Cooperative Program in the Medical Sciences listed its objectives in leprosy research, beginning as follows:

- “1. The inability to grow *Mycobacterium leprae in vitro* is a major impediment to leprosy research.”

(This followed two conferences by the U.S. Public Health Service on leprosy research held at Carville in 1956 and 1958.)

Since then our understanding of leprosy has been increased by studying the etiological agent (*Mycobacterium leprae*) and infection in man, its only host. Nevertheless, *M. leprae* has never

been cultured, as have other mycobacteria and most other bacteria.

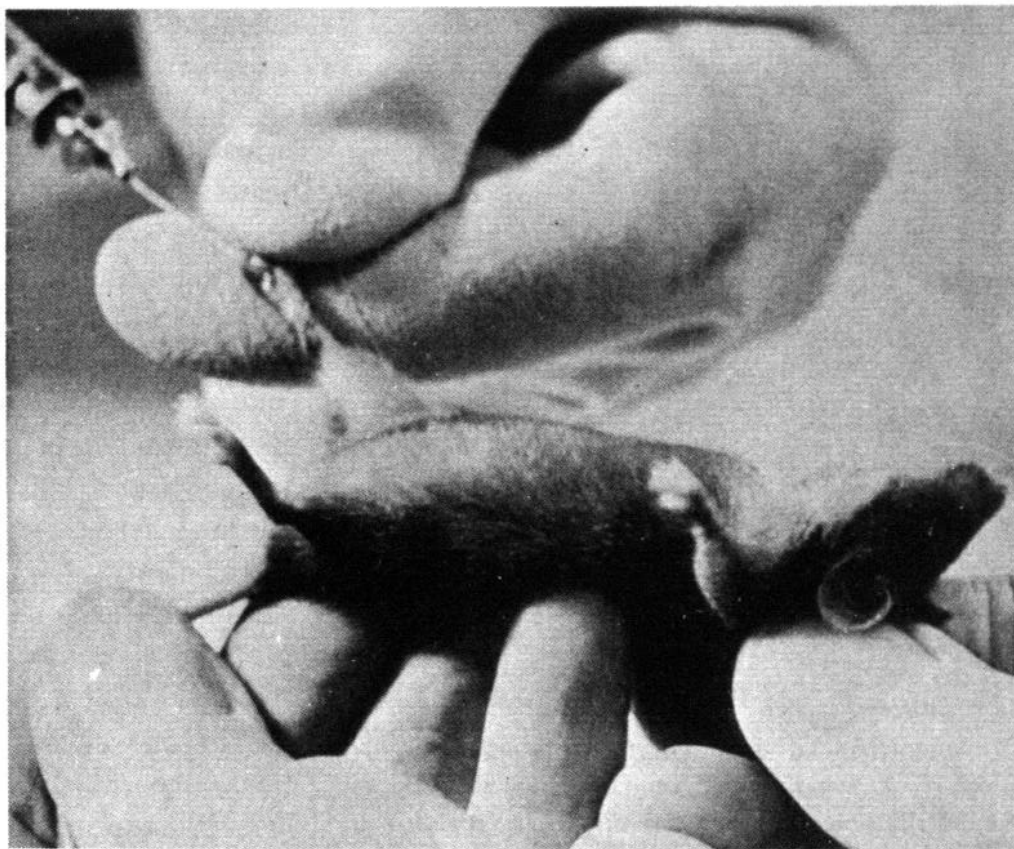
Until the present decade, perhaps the greatest single step forward in leprosy research and *M. leprae* identification was the discovery by C. C. Shepard that injection of *M. leprae* into a mouse footpad produced a characteristic growth pattern (9). When solid-staining bacteria constituted almost all the inoculum, the typical growth in the mouse footpad was reproducible. When the bacilli injected were predominately beaded or fragmented and showed no cell wall (a form in times past called “lepra dust”) little or no growth occurred.

From the observation that solid-staining bacilli were associated with active disease and granular bacilli with improving disease came the Morphological Index (MI) (10). This indicates the ratio of the total number of bacilli in a field to the number of solid-staining bacilli. The solid-staining bacilli are considered viable, while the beaded and fragmented ones are considered non-viable. This index is used in some clinics to study the individual patient's response to treatment.

Pettit and Waters (11) used the MI to show that after weeks of treatment with DDS (4,4'-diamino diphenyl sulfone, or dapsone), the number of solid-staining bacilli were reduced. After six months had elapsed and the MI had clearly started to drop, *erythema nodosum leprosum* (ENL) began to make its appearance. This was felt to confirm what had long been observed clinically—that when improvement began to take place owing to effective destruction of bacilli, resulting bacterial breakdown products provoked an Arthus-type reaction. Effective treatment with other drugs such as Clofazimine (Lamprene or B663), while causing improvement, did not produce the concomitant appearance of ENL. Studies using Clofazimine have shown it to be effective against ENL as well as for antileprosy treatment (12, 13).

Pettit has also shown that the mouse footpad technique could establish when a suspected case of resistance to DDS was true *M. leprae* resistance, as opposed to cases in which the

Inoculation of a mouse footpad with leprosy bacilli. Development of this method for cultivating *M. leprae* represented a major forward stride in leprosy research.



patient had simply failed to take the drug (14). If mice are fed DDS in their diet, the growth pattern in their footpads will be more or less normal if the bacilli are truly resistant, but will fail to develop if the apparent resistance actually has some other cause.

This test has revealed that one-third to one-half of the patients who are apparently DDS-resistant are in fact not taking the drug, as their bacilli are completely sensitive (15). (Urine and blood DDS levels can reveal if the patient is taking his drug, but only the footpad test determines if there is drug resistance.) (16) The same technique can be used to determine the effectiveness of new drugs in treating patients.

Perhaps one of the most important current concerns of leprosy research is the biochemical and anatomical classification of *M. leprae*, the organism accepted as the cause of the disease. It has been shown that bacilli taken from a number of tissues excised from different sources of lepromatous and borderline leprosy fail to retain their acid-fastness after treatment with pyridine (17, 18). Further research has indicated that under certain conditions ultra-

structural changes in bacteria isolated from leprosy cases give rise to unusual strains differing from other bacteria (19). Two of four such strains examined were related to *Corynebacterium acnes*.

Animal Experimentation

The mouse footpad work of Shepard was later confirmed by others (20-23), and successful efforts were made to transmit leprosy bacilli to other small rodents—including white rats (24), Syrian and Chinese hamsters (25, 26), and a species of *Mystromys* (27). Some success has also been achieved with chimpanzees (28).

In addition it was observed that typical *M. leprae* growth in the mouse footpad was followed, after about 20 months, by lesions resembling borderline or borderline-lepromatous disease in the inoculated foot and other hairless regions such as the nose, ears, and the other feet (15, 29).

Following the procedure of Miller (30), Rees performed studies on mice which had been thymectomized at 4-8 weeks, exposed to whole-body radiation one week later, and given



A nine-banded armadillo (*Dasyus novemcinctus*)—the first experimental animal to have developed human leprosy and died from it, thus providing an animal model for laboratory studies and research.

a transfusion of syngeneic bone marrow cells 24 hours after that (31). As a result of long-lasting immunological depression (especially with regard to cellular immunity) *M. leprae* growth in these mice appeared enhanced. After the initial logarithmic growth phase, there was continued bacterial multiplication, as well as more visible signs of disease mimicking lepromatous leprosy at the local site and at other distant hairless sites (32). The technique of Rees has since been modified by Binford (33), using a lead shielding device for a bone marrow segment during irradiation which obviates the need for the syngeneic bone marrow cell transfusion.

In 1971 Kirchheimer and Storrs (34) reported using the armadillo (*Dasyus novemcinctus*) as a model for the study of leprosy. At the time of that report, 44 armadillos had been injected by various routes with different amounts of inoculum. Since then, several more armadillos injected at different times and by different routes have developed disseminated leprosy. It is too early to tell what actual percentage of these animals are highly susceptible and will therefore develop lepromatous

disease. However, Kirchheimer has used susceptibility tests employing killed bacilli to show that an average of two out of 12 inoculated armadillos can be expected to develop lepromatous disease (35).

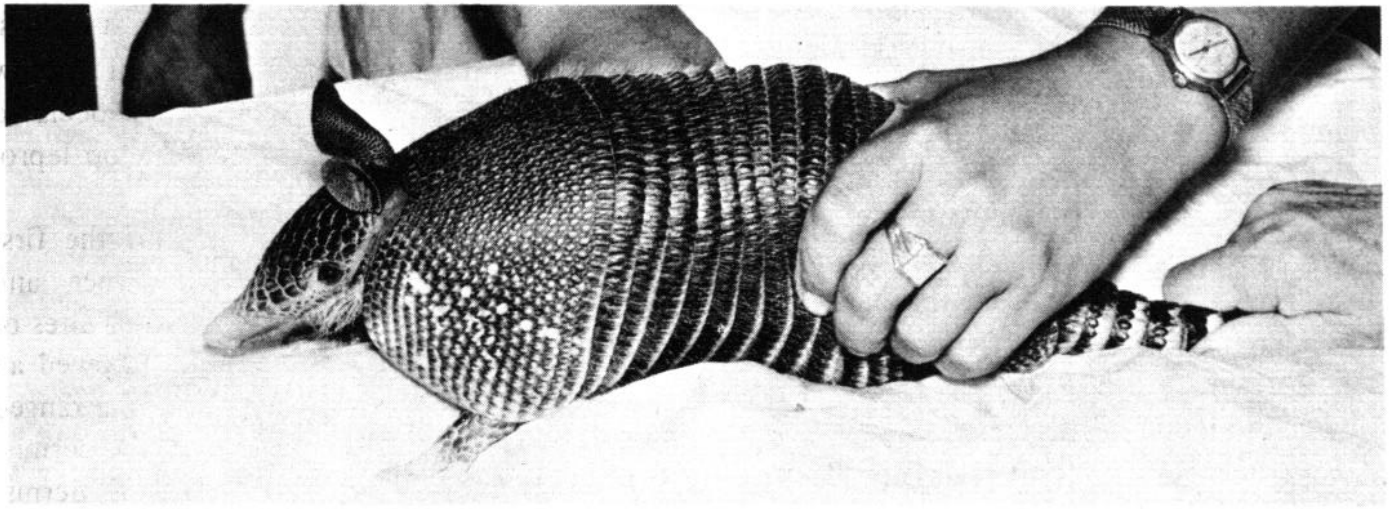
After more than a year, one of the first armadillos inoculated by Kirchheimer and Storrs showed infiltrated lesions at all sites of injection. Histologic examination "showed an enormous number of acid-fast bacilli arranged in clumps within macrophages in the dermis, typical lepra cells, and invasion of dermal peripheral nerves by acid-fast bacteria and cellular elements" (34). This was noted in both inoculated and uninoculated skin. Acid-fast bacteria were also found in the buffy-coat of the blood.

The animal also had bacterial loads in the tissue that were much higher than those found in human lepromas. These were reported to be 2.0×10^{10} bacilli (20 billion) per gram of tissue, as compared to human lepromatous tissue loads of 1.0×10^7 to 1.0×10^8 bacilli per gram (36).

Besides offering an animal model for research on human leprosy, the armadillo has thus demonstrated its value as a source of *M. leprae* bacilli (a scarce commodity) for scientific study.

Other armadillos subsequently injected with material from the above-mentioned animal have developed disease, and another has been infected with material from a mouse footpad previously inoculated with human leprosy bacilli (37). At least one animal has shown evidence of initial disease dissemination as soon as four months after inoculation.

Dr. Muñoz Rivas, with assistance from the Pan American Health Organization, is currently studying the acid-fast bacilli found in wild armadillos (38), and other armadillo studies are being carried out at the Pan American Zoonoses Center in Argentina. Other armadillo species (*Chaetophractus villosus*, *C. minor*, and *Dasyus hybridus*) are also being raised in captivity at the Zoonoses Center, and studies using *D. sabinicola* are presently underway in Caracas. Present indications are that the same



Attempts are now being made to develop leprosy in other types of armadillos, such as the small species *Dasyus sabinicola* shown here.

methods used to domesticate *D. novemcinctus* can be used for these other species.

Immunology

Mitsuda (42) was the first to show the value of a skin test using a lepromin from leprosy nodules. This test is read after 3-4 weeks and is similar in appearance to the tuberculin skin test. More recently, Fernández (43) has demonstrated that this positive "late" response (Mitsuda reaction) is usually preceded by a Tuberculin-like early response (Fernandez reaction) 24-28 hours after the test begins. The lepromin test is still used to confirm clinical type classification and to measure the susceptibility in known contacts of infectious cases; it has also served to clarify much of our earlier understanding of the immunological basis for the manifestations of the disease.

In recent years immunology research has made great strides in helping us to understand infectious diseases. Still, it seems to have come as a surprise to some that leprosy offers such an excellent opportunity to study immunological phenomena that have quite visible external signs. Because leprosy is essentially a disease of the skin and nerves, the immunological spectrum of the agent/host reaction can be clinically observed. This gives the clinician a good opportunity to observe immune phenomena directly and enables the immunologist

to correlate his studies with visible clinical signs. The use of such a model for teaching about infectious disease also offers many clear advantages.

In 1968 a study group was convened by WHO to examine and define immunological problems in leprosy research (39). It was recognized at that time that patients with the tuberculoid form of the disease generally had a well-developed, specific, cell-mediated immunity, but that in lepromatous cases the specific cell-mediated immunity to *M. leprae* (and sometimes to other antigens) seemed deficient, even though the circulating antibody response was well-developed.

Transfer factor has been studied in leprosy by Bullock (40) and Lim (41) with varying results. These and other new and exciting developments in the field of immunology and in use of the biological approach to treat and control leprosy continue to suggest that better treatment methods are waiting in the wings to give a more effective performance than can be given even by the greatly improved methods available today.

Diagnosis and Classification

Perhaps the most important progress of recent decades in understanding leprosy has been development of a disease-type differentiation based on the host's immunological re-

sponse. Fifty years ago leprosy classification was based entirely on the clinical appearance of the disease, and the terminology used in different geographic regions varied greatly.

At the Leonard Wood Memorial Conference in 1931, two types of leprosy, "neural" and "cutaneous," were recognized. Following this conference, Dr. H. W. Wade travelled around the world in an attempt to establish this classification, especially with regard to the tuberculoid lesion (44).

Recognizing the unsatisfactory features of the term "cutaneous" leprosy (since "neural" leprosy also has cutaneous manifestations) the Cairo Conference of 1938 adopted the term "lepromatous" leprosy. A classification of clinical subtypes was also accepted which gave a clearer picture of the status of the infection, its progression, the clinical response to treatment, and the prognosis.

As early as 1947 Cochrane (45), noting that the disease type was based on host resistance (measured by the lepromin response and the presence of bacteria), saw fit to utter a word of caution regarding classification. He felt that any classification should be viewed from the points of view of both the clinician, whose circumstances were such that he could not use the elaborate or time-consuming methods of differentiation, and the specialist, who employed special methods of investigation. He went on to say that "histological examination and the lepromin test are useful adjuncts to classification, but must be used only as aids and not as a basis for classification."

Since then international agreement on classification has nearly been achieved. Today leprosy classification is based on the clinical and histopathological aspects of the disease, which in turn depend on the host's immunological response. Thus, after the disease passes through an apparently indeterminate phase, two distinct polar forms are recognized. The more common "tuberculoid" form is found in the patient that has a good immunological response and should therefore be able to cure his own disease without antileprosy drugs, while the "lepromatous" or disseminated

form results from a failure of the patient's immunological mechanisms. In between these two polar types is an intermediate form termed "dimorphous" or "borderline" leprosy, which shows clinical and histopathological characteristics of both types—tuberculoid or lepromatous features predominating in accord with whichever polar type the disease more nearly resembles.

Using this system, classification of a given case of leprosy will parallel its clinical diagnosis. Typical tuberculoid cases, for example, will have dry, scaly, anesthetic lesions that are single or few in number and have sharp, clearly defined borders. Few if any bacilli will be found on smear or biopsy. The histopathological infiltrate will present an epithelioid granuloma with giant cells and no clear zone between the dermis and epidermis. The lepromin test will be strongly positive.

In contrast, the typical lepromatous case will have many lesions symmetrically located all over the body, with faint borders which often blend into skin that appears normal. However, some cases will have generalized dissemination showing few if any lesions. Anesthesia will be more widely disseminated and perhaps less intense. Bacilli will be found in great abundance in the skin, often producing globi in the form of huge clumps accumulated within the macrophages. Several of these groups together form giant globi. Histopathologic features will include a histiocytic cellular infiltrate and the foamy cells of Virchow ("lepra cells," which are considered pathognomonic of leprosy). The lepromin test will of course be negative.

As in the clinical picture, dimorphous (borderline) lesions will have characteristics resembling whichever pole of the disease they are nearest. Accordingly, the lepromin test may be either positive or negative depending on the pole most nearly approximated.

To assist in furthering international agreement and understanding of leprosy classification, WHO recently designated the National Institute of Dermatology in Caracas, Venezuela, as the International Reference Center for the Histopathology and Classification of Leprosy.

Treatment

Prior to introduction of Chaulmoogra oil, leprosy treatment was symptomatic only. Then, more than half a century after it was introduced, excitement over another possible advance of major proportions stemming from work with an ester of Chaulmoogra oil was reflected in the pages of the July 1922 *Boletín*. By comparison the new ester did represent something of an advance, contributing to continued support for the oil. Even twenty-five years later, Cochrane wrote that "... it cannot be too strongly stressed that no departure should as yet be made from the well-tried and accepted derivatives of hydnocarpus oil." (46) This statement came four years after Faget and others at the U.S. Public Health Service Hospital in Carville, Louisiana, reported on the beneficial effect of Promin, a derivative of 4,4'-diaminodiphenyl sulfone (DDS), in treating human leprosy.

Since then the sulfones have proved to provide effective treatment for leprosy. Especially when introduced in the early stages, they can cure or arrest the disease and prevent deformity and disability. From the public health standpoint, such treatment reduces the infectious reservoir of the disease and thereby brings about control by reducing its spread.

Leprosy therapy was recently reviewed by a WHO consultant group (47), which indicated that DDS (used orally in most of the world) was still considered the drug of choice. As in all anti-leprosy treatment, however, a period of years is necessary to fully evaluate ultimate clinical results. Therefore, controlled studies are still being carried out in Venezuela, where monthly injections have continued to achieve apparent good results. (48).

The diphenyl thioureas (thiambutosine and thiocarbonylimide) have also produced good therapeutic results in small groups of lepromatous patients. However, difficulties posed by their cost, utilization problems, and the tendency of infections to develop resistance have made them second-choice drugs for leprosy treatment.

Clofazimine has made a greater contribution. This phenazine dye has been found most useful in cases resistant to the sulfones and those where lepra reactions (primarily ENL) have been a serious problem. It has thus provided a valuable alternative to DDS and has allowed antibacterial treatment to continue when reactions have been so severe as to negate effective treatment with the sulfones. The unwanted side-effect of skin discoloration is well-known to all who have prescribed its use, but the drug's worth has been shown to far outweigh its disadvantages when resistance to DDS develops or ENL becomes a serious problem.

Clinical trials using 4,4'-diacetyldiaminodiphenylsulfone (DADDS) are still being conducted. Russell, *et al.* (49) reported findings from treating natives of the Karimui in New Guinea, a region with a high incidence of leprosy. The entire population of this remote area was examined for the disease. Those with leprosy were started on treatment in November 1967 with 225 mg of DADDS, a dose repeated every 77 days. The clinical results noted after 750 days were comparable to those produced by standard doses of DDS; they showed an early reduction of the MI and a much slower reduction of the Bacterial Index (BI). It was concluded that the BI was not as useful as the solid ratio in the first six months, but that after 12 months the BI became an important indicator of continued drug response. By 1971, more than 430 patients had completed their fourth year of DADDS treatment and were continuing to respond well (50). Thus the value of this convenient form of treatment is evident. From a public health standpoint, the early and continued drop in infectiousness would be of significant help in reducing the reservoir of infection. Also, because DADDS is given by injection, one can be assured that the drug is being taken—which is not always the case with oral DDS.

The most recent, and perhaps the most promising anti-leprosy drug is the new semi-synthetic antibiotic rifampin, which belongs to the group of rifamycins. Rifamycin SV was first

used by Opromolla (51, 52), who reported that it had remarkable clinical activity. However, the need to inject it twice daily limited its possibilities. Leiker (53) later reported good results with the semi-synthetic rifampin, and Rees *et al.* (54) showed rifampin to have a rapid effect on bacterial morphology.

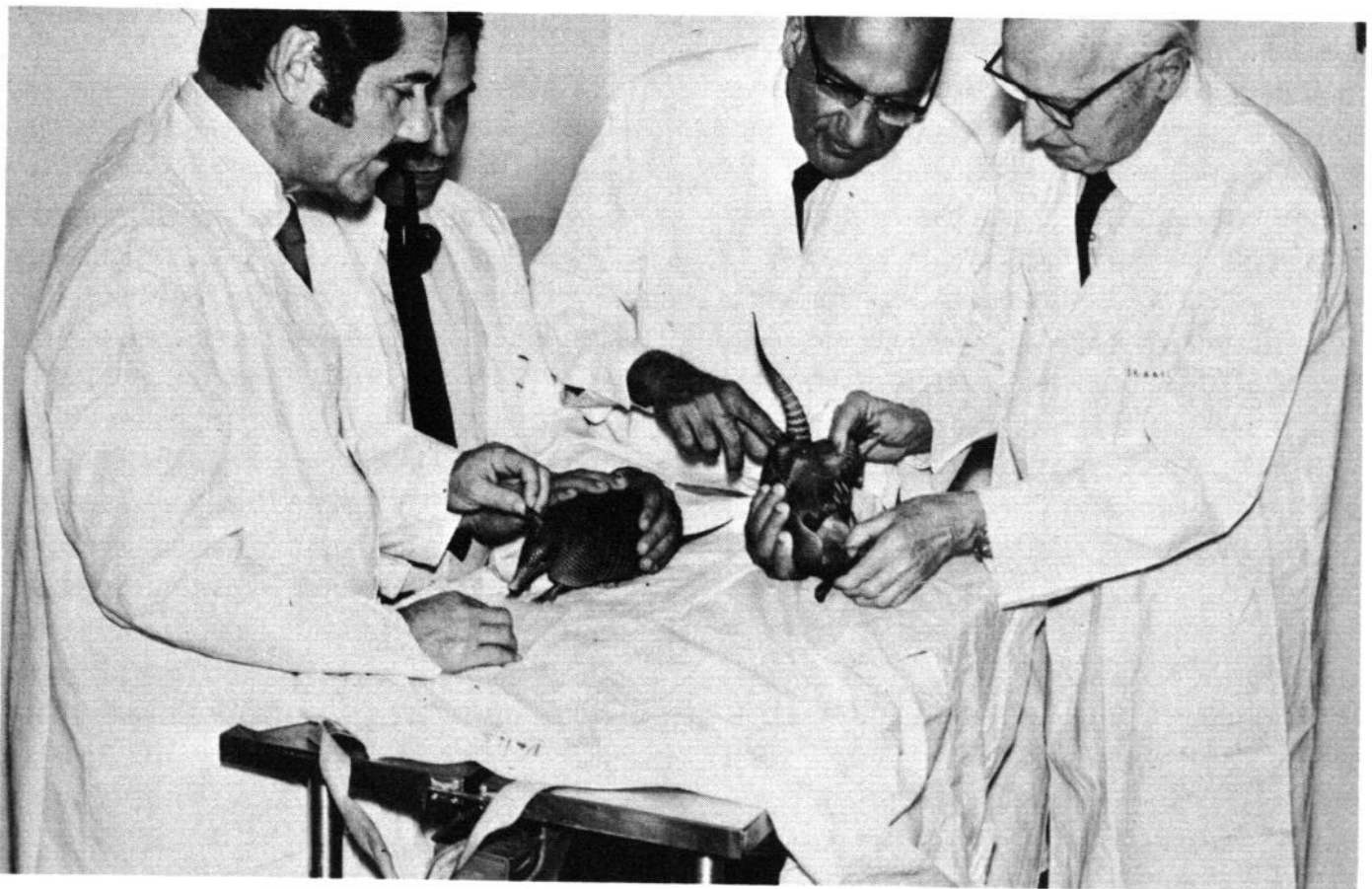
Shepard (15) has shown rifampin to be the most rapidly bacteriocidal of a variety of anti-leprosy drugs tested. Five patients with lepromatous leprosy were treated with 600 mg of rifampin daily, and the viability of bacilli in their skin lesions was tested by inoculation into mice. The first few samples collected after treatment began (seven days afterwards in the case of four patients and 14 days in the case of one) gave results indicating that infectivity for mice had disappeared. The same method applied to control patients given 50 mg of dapsone daily showed infectivity to be lost much more slowly; e.g., infectivity had decreased but was still present after 120 days. By comparison, no bacilli were found in test mice

inoculated 24 days after rifampin therapy began.

Further studies on rifampin are being carried out at present. Though more costly, it appears to have a more rapid clinical effect than any drug available today. Resistance to rifampin, though clearly a possibility, has not yet been encountered; however, administration of rifampin in combination with other antileprosy drugs, as suggested by Dr. Opromolla in 1963 (51) may still prove to be the most desirable way of using it.

Control and Rehabilitation

Leprosy control is a subject to command an entire treatise by itself. Suffice it to say here that the means are available, which if properly applied, would control and ultimately eradicate leprosy. Methods of administration were introduced and reported on in two meetings in the Americas organized by the Pan American Health Organization in Cuernavaca in 1963 and



Dr. Jacinto Convit (center), Director of the PAHO International Center for Training and Research in Leprosy and Related Diseases, and Dr. Chapman H. Binford (right), Director of the United States Armed Forces Institute of Pathology, discuss ways of inoculating the armadillo *Dasypus sabanicola* with *M. leprae* bacilli at the Center.

Guadalajara in 1968. These meetings established norms for administrative methods for leprosy control programs which are still in use in the Americas today, and which can lead to successful control if properly administered.

The future of leprosy control in the Americas will depend largely upon the commitment of those responsible for its control. To assist this commitment and foster greater uniformity of control methods, PAHO has established an International Center for Training and Research in Leprosy and Related Diseases in Caracas, Venezuela. Closely associated centers throughout the Hemisphere will collaborate with the Caracas Center in carrying out field studies leading to better control programs.

Deformity resulting from leprosy has been one of its most serious consequences, causing untold loss to affected individuals and to society. Brand, in his earlier work in India, developed reconstructive surgery methods for hands and feet deformed by leprosy (55). Since then, working at the Public Health Service Hospital in Carville, Louisiana, he has continued to develop the concept of preventive rehabilitation, creating methods to prevent both initial deformity and the extension thereof. These and other efforts have made leprosy appear less hopeless, and have helped make patients more willing to seek early care than in times past. As a result, many more patients have again become useful contributing members of society. Rehabilitation in leprosy has therefore measurably influenced leprosy control efforts.

Conclusions

In the past 50 years a clear trend has developed that has tended to move both leprosy and the leprosy patient away from strict isolation and social ostracism into the medical mainstream of society. Though this movement still has far to go, in some countries it has led to integration of leprosy care and control into the general health services—and an increasing number of countries are hospitalizing

leprosy patients who require special knowledge and care as they would any other diseased person. In this vein official rejection of the term "leper," by emphasizing this trend, has helped remove much of the stigma attached to the disease.

In addition, ambulatory care has perhaps done as much as any act of health education to change the image of leprosy from a disease whose victims were destined to be social outcasts to one where early diagnosis and good treatment could prevent disability and disease transmission. Such care has also very significantly reduced high costs (for countries that can usually ill afford them) by directing efforts away from costly institutional care and toward acceptable public and patient practices. Even more important were accompanying periods of human suffering previously resulting from treatment delays caused by the infected person's fear of being confined. Since such delay occurs when the disease is infectious, the early diagnosis and treatment also promoted by ambulatory care helps to reduce spread of the disease.

Our knowledge of infectious disease has been increased by recent immunology studies, among which those dealing with leprosy have made significant contributions. In addition, the clinical application of biological techniques currently suggests that exciting new approaches to leprosy treatment and control may soon emerge.

Greater understanding of the agent/host relationship has resulted from development of the mouse footpad technique for growing *M. leprae*. This technique, along with other tools such as newer histopathological techniques, has given us instruments with which to study and evaluate the disease. Now it is possible to analyze leprosy progress and institute preventive efforts where before only clinical observations and attempts at rational interpretation of these observations could be made. The discovery that the armadillo can serve as a source of leprosy bacilli, and as an animal model for study of the disease process and control methods, has created an aura of

expectancy concerning the chances for significant progress in the immediate future.

The once purely clinical classification of leprosy has also undergone considerable change during the past 50 years. The disease now can be classified by correlating clinical observations based on the host's immunological response, and a person with an understanding of the host response can use the histopathological findings to classify the disease with considerable accuracy. This knowledge, properly applied, is thus vital for appropriate clinical treatment and prognosis, as well as for obtaining reliable epidemiologic data needed to evaluate the effectiveness of programs and to determine disease trends.

Likewise, there have been great changes in the effectiveness of available drugs. With the introduction of the sulfones in 1943, leprosy treatment for the first time began to be truly effective for the patient. Clinical trials with DADDS now seem to indicate that a smaller dose of sulfone, administered by injection, can be as effective as DDS in treating leprosy infections and perhaps in prophylactic treatment of high-risk groups. Clofazimine has also offered new hope to patients with severe ENL

or infections resistant to DDS. Furthermore, the new semi-synthetic rifampin has produced dramatic results in a limited number of animal and clinical trials and may eventually be used in combination with other antileprosy drugs.

For years the ENL reactions in leprosy have been far more devastating than the disease itself. Since thalidomide has been found to be dramatically effective in managing these reactions, administration of steroids and all the resulting undesirable side-effects have been reduced, and the ENL have been more effectively controlled. Unfortunately, the well-known teratogenic effects of thalidomide have limited its use.

Progress in rehabilitation, though only briefly mentioned in this paper has made a most significant impact on disability caused by leprosy. Proper application of the concept of preventive rehabilitation has succeeded not only in restoring the function and usefulness of disabled members but has prevented extension of the disability process itself. By dealing with the whole person, such rehabilitation has also been influential in salvaging and restoring many patients to their positions as useful family and community members.

SUMMARY

Many outstanding developments in leprosy research and treatment have marked the past 50 years, most of them having come in the past decade. This paper reviews these events and discusses current animal studies and immunological research that offer an exciting glimpse of future possibilities.

In 1922 leprosy control was based entirely on segregation of the victim of this disease; at that time new esters of Chaulmoogra oil were being heralded with enthusiastic optimism. Since that time, thanks to the emergence of new treatment and control methods, the individual with leprosy can hope for effective

treatment. If diagnosed early and properly treated, he can expect his disease to be cured or arrested and disability or disfigurement prevented.

From the public health standpoint, early diagnosis and treatment reduces the infectious reservoir and can thereby have a major impact on control of the disease. Unfortunately, adequate and effective use has not been made of these treatment methods as often as one might have hoped. As a result, leprosy continues to increase and to pose a major health hazard throughout the world.

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YELLOW FEVER VACCINATIONS

On 10 November 1972 the United States of America stopped requiring arriving travelers coming from areas infected with yellow fever to carry the international certificate of vaccination against the disease. However, the U.S. Public Health Service continues to recommend yellow fever vaccination for the protection of U.S. travelers going to infected regions. [*Weekly Epidemiological Report* of the Pan American Sanitary Bureau, 44 (46) 269, 1972.]