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CARVILLE CENTENNIAL

INTERNATIONAL COLLOQUIUM ON THE FUTURE OF HANSEN'S DISEASE CONTROL AND RESEARCH*

Crown Sterling Suites
Baton Rouge, Louisiana, U.S.A.
1–2 December 1994

SCIENTIFIC PROGRAM

Thursday, 1 December 1994

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Marilyn H. Gaston, M.D.
Assistant Surgeon General, U.S.A.
Director, Bureau of Primary Health Care

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* Reprint requests to: Dr. J. L. Krahenbuhl, Chief, Laboratory Research Branch, GWLHD Center at Louisiana State University, P.O. Box 25072, Baton Rouge, LA 70894, U.S.A.

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Closing Comments

Robert R. Jacobson, M.D., Ph.D.
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Director, Gillis W. Long Hansen's Disease Center
Carville, Louisiana, U.S.A.

Opening Remarks

Marilyn Gaston, M.D.
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Director, Bureau of Primary Health Care
Health Resources Services Administration
U.S. Public Health Service
Washington, DC, U.S.A.

It is quite an honor to be asked to open this important and timely *Colloquium on the Future of Hansen's Disease (HD) Control and Research.* As we celebrate Carville's past it is important to look forward to the future. I want to personally thank all of you for coming to celebrate the miracles of the past 100 years which are extraordinary and which represent some of the greatest public health successes in the world and certainly in the history of the United States Public Health Service (PHS).

As you all know, HD is readily treatable, quarantine is unthinkable, deformities and morbidity are better controlled, and rehabilitation methods have been developed to protect life, limb, and livelihood. Like many miracles of modern science the translation of scientific advances to patients, to their families, to their clinicians, to the medical community and to the larger community really occur only with great difficulty. In the United States patient misdiagnosis and mismanagement by health care professionals continues. Clearly much work needs to be done.

The PHS is prepared to mainstream the care of HD so that accurate and timely community-based diagnosis and quality treatment are readily available in those areas of the U.S. with abundant cases of HD. We will try to integrate HD care into routine primary health care. This is especially important in the present U.S. climate where the face of health care is changing, and these changes are being actively implemented at the state level and in the local community. How do we integrate our knowledge with a medical community still so ignorant of the physical, emotional and social aspects of this disease? Training of health care professionals remains a major job for all of us. We certainly have a long way to go to change the negative picture of this illness by the general lay community here in the U.S. and throughout the world. The social stigma of HD remains present and pervasive, leading to the emotional, social and physical isolation of the patient and this must be changed. There is much work to do.

The problems of HD remain entrenched in many parts of the world despite multidrug therapy (MDT). Prevalence is falling but is the incidence of new disease decreasing as expected? The World Health Organization (WHO) goal of the global elimination of HD as a public health problem by the year 2000 is an exciting expectation, but clearly the reality of attaining this goal at any point in time reminds us of how much work we have to do around the world.

We are all aware of the problems of the loss of sensation in HD and the need to better understand the magnitude of the problem of patient deformities associated with this disease. More work is needed to understand and prevent nerve damage. We need to understand better how HD is transmitted and how to interrupt transmission. Better case-finding tools are needed. We need to find new bactericidal drugs and improve chemotherapy regimens. Translation of HD research breakthroughs to related diseases such as tuberculosis and diabetes has only recently become a reality.

This is all very exciting and why this Colloquium is so important in exploring where we are heading. The future of HD research will be discussed as it relates to clinical aspects, rehabilitation, technology transfer and psychosocial challenges. We will hear discussion of HD control in two countries where HD is endemic, Brazil and India. We plan to review the status of mycobacterial research from the National Institutes of Health (NIH) perspective and tuberculosis and epidemiology from the Centers for Disease Control (CDC) perspective. We will explore the future of HD research relating to immunology, microbiology, molecular biology, epidemiology, drug development and chemotherapy. These topics will all be discussed by very distinguished scientists. This promises to be an informative and productive colloquium.

SELECTED ABSTRACTS

Carville and Hansen's Disease Control: Past, Present and Future

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I'd like to open the colloquium by briefly discussing why we have to be concerned about the future of Hansen's disease (HD) research. Thus, although others at this Colloquium will discuss multidrug therapy (MDT) in more detail a few comments about it and the World Health Organization (WHO) HD elimination goal as they relate to the future of HD control and research are appropriate since these topics are clearly interrelated.

The success of MDT and the elimination effort raises several concerns: 1) The presently low relapse rate might rise as the follow-up interval since treatment increases. 2) If prevalence and incidence continue to fall there is concern that vertical control programs will be disbanded and the responsibility for HD control placed in primary health care programs. In many areas this will probably work very well; in others it might allow a resurgence of HD as happened with tuberculosis (TB) in the U.S. Thus, the question of whether leprosy care can routinely be successfully integrated from a vertical program into a primary health care program needs to be addressed. 3) What will happen to millions of disabled leprosy patients as the vertical program disappears? 4) To make integration work, therapeutic regimens for both treatment of the disease and containment of reactions, diagnosis and rehabilitation methods may need improvement. For example, even 2 years of MDT for multibacillary (MB) disease may be too long in a primary health care setting. Clearly then, it is important to emphasize that we must maintain expertise in HD and HD research in a world that will have less and less disease as time goes by if that trend is to continue.

Turning now to Carville's role in HD control, 100 years ago the earliest goal of the Center, providing humane treatment for HD patients, was readily attained by the Daughters of Charity. The facility then began attracting patients from other states because it provided the best possible treatment available and this, in turn, ultimately led to its transfer to the Federal government in 1921. Research was encouraged from the beginning: the effectiveness of chaulmoogra oil and hyperthermia were tested and other means of killing *Mycobacterium leprae* and even a vaccine were tried. Sulfa drugs were tested in 1940 but proved too toxic. Human TB findings and work with *M. lepraemurium* infection in mice led Dr. Faget in 1941 to test the sulfones in 22 HD patients, resulting in the "miracle at Carville." Thereafter, dapsone became the treatment of choice for HD and still remains part of the MDT regimen. Relapses were noted at Carville if treatment was ended too early, and the sulfone-resistant cases which ultimately resulted were studied. Clofazimine was found to effectively manage sulfone-resistant cases. In 1971, a Carville regimen of 3 years of dapsone + rifampin became the first standard MDT for leprosy, ultimately ending problems with relapses and sulfone-resistant disease at Carville. Thalidomide was tested extensively and its use in reactions quantified at Carville. Clofazimine and thalidomide subsequently have proved useful in non-HD diseases such as AIDS, and Carville served as a source of the drugs and information for this work. Rifabutin was found to be somewhat more effective than rifampin, but too expensive to serve as a replacement. Carville is also well known for its work with the armadillo as the source for leprosy bacilli. As a result, the Laboratory Research Branch (LRB) provides lepromin and *M. leprae* for leprologists and researchers worldwide. Epidemiologic research on naturally infected armadillos may provide a model for HD epidemiology, and it emphasizes the possibility of sources of disease other than human-to-human transmission. More recently, methods for rapidly screening drugs for their effectiveness against HD have been developed at Carville, and the highly bactericidal anti-HD effect of clarithromycin was discovered here.

Carville is a part of the U.S. Public Health Service (PHS) and within the PHS others who are working independently or with assistance from Carville to varying degrees also have made important contributions. Charles Shepard at the Centers for Disease Control (CDC) developed the mouse foot pad model of infection using infected human tissue provided by Carville. The National Institutes of Health (NIH) first tested clofazimine in HD in the US, but transferred the IND to Carville in 1965. In San Francisco, Levy demonstrated the highly bactericidal effects of rifampin against *M. leprae* developing, in part, the basis for the way this drug is used in WHO's MDT regimen and, more recently, Gelber showed minocycline to be highly bactericidal against *M. leprae.*

Presently at Carville the LRB continues extensive studies on all aspects of HD and has extended its expertise into TB. Some of this work will be discussed in detail during the program. The Rehabilitation Branch is making major advances in the diagnosis, management and prevention of disabilities in HD patients. Our Ambulatory Care Program cares for the 6000 patients in the U.S. who cannot come to Carville but receive treatment at our 10 regional clinics, or through the private physician program funded by us. We also maintain a National HD Registry. Training in the diagnosis and management of HD at Carville has been provided in the form of seminars and publications since the 1930s, and researchers from the U.S. and around the world are trained in the LRB with Heiser Foundation, WHO, or NIH funds. Carville staff persons also regularly serve as consultants for various international organizations such as WHO.

In the future Carville will continue to be a referral center for the management of HD cases with complications and will continue the care of those remaining HD patients at Carville eligible for lifetime care. Basic research on *M. leprae* and other mycobacteria and the immune response to infection will be continued. Early diagnosis and case detection will remain important goals and drug research and development for the chemotherapy of mycobacterial infections and management of HD complications will continue. Intra- and extramural technology transfer of our findings applicable to other diseases, such as TB and diabetes, will continue. Rehabilitation research remains committed to the management of disabilities that chemotherapy alone cannot cure or prevent since, even if there is control of leprosy in terms of the WHO criteria for success, there will be a large worldwide backlog of cases with disabilities. We will maintain a training effort in HD and other diseases, and share our expertise through international consultantships, seminars, videos, and other training materials. We also will continue to integrate U.S. HD care into primary healthcare programs to whatever extent possible as an example of how this can be accomplished with a complex disease of low endemnicity.

In conclusion, our work is cut out for us over the next decade or two. Hopefully, Carville and other HD centers will be able to maintain their facilities and expertise in this disease throughout this interval just in case things do not go as well as expected in HD control.

Rehabilitation of the Hansen's Disease Patient: Past, Present and Future*

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The history of Carville can be divided into two distinct eras. The first era, or distant past, I define as the early period of Carville up to approximately 50 years ago. The second era, or recent past, began with the introduction of sulfones for the treatment of leprosy about 50 years ago. The excitement that accompanied the introduction of sulfones was incredible and began the debate concerning predictions as to how soon leprosy would be eradicated. While this new antimicrobial therapy was miraculous, the stigma associated with debilitating conditions secondary to the infection remained. The outward (physical) and inward (psychological) stigmatizing effects of the disease remain today and continue to be an overlooked, yet major obstacle to total re-

* Summary prepared by GWLHDC Laboratory Research Branch from videotaped presentation.

habilitation of the patient, even as newer and more sophisticated treatments for the infection evolve.

One-hundred years ago dedicated members of the Daughters of Charity and the physicians who worked with them began to make a new life for Hansen's disease patients from New Orleans. They welcomed them ashore, at Carville, from the barge that brought them upriver. They gave them dignity where before they had experienced rejection. They treated them as fellow human beings; they dressed their ulcerated feet; they gave some of them tracheostomies to enable them to breathe and crutches to help them walk. They all thought that by so doing they were exposing themselves to a severe risk of contracting the disease themselves. They did not have the tools and techniques that we now have but they provided a caring environment, and that is rehabilitation. We should salute them today.

The discovery of the effectiveness of Promin, here at Carville, followed by DDS or dapsone and Diasone, helped to raise the hopes of patients and doctors alike that there might be a cure for the disease, and then meaningful life ahead for people with Hansen's Disease. The possibility of a cure for the disease was a stimulus to the search for the correction of the deformities and paralysis and blindness which would frustrate the return of cured patients to normal life. Not only was there a need to correct what had already happened to a patient, there was a great need to understand the causes of deformity and disability so that they could be prevented.

To leprosy patients the disease is deformity. This concept needs to be kept in mind so that as new drug regimens are used to control the bacterial infection the treatment does not end there. Early work at the leprosy hospital in Karigiri, India, demonstrated the importance of combining rehabilitation, including surgery, with chemotherapy as an integral part of leprosy treatment and control. It was shown that at treatment centers only dispensing drugs dropout rates of 75% were being experienced by the third year of treatment. In contrast, the integrated program at Karigiri was maintaining an 85%-90% attendance rate in clinics and was linked, in part, to the strong emphasis on rehabilitation of the patient correcting outward and inward stigmatizing effects of the disease.

Carville, and other centers of excellence like it, provide the necessary "high technology" environments where field observations can be thoroughly studied and understood. This understanding can then be returned to the field at the appropriate level of sophistication to make a difference for the patient. This has been a strong point at Carville and should be encouraged to continue.

The World Health Organization's current strategy for eliminating leprosy through multidrug therapy (MDT) should be commended. At the same time we must be aware of the expectations that accompany such an ambitious program. Expectations can lead to the discontinuing of dedicated programs, the loss of which may have negative effects on patients cured of the bacterial infection but with remaining disabilities. Therefore, continued monitoring of MDT control programs is imperative. In addition, expanded educational efforts aimed at dispelling the stigma associated with leprosy should be encouraged, so that effective control programs can reach leprosy patients who continue to be afraid to seek early treatment.

A Clinicians's View of Present and Future Problems in Hansen's Disease Control

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May I congratulate the GWL Hansen's Disease Center for the 100 years of fruitful service to Hansen's disease (HD) patients. I would like to convey greetings from HD patients and workers, especially from India, on this auspicious occasion. We are deeply grateful for the many contributions you have made in the field of HD. We see that in the near future HD as a public health problem will be eliminated. However, the complications, after effects, and stigma of HD will be with us for many more years to come. We hope and pray that the services of the GWL HD Center will persist in the HD world as a guiding star.

Magnitude of global HD and its recent rapid decline. The magnitude of the HD problem in the world has shown a rapid

decline during the last decade. This reduction in prevalence may be attributed to many facts, the most noticeable of which is the implementation of multidrug therapy (MDT) throughout the world under the leadership of the World Health Organization (WHO).

Problems in the wake of MDT. The intensive mass treatment of HD patients with assured "cure" of multibacillary and paucibacillary patients at the end of 2 years and 6 months, respectively, has left a group of patients who need, for various reasons, long-term care and specialized attention. Now is the time to seriously plan for active care of these patients who feel that they are offered "cure without care." The magnitude of the problem of these patients who suffer from loss of sensation, paralysis, disfigurement and disability should be properly assessed, and programs should be instituted on a fairly large scale without delay. Research and teaching in this area should be encouraged and funded liberally.

Integration of leprosy with general medical services. Although the vertical programs for leprosy control and for the elimination of HD continue to report great success in their endeavors, dissemination of scientific knowledge of HD and its management and the integration of HD into the mainstream of medicine has not been so successful. The knowledge of medical graduates qualifying from teaching institutions, even in countries endemic for HD, is woefully inadequate. The "stigma" appears to be universal and continues to prevail, especially among the general medical teaching and service personnel. Measures should be taken—with the same intensity and vigor as employed in the implementation of MDT programs—to educate teachers, students of medical colleges and the health workers of general medical services. These measures will ensure that the tremendous success reported in the control of leprosy will be maintained in the new set up.

Research in leprosy. There are many unsolved problems in leprosy. To mention a few: 1) *Mycobacterium leprae* has not been cultured in laboratory media. 2) An animal model in which all clinical aspects of leprosy can be studied is not yet available. 3) Susceptibility of some people to leprosy is not fully understood. 4) The immunological or other defects that cause lepromatous disease remain a mystery. 5) There is no vaccine for the prevention of the disease. 6) Early identification of infection with *M. leprae* is not yet possible. 7) The pathogenesis of nerve lesions is not yet fully understood. 8) The stigma of leprosy continues to be insurmountable. The importance of continuing the investigative studies in these areas cannot be overemphasized.

Maintenance of centers of excellence in HD. We are glad that there is a definite possibility of HD being eliminated from the world as a serious health problem. But we are also aware that the disease and its associated problems will linger for many more years to come. We know that HD cannot be as completely eradicated as smallpox was, for well known reasons. We are also not sure what the HD picture will be in another 30 years from now. We should be prepared for all eventualities. Therefore, it is important to fund and to maintain some centers of excellence in HD throughout the world which would continue to retain the expertise in HD management, to do research, and to offer training to health personnel. We are confident that the GWL HD Center will offer this leadership for many years to come.

Rehabilitation Research at Carville Today

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After World War II, two orthopedic surgeons began their quest to determine ways to restore function to patients with muscle imbalances in the hand as a result of Hansen's disease (HD). Daniel Riordan began treating patients at Carville (a United States Public Health Service Hospital). In 1949, he performed his first tendon transfer operation on an HD patient. In Vellore, India, Paul Brand also began practicing orthopedics in an attempt to restore function of the patients' hands. In 1953, Paul Brand visited Dan Riordan at Carville as part of a traveling fellowship to discuss procedures each was performing to restore function to HD

patients' hands. Prior to this time it was assumed that the tissue of the patients was "bad" and that there was no way to restore function. In 1966, Paul Brand was given the opportunity to come to Carville to create a research laboratory and to investigate the principles on which he based his procedures. A unique team approach was undertaken. The team included orthopedic surgeons, engineers and therapists (both physical and occupational).

Brand investigated the causes of the foot ulcers of HD patients in laboratory mice. The foot pads of one set of mice were cyclicly loaded with a pressure of 20 lbs/in^2 for 10,000 cycles for 10 days. The second set of mice received 8000 cycles 5 days/week for 4 weeks. The feet of the second set of mice hypertrophied but did not ulcerate and necrose as in the first set, allowing Brand to conclude that repetitive stress injuries (ulcers) could be avoided if the area ulcerating was protected from the load. Later studies showed the total contact casting of the foot to heal ulcers. Modifications to shoe wear alleviated areas of high pressure, preventing future ulcers. This model for ulcer healing of insensitive limbs also has been applied to other diseases with peripheral neuropathy (diabetes). Today, computerized analysis systems are used to allow the therapist to monitor the foot-shoe interface and to modify insoles, thereby reducing the pressure encountered by the foot.

Brand's investigations into the mechanics of the hand, to define successful tendon transfer surgeries to restore balance to the paralyzed HD hand, led to several fundamental works in hand surgery research and to the development of a computer simulation of the mechanics of the normal and paralyzed hand. Studies of the excursion and tension producing capability of the muscles of the forearm allow surgeons to pick candidate tendon transfer muscles to replace the paralyzed muscle. Studies are now conducted to determine mechanical analogs for the joints of the hand. This information is then melded into a computer graphics simulation, allowing visualization of the bones of the hand generated from computerized tomographic scans and the analysis of the mechanics of the hand for a given functional position. The results of the simulation inform the surgeon of the mechanical effects of each tendon and the loading of the bones. The system can be modified to analyze the effectiveness of a proposed tendon transfer to restore function due to paralysis also.

The future holds much promise for further studies of hand and foot mechanics to determine the effectiveness of tendon transfer surgeries for restoring balance to the fingers and the foot. The methodology of applying known loads to quantify joint stiffness with contracture also add input into the possible success of tendon transfer operations. The outgrowth of this unique team approach devised by Paul Brand continues to further the knowledge base in the biomechanics of the hand and foot.

Technology Transfer: Implementing Carville's Diabetic Foot Program in a Community Health Setting*

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Physicians and scientists at the G. W. Long Hansen's Disease Center (Carville) are well recognized for their extraordinary technological advances in the care and treatment of insensitive limbs. This basic technology has benefited leprosy patients worldwide and could help others with sensitivity problems, especially persons suffering from diabetes. Carville's approach to managing the insensitive patient is low-tech, noninvasive and emphasizes health education. Establishment of any new health care regimen faces many obstacles, and this particular type of therapy might best be applied in the community setting. Carville is actively seeking to transfer this technology to the private sector, and has joined in a pilot program with the Jackson-Hines Community Health Center, Jackson, Mississippi, U.S.A., for treatment of diabetic foot problems. Jackson-Hines was founded in the 1960s and today cares for approximately 40,000 low-income persons in a medically underserved region in the state of Missis-

* Summary prepared by GWLHDC Laboratory Research Branch from videotaped presentation.

sippi. As a free-standing community-based organization, we have a reputation for innovation and an appropriate infrastructure for programs which emphasize health education.

Establishment of this trial program required allocation of space, equipment, personnel and budget resources on the part of Carville and the Jackson-Hines Center. These administrative problems were the singular greatest difficulty encountered in transferring the technology. The trial focused originally on 873 diabetic patients who were concurrently enrolled in a diet-management health education program. The general sense among our underserved patients was that if persons with diabetes lived long enough, then they were bound to lose a limb.

A foot clinic operated by Carville staff was scheduled every 2 weeks, and two Jackson-Hines nurses were trained in the Carville methods to screen and educate the patients. Word spread rapidly among our patients and throughout the community that an innovative therapy was available for persons with foot problems. Our reputation for success built so rapidly that the clinic now treats an average of 110 cases every week from among our own high-risk groups, self-presenting cases and others from professional referrals. Demand for therapy and training in this treatment methods is high. The Mississippi State Nursing Board already has accredited Jackson-Hines as a training center for diabetic foot care and certifies our nurse-trainees for foot treatment. Perhaps most importantly, Jackson-Hines patients no longer have the sense that they are destined for amputation.

This early analysis of our pilot program suggests that Carville's methods for foot treatment are highly successful and appropriate for application in the community setting. Our budgetary analysis of the program suggests that it will be entirely self-sustaining by its second year of operation and will recoup all invested costs by the third year of operation. The state of Mississippi has an estimated 72,000 persons suffering from diabetes. Approximately 20% of them are considered at risk for amputation. Further application of this program and its spread to new centers could significantly benefit the health of our citizens.

The Psychosocial Challenge: Integration, Dignity, and Economic Avancement

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The Medical Commission of the International Federation of Anti-Leprosy Associations (ILEP) recently posed two questions: 1) When is a leprosy patient not a leprosy patient? 2) What causes the stigma associated with leprosy? Answering these clearly interrelated questions represents the challenge confronting the world of leprosy as we move into the 21st century. Whether or not leprosy is eliminated as a "public health problem" by the year 2000, these two questions will remain with us as long as leprosy continues to be a "human problem." IDEA, the International Association for Integration, Dignity and Economic Advancement, has been established to focus on these social and economic issues and serve as a forum for their discussion.

When is a leprosy patient not a leprosy patient? It is easier to answer this question clinically than socially or psychologically. Clinically, some government programs feel that individuals should no longer be classified as "leprosy patients" when multidrug therapy (MDT) has done its work and they are bacteriologically negative. However, if disabilities are present, it is difficult for many individuals to forget that they have had this disease and simply relegate the experience to a distant memory. Thus, cured individuals often continue to feel like "patients," especially if society continues to treat them that way. In addition, disability is all too often linked with the inability to be economically independent and this, in turn, prevents an individual from becoming fully integrated into society, thus remaining a "patient" in the eyes of the community.

Stigma also has a great influence on whether or not a person continues to be regarded as a "leprosy patient" after he/she is cured. Some attribute the stigma to physical disabilities while others say that the stigma results from poverty. However, there are clearly instances of individuals with no

disability who cannot find employment or acceptance due to the stigma. Similarly, there are examples of extremely wealthy individuals who, because of the stigma, do not tell their families that they have the disease. Stigma also has been attributed to tradition, folklore, racism and terminology. Some believe that the stigma is actually a result of efforts by social scientists and others to eliminate the stigma.

These two questions of labeling and stigma will require much creative thought and action long after the triumph of eliminating leprosy as a public health problem is achieved. Until these and other psychosocial issues are resolved, leprosy will continue to be a part of this world and an ongoing factor in the lives of millions of people.

Hansen's Disease in Brazil: Treating Difficult-to-Reach Patients

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Brazil has the second highest number of leprosy patients in the world. In December 1993, 197, 588 cases were registered (prevalence = 13/10,000). Implementation of multidrug therapy (MDT) began in 1986 and the present MDT coverage is 54%. In 1993, 32, 988 (22/100,000) new patients were diagnosed.

Factors underlying low MDT coverage in Brazil. In the most developed areas of Brazil (south and southeast), where 100,099 patients are registered, many leprosy managers and/or dermatologists were reluctant to use MDT. For example, the state of São Paulo started MDT as a routine only in July 1991. There are over 3000 dermatologists in Brazil, and many of them who have a very important role in the leprosy control program (LCP) remain convinced that MDT is not adequate to treat leprosy. In centers of excellence MDT is progressively implemented through the training of a complete staff—doctors, social workers, biochemists, nurses and health workers. But there are difficulties in training and keeping trained health professionals at the district level in the country. There are problems in delegating the administration of the monthly supervised doses of MDT at the peripheral level, and difficulties in treating patients in remote areas such as the Amazon Basin.

Status of leprosy control in the state of Amazonas. Leprosy control in the Amazon Basin varies from state to state but 41, 905 (21% of Brazil's patients) live in that area (prevalence = 28/10,000). Our experience is based mainly in the state of Amazonas, an area of 1, 564, 445 km^2 with 2, 263, 436 inhabitants, 50% of whom live in Manaus, the state capital. In December 1986, there were 21, 973 registered patients (prevalence = 120/10,000), 45% multibacillary (MB) and 55% paucibacillary (PB).

MDT was begun in Manaus in 1982 and implemented in the whole state by 1985. The impetus to initiate MDT stemmed from suspected secondary dapsone resistance in 73 cases, 32 of whom were documented by mouse foot pad studies. By December 1993, 99% of the state districts were covered by MDT. The number of registered patients declined to 8835 (71.5% MB and 28.5% PB) with a prevalence of 39/10,000.

Factors that underly MDT success in Amazonas. These factors include the political decision to start and implement MDT, the training of health professionals, decentralization of the LCP at all levels, and national/international financial resources (mainly GLR/WHO). Regular trips with three government boats were essential for the implementation of MDT along the main endemic tributaries of the Amazon River. Presently, MDT is successful and no relapsed cases have been confirmed (six recent suspected relapses proved to be reactions, not relapses).

Future of MDT in Amazona. In spite of these results, some aspects of our LCP deserve consideration: 1) As of December 1993, only 60.3% of the 8835 registered cases were under MDT. 2) 80% of the patients not on MDT are MB. 3) Incidence is still high: 1477 patients were detected in 1993 (62% MB, 38% PB). 4) The incidence among children (0–14 years) is 32% of the total. 5) Patient referral in rural areas is always a problem; the nearest reference center may be days or weeks distant by canoe or boat, resulting in late diagnosis, irregularity of treatment and difficulties in contact examinations which culminate in an increase in

the number of new patients with disabilities. 6) At one point government boats became unavailable and only a few regular trips are being conducted in the main endemic rivers. 7) Primary health care worsened in the last few years, and this represents a serious constraint for the LCP, especially in the interior of the state.

In spite of these difficulties, the LCP staff is very active and efforts are being made to overcome the problem of monthly supervised doses in remote areas. Training of primary health workers and nonhealth professionals to help in the monthly supervised doses or giving medicine for 2 or 3 months of unsupervised treatment are the only possible strategies for the moment. The goal of elimination by the year 2000 in the the Amazon region will be difficult to reach unless another therapeutic regimen becomes available.

Hansen's Disease Control in India: Problems and Solutions

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Control of leprosy achieved by the application of World Health Organization multidrug therapy (WHO MDT) at the global level, and particularly in India, over the past decade has, indeed, been unique in the history of disease control in general. The "Hanoi Declaration" at the conference organized by WHO and cosponsored by the Sasakawa Memorial Health Foundation reiterates our hope that the goal of eliminating leprosy by minimizing the transmission rate by the year 2000 A.D. can be reached.

However, the complacency exhibited by many countries throughout the world, particularly India which has been even now contributing maximum numbers of patients, should not stifle the quantum of leprosy-related research which is still needed. Eliminating the empiricism and the stigma associated with leprosy is as important as eliminating leprosy, the strategy for which at present is based mainly on using chemotherapy.

A change in the epidemiological pattern of the disease resulting from the reduction in the prevalence rate itself causes some special logistic problems due to sporadic distribution of multibacillary leprosy, causing transmission at a low level. Methods of identifying such cases at the field level are still not available. Although the use of short-course chemotherapy and documentation of its effectiveness are available, ideal methods for counseling patients who are bacteriologically cured but nevertheless symptomatic have not received attention by the social scientists. While immunotherapy offers hope in this area, carefully planned, large-scale, controlled clinical trials are called for.

The subject of relapse is poorly understood. How far the indicators of viability of *Mycobacterium leprae* through sophisticated laboratory tests truly indicate the possibility of clinical relapse necessitates long-term field observations.

People talk of eliminating leprosy as a "public health problem" by which they imply bringing down the communicable component of the disease. It should not be forgotten that the noncommunicable facets of the disease relating to nerve damage, resultant disabilities (primary as well as secondary) and the problems posed by rehabilitation, etc., also are to be considered as public health problems relating to the disease. There is no evidence at present that research needed in the operational aspects of this component of the disease is receiving proper attention. In fact, the epidemiology of disabilities as an exclusive entity is poorly understood. Field care of such patients is in its infancy.

Will the lowering of immunity among the rapidly proliferating HIV positives, particularly in India, have an impact on the clinical and epidemiological aspects of leprosy, including relapses and reactions? It is hoped that research on this subject will receive due attention in the coming years.

The large army of paramedical and medical staff (27,000) in India needs to be retrained with the object of optimal usage of manpower, in the changing scenario of leprosy, with the realization of the need for low-cost technology particularly suitable for developing countries with poor economies. Understanding the ideal communication

technique suitable to offer effective training to health personnel so that leprosy management can be integrated at the primary health care level is imperative. Some expertise has already been gained in this area and it is foreseen that this subject would be increasingly investigated in future. Admittedly such research is in its infancy today; retraining workers in the usage of short-acting newer drugs will be most challenging.

There seems to be a certain degree of uncoordination between laboratory scientists and field workers in the leprosy research scene today. While one should not minimize the tremendous knowledge accrued in laboratory research in the past two decades, it would seem necessary to balance the quantum of scientific endeavor with the realities of field situations. Leprosy research should be undertaken in a need-based manner.

Effective Application of Modern Immunotherapeutic Measures in the Treatment of Leprosy*

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The immune response can be broadly divided into two categories: cell-mediated immunity (CMI) and the humoral, or antibody, response. CMI is induced by Th1-type cells and is characterized by the production of cytokines such as interferon-gamma (IFN-γ) and interleukin-2 (IL-2). The humoral response is mediated by Th2-type cells and involves cytokines such as IL-4, IL-5, IL-6, and IL-10. Furthermore, the products of one response can downregulate the other response. Interestingly, the polar forms of leprosy display either an intense CMI with little antibody production and few *Mycobacterium leprae* present in the lesions (tuberculoid leprosy) or high levels of *M. leprae*-specific antibody generated with poor CMI and enormous numbers of bacilli present in the lesions (lepromatous leprosy). Thus, our leprosy research has focused on the possibility of modulating levels of immunity in leprosy patients, thereby enhancing recovery through the administration of cytokines along with chemotherapy.

IL-2 injected into the skin of lepromatous leprosy patients induces a dose-dependent increase in induration and infiltration of protective CD4+ lymphocytes as well as a decrease in the number of bacilli in the lesions. A series of IL-2 injections given in addition to standard multiple drug therapy (MDT) for leprosy caused a 0.6 log reduction in the bacterial load over a 12-month period. Thus, IL-2 plus MDT accelerates bacterial clearance.

A second cytokine studied was IFN-γ. IFN-γ immunotherapy causes an increase in keratinocyte Class II expression as well as an increase in the number of granulomas and the number of monocytes and T cells in the lesions. Combined with chemotherapy, IFN-γ also induces a decrease in the number of *M. leprae* in the lesions. Unfortunately, 60% of these patients showed signs of developing erythema nodosum leprosum (ENL).

In ENL, a painful inflammatory reaction in leprosy, there is an increase in tumor necrosis factor-alpha (TNF-α) levels in the serum. Thalidomide relieves the symptoms of ENL, and this correlates with a decrease in serum TNF-α, suggesting that TNF-α is associated with the clinical manifestations of ENL. Furthermore, cells isolated from ENL patients produce much higher levels of TNF-α when stimulated with BCG or lipopolysaccharide than leprosy patients not undergoing ENL. This implies that ENL activates cells to generate elevated TNF-α in response to agonists.

Elevated serum TNF-α also is observed in persons with HIV-1 infection and tuberculosis, especially if the individual is coinfected. In addition, TNF-α has been shown *in vitro* to activate HIV-1. Thalidomide, through its selective inhibition of serum and cellular production of TNF-α, reduces the toxic symptoms associated with tuberculosis and HIV-1 infection (e.g., patients gain weight) and inhibits the activation of HIV-1 in patients' cells without inducing immunosuppression.

Preliminary studies on borderline tuberculoid leprosy patients coinfected with HIV-1 have demonstrated that these patients have a lower Mitsuda reaction and a hyperactivation of cytokines in the circu-

* Summary prepared by GWLHDC Laboratory Research Branch from videotaped presentation.

lation. Interestingly, however, in tuberculoid patients with advanced HIV-1 disease (i.e., virtually no T cells in the circulation), the tuberculoid lesions show a classical appearance with increased numbers of CD4+ cells, local IFN-γ production, and keratinocyte Class II expression. Therefore, unlike tuberculosis, HIV-1 disease has shown little impact thus far on leprosy.

Overview of the Immunology of Leprosy*

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A developing hypothesis in immunology regarding regulation of the immune response places T-cell subsets and their cytokines at the center. In well-studied murine systems CD4+ T cells can be segregated into subsets. The TH1 subset is associated with cell-mediated immune (CMI) responses, and produces a limited array of cytokines, primarily interleukin-2 (IL-2), interferon-gamma (IFN-γ), and lymphotoxin. The TH2 subset is thought to be involved in supporting humoral immunity with the production of IL-4, IL-5 and IL-10, which also have been shown to suppress CMI. A third subset possess the ability to produce most of the cytokines found in both the TH1 and TH2 subsets and is referred to as TH0. These subsets have been described in detail in murine models of infectious diseases but remain less well characterized in humans.

Cytokine studies in lesions from humans with leprosy have suggested a general TH1/TH2 split between the tuberculoid and lepromatous forms of the disease, respectively. Similarly, reversal reactions, believed to be associated with heightened CMI and delayed-type hypersensitivity, show cytokine profiles of the TH1 type, while lesions from erythema nodosum leprosum (ENL) patients have been shown to exhibit TH2-like profiles in keeping with the concept that antibody formation and immune-complex deposition may be involved in this reactional state of leprosy. We have analyzed T-cell subset profiles from various forms of leprosy by measuring both cytokine and mRNA production from peripheral blood monocytes *in vitro* when stimulated with *Mycobacterium leprae* antigen. Our results showed that TH0 cells were present in 50% of all leprosy patients. TH1 cells predominated in 40% of tuberculoid patients and 50% of all lepromatous patients demonstrated TH2 profiles. While this is not as clear-cut as the lesional data presented thus far, it is likely that the peripheral blood compartment from which T cells emigrate to lesional sites may be different. Further studies showed that *M. leprae* antigen was unable to shift TH-type *in vitro,* suggesting that when disease is manifest the TH phenotype/cytokine profile is stable and cannot be influenced by related antigens of the pathogen.

The suppressive activity of IL-10 and prostaglandin E_2 (PGE_2) was examined in cells from lepromatous leprosy patients using antibody to IL-10 and indomethacin, respectively. The results showed that both IL-10 and PGE_2 act to suppress *in vitro* proliferative responses from lepromatous patients' mononuclear cells. While both molecules appear to suppress, their relative importance and order of action remain to be determined.

Serological screening of leprosy patients revealed that polyclonal antibodies directed against selective sequences in the LSR protein of *M. leprae* were present in lepromatous leprosy patients undergoing ENL reactions. We have been able to describe the fine specificity of the reactivity and have ascribed antibody reactivity to three distinct regions, GVTY, NAA, and RGD. Antibodies against NAA were found only in patients undergoing active ENL. This was in contrast to the results for the RGD motif, which was recognized in all ENL patients, irrespective of the clinical status. Although GVTY was recognized in both groups of patients, its recognition was masked by the flanking glutamic acid residue. These findings point to a specific molecular recognition pattern that emerges when a lepromatous leprosy patient undergoes immune perturbations leading to ENL. Moreover, the fine specificity of immunological rec-

* Summary prepared by GWLHDC Laboratory Research Branch from videotaped presentation.

ognition changes during the natural evolution of the host-parasite interaction.

Immunology Research at Carville

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Over the past 25 years, immunology research at Carville has included laboratory and clinical trials of the efficacy of the transfer factor in the immunotherapy of leprosy, studies of adoptive transfer of T-cell subsets in *Mycobacterium leprae*-infected nude mice, development of armadillo-specific immunological reagents and assays, and an on-going investigation of the mechanisms of action of thalidomide and its analogs in ameliorating erythema nodosum leprosum (ENL).

Leprosy, with its clinical and immunopathological spectrum, represents an ideal model for investigation of the pathogenesis of an infectious disease and the immunoregulation that culminates in the host's response. Consequently, much of our research effort has also been directed at basic immunological questions. Central to an understanding of host resistance in leprosy is an awareness of the role of the principal host cell for *M. leprae,* the mononuclear phagocyte or macrophage (MAC), and its success or failure in coping with the leprosy bacillus. Using Carville's valuable resource of a continuous supply of nude mouse-derived, viable *M. leprae,* a variety of techniques, including our own adaptation of radiorespirometry, allowed us to show that activated murine MAC had a marked deleterious effect on *M. leprae in vitro.* Investigation of the mechanism of this effect revealed the L-arginine-dependent production of reactive nitric oxide to be a key antimicrobial mechanism directed against the leprosy bacillus.

In other studies, the leprosy bacillus itself was shown capable of downregulating the MAC afferent and efferent effector function as demonstrated *in vitro* in MACs gorged with *M. leprae* isolated from the lepromatous foot pads of nude mice. The defective MAC effector function also was demonstrated *in vitro* with mouse MAC infected with viable *M. leprae,* where the bacterial load of the MAC was a critical variable.

Studies of the traffic of bone marrow-derived MAC into the lepromatous lesions of nude mice revealed a surprisingly rapid rate of turnover. Natural killer cell lysis of *M. leprae*-infected MAC was shown to be one possible mechanism resulting in the release of bacilli from their host cell. The cytotoxic capacity of the new MAC themselves also could play an active role in the acquisition of *M. leprae* from the older target MAC.

A key cell-wall constituent of *M. leprae* (and other mycobacteria) that downregulated MAC function was found to be lipoarabinomannan (LAM), and studies continue to determine the role of LAM and other constituents in successful intracellular parasitism by *M. leprae* and other mycobacteria.

Carville's basic immunology research agenda will continue to be concerned with leprosy as an approachable model of a slowly developing, non-life-threatening human disease that is under important immunoregulatory influences because we are able to borrow freely from the methods and discoveries of this larger field. However, it is especially important in the coming years that we be primarily focused on the goals of the worldwide leprosy elimination program where our studies can have an important bearing on immunoprophylactic and immunotherapeutic approaches to leprosy control and on possible mechanisms of peripheral nerve damage.

Will We Understand Leprosy Before It Disappears?

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Although it is sometimes argued that a thorough understanding of a disease is necessary in order to ensure appropriate control, there is rhetoric announcing the imminent elimination of leprosy ("as a public health problem") despite the fact that it is arguably the least well understood of all the

great infectious diseases of humans. The pathogen cannot be cultured, the sources and modes of infection transmission are still contentious, and we cannot recognize infected individuals. The frequency and determinants of disease among infected individuals are likewise unknown. Although gender and an HLA-associated genetic determinant have some influence upon the type of ultimate disease, other yet undefined factors probably play much more important roles. There is evidence that BCG vaccination imparts protection against leprosy, but to a degree which varies between populations. As with tuberculosis, the reasons for this variation are unknown. Even as the mechanisms of infection and disease remain mysterious, we are unclear as to the amount of either which is extant in the world today, and whether they are indeed on the brink of elimination. Most of the available data are poor, in particular where the problem appears to be greatest. Although there is much evidence that leprosy is declining in Africa, most of Latin America (except for Brazil?) and Southeast Asia, India appears to hold more than 90% of the world's leprosy patients and shows little evidence of the declines evident elsewhere. There is some evidence that this stability in the number of leprosy cases is attributable, at least in part, to nonspecific diagnoses encouraged by target setting. Clarification of the trends in India thus assumes prime importance among the outstanding issues in practical leprosy epidemiology. Those who wish really to understand the disease before it all but disappears must now work overtime since funds and research are at least equally as eliminable as *Mycobacterium leprae.*

Experimental Animal Models and the Future

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Mycobacterium leprae cannot be propagated on artificial laboratory media and animal models play a critical role in leprosy research. Some early failures at infecting animals experimentally were probably related to the poor quality of inocula used and to a lack of appropriate methods for detecting leprosy infection. However, only a few animal species have been found that will support replication of *M. leprae.* These include some nonhuman primates, laboratory rodents and nine-banded armadillos. The characteristics of infection among these species can simulate the entire leprosy spectrum and recommend the animals for different uses.

Nonhuman primates were once believed to be resistant to leprosy infection, but there have been occasional reports of spontaneous leprosy among some primates in captivity. Using inocula obtained from one of these spontaneous occurrences (SMML) one group of workers has shown that mangabey monkeys and small numbers of other primate species may actually develop borderline-type disease upon experimental infection. Whether the SMML isolate is more pathogenic for animals or the success of these infections is the result of better quality inocula is still unclear. Unfortunately, because of their high maintenance costs, ethical constraints in experimental use and discovery of a contaminating simian immunodeficiency virus, progress with nonhuman primate models has been limited.

It was not until the 1960s that laboratory rodents were shown to support limited replication of *M. leprae* within cool regions of their body. Inoculation of 10^{3-4} leprosy bacilli into the plantar surface of the mouse foot pad produces a localized infection in 120–240 days which may contain up to 10^6 bacilli. The use of smaller inocula numbers or more extensive growth is limited by a T-cell immunity. Consequently, immunocompromised or-deficient rodents have been used extensively in leprosy research. Congenitally athymic nude mice can be inoculated successfully with fewer bacilli, tolerate growth to greater numbers, and may have some hemotogenous dissemination. Studies at Carville have shown that these animals are susceptible to percutaneous or respiratory infection, and inoculation of 10^{6-7} *M. leprae* can give rise to up to 10^{10} bacilli in 18 months. Although conventional mice originally served important roles in pharmocologic studies and for evaluating the drug susceptibility profile of patient isolates, these applications are being supplanted by

modern molecular probes, antigenic analysis and other *in vitro* screening methods. Presently, however, inoculation of animals remains the only means to confirm infectiousness of organisms or to evaluate effects on bacterial division.

Extending on a thesis that cool body temperatures favor growth of *M. leprae,* investigators from Carville and elsewhere began experimenting with nine-banded armadillos in the 1970s. This animal's normal body temperature averages 34°C and those early studies showed that armadillos uniquely develop a lepromatous type of disease. Intravenous inoculation of 10^8 *M. leprae* into armadillos regularly results in a fully disseminated infection with 10^{12} bacilli recoverable from their internal organs in about 14 months. Other studies at Carville have shown that armadillos are equally susceptible to infection by respiratory instillation, and that they will eventually develop disseminated disease after inoculation through their foot pads. The infectious dose for armadillos may be as low as 1000 *M. leprae* but larger doses make for more rapid progression of the disease. Armadillos and nude mice are the principal sources of leprosy bacilli for the modern research community. Mice are well developed as a source for small numbers of highly viable bacilli and are susceptible to relatively small numbers of *M. leprae.* Armadillos remain the primary resource for large-scale expansion of different isolates. They are the only propagation system which can produce sufficient numbers of bacilli for biochemical or antigenic analysis with minimal batch-to-batch variability. Nude mice can efficiently compliment armadillos in a propagation program as a convenient controlled source of inocula to be expanded in armadillos.

In the past, experimental animals served mainly as vehicles for the propagation of leprosy bacilli. Today, they are contributing to our understanding of the pathogenesis of infection and will likely become essential tools in studies on the immunology and epidemiology of leprosy in the future. Armadillos respond to *M. leprae* skin-test antigens with granulomas that are histopathologically similar to those seen across the spectrum of human leprosy, and the results of experimental infection correlate with skin-test results. Armadillos may be particularly useful in future attempts to develop new skin-test reagents and other tests for the early diagnosis of leprosy. A leprosy-like disease was first discovered among wild armadillos in 1975. Since that time, the etiologic agent has been confirmed to be *M. leprae* and today nine-banded armadillos are recognized as highly endemic natural hosts of leprosy. Leprosy appears to be indigenous to armadillos but follows a distribution pattern similar to that seen among humans. Armadillos are a unique parallel population, and additional studies on these animals may reveal important new information on the ecology and epidemiology of leprosy. As the prevalence of human leprosy declines, animal models of the infection will become increasingly important in order to develop and evaluate technologies that may lead to the ultimate eradication of leprosy.

Treatment of Hansen's Disease

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In the approximately 35 years spanning the introduction of dapsone for the treatment of leprosy until the mid-1980s there had been a total of 4 drugs recognized as legitimate antileprosy agents: dapsone, rifampin, clofazimine and the thioamides. In the past 10 years alone, however, this number has nearly doubled with the recognition of several fluoroquinolones, macrolides and tetracyclines as having antileprosy activity. Ofloxacin, pefloxacin and minocycline were first shown to have antileprosy activity in the mouse foot pad model. Development of *in vitro* radiorespirometric assays allowed for large-scale antileprosy drug screening using small quantities of drugs and ended the absolute dependence on favorable mouse pharmacokinetics. These assays made possible the determination of structure-activity relationships and facilitated the recognition of the potent activity of sparfloxacin and clarithromycin. A number of other agents have demonstrated antileprosy activity in *in vitro* and/or *in vivo* systems, including fusidic acid, deoxyfructoserotonin, bromi-

doprin, roxithromycin and other fluoroquinolones, and some have shown clinical efficacy. Short-term monotherapy trials of ofloxacin, sparfloxacin, minocycline and clarithromycin have demonstrated rapid bactericidal activity in multibacillary patients, and these agents are currently being employed in clinical trials of short course multidrug regimens. The challenge heading into the next century is to determine the optimal drug combinations in attempting to significantly shorten the duration of therapy without increasing the risk of relapse. An equally important challenge would be to identify regimens which also might reduce the frequency and/or severity of lepra reactions.

Short-Course Regimens for the Treatment of Hansen's Disease

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Short-course regimens for the treatment of Hansen's disease could be defined as regimens with a maximum duration of 1 year. A summary and updating was presented of previous and more recent chemotherapy trials in paucibacillary (PB) and multibacillary (MB) disease. Regimens in PB leprosy varied from 1 year to 1 day. All regimens except a single dose of rifampin (RMP) were comparably effective. A single dose of RMP together with a single high dose of clofazimine (CLO) was a satisfactory regimen. The value of the recently discovered bactericidals (quinolones, minocycline and clarithromycin) is being studied. Remaining questions in relation to PB treatment are: the slowness of histopathological cure, the moment of the decision to re-treat a PB patient, and the differentiation of reversal reactions and relapses.

For MB disease the only acceptable regimens, using the older drugs in which ethionamide could be replaced by minocycline, are those with a duration of 52 and 34 weeks. Relapses should be suspected by very careful clinical examination, and they should be documented accurately by all means available. Reports of early relapses (within 3 years after treatment) point to inadequate treatment. The absence of early relapse is no guarantee for the efficacy of a regimen in the long run.

Since there are presently no means to distinguish relapse from re-infection with new strains of *Mycobacterium leprae,* the deep-freeze storage of pretreatment skin-biopsy specimens is recommended, should typing techniques become available to examine apparent relapses. New trials have been started to find out whether short-course therapy of 3 months or less with the newer bactericidal drugs (RMP, quinolones, minocycline and clarithromycin) will be successful.

Prospects for Contributions from Basic Biological Research to Leprosy Control

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In reflecting on these past 15 to 20 years of outstanding achievements in leprosy research at the molecular and immunological levels, one must conclude that, nevertheless, our contributions to the control of leprosy have been insignificant. Our understanding of the genome, phenotype and immunological response of *Mycobacterium leprae* has exceeded all expectations of 15 years ago. However, a generation of research on serological and genetic approaches to early diagnosis and to the epidemiological monitoring of disease incidence has yielded little of practical value. Perhaps, throughout these years of intensive laboratory effort, we did not pay close enough attention to epidemiologists and their insistence on specificity, sensitivity and ease of application. For too long, also, during the heyday of leprosy research under the auspices of the WHO/TDR/IMMLEP program, we failed to clearly classify our molecular and immunological research into that which addressed leprosy as a model of a unique disease with exceptional immunological and obligate intracellular dimensions and into that which addressed the more pressing need for tools and tests for early diagnosis, epidemiological assessment of incidence and alleviation of nerve damage. Yet, it is not too late to make amends. Despite a massive afflux of investigators to tuberculosis research, the disappearance of

major intellectual forums and funding sources, and the dramatic decline in disease prevalence, there is still opportunity for researchers to contribute to the elimination of leprosy.

We in basic research have the unique opportunity to contribute to the eradication of a disease. In our dealings with fellow researchers, funding agencies, etc., we should emphasize this extraordinary opportunity rather than be naysayers, warning against drug resistance and citing the old bugaboo, "No bacterial disease was ever eliminated through chemotherapy alone."

The immediate needs in our realm of leprosy research are: 1) an international forum to define research priorities in the context of the elimination program; 2) the maintenance of a minimal research infrastructure and special materials and resources, just in case present predictions on declining disease prevalence, the virtual absence of relapse/drug resistance, and the lack of an association between HIV and leprosy do not hold up. Pending such a consensus conference, I propose that the more pressing research needs in the context of the "new leprosy" are: 1) the continuing testing of new drug combinations arising from tuberculosis and other antibacterial research in the mouse foot pad and in limited human trials; 2) development of tests applicable to early diagnosis and the epidemiological monitoring of the extent of latent leprosy. Serology and gene amplification hold little hope. The best prospects lie in a test based on the cell-mediated immune response, probably the development of a new generation of skin-test antigens; 3) research on the immunological basis of pathogenesis leading to neuropathy, nerve damage and reactions, and the development of corresponding therapeutic interventions.

The broad consensus meeting which I propose should deal with the questions of whether research on the identification of correlates of protective immunity, the development of subunit vaccines in nude mice or humans, serology, polymerase chain reaction, growth of *M. leprae*, etc., should proceed in the context of our understanding of the dimensions of present-day global leprosy. In addition, we should try to identify means for the continuing support of current outstanding research that transcends leprosy as a disease, such as sequencing of the *M. leprae* genome and the basic understanding of the variable immune response throughout the various aspects of the disease.

We should realize that, within these new guidelines, there is ample challenge for the best of our scientists. It is regretful that, faced with the opportunity to annihilate a disease of one-time awful proportions, so many of us choose instead to again pursue, in the context of tuberculosis, questions that are clearly scientifically meritorious but again will probably not help in the control of that disease.

Basic and Applied Research Emerging from the *M. leprae* Genome

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Leprosy control has evolved over the years as our understanding of the disease has advanced. Basic research has guided much of our understanding of leprosy and has led to breakthroughs which have improved the care and treatment of the disease. The major strategies for controlling leprosy today are diagnosis, treatment and prevention. Diagnosis of leprosy is focused on early detection to minimize pathologic effects associated with the chronic nature of the disease. Simple tests are still needed with diagnostic and predictive capabilities. Treatment of leprosy has improved significantly over the past few years, and current experimental protocols are being tested to define minimal dosages and drug combinations necessary to control the infection. Prevention of infection remains the best hope for the control and eventual eradication of leprosy. Research in the areas of epidemiology (transmission), vaccinology and the basic pathogenesis of leprosy should eventually lead to an integrated approach for designing a vaccine, the ultimate goal for controlling leprosy.

Why have the answers to many seemingly simple questions concerning leprosy remained elusive for over 100 years? Part of

the answer is due to unique obstacles associated with leprosy research. For example, *Mycobacterium leprae* is an obligate intracellular parasite; it has never been cultured *in vitro,* and it has an extremely slow growth rate (doubling time = 13 days). To circumvent some of these problems researchers have had to take indirect approaches to attempt to answer basic questions regarding leprosy. Early on, these approaches included surrogate bacteria as models and, more recently, they have focused on static biochemical and genetic studies of the bacilli in lieu of dynamic studies with culturable bacteria. Nevertheless, these approaches have provided insights into the pathogen and may suggest new models for studying the disease.

Some of the most intriguing results have come from studies defining the genetic characteristics of *M. leprae.* For example, *M. leprae* appears different from other *Mycobacterium* species in that it has a guanosine plus cytosine (G+C) content of 56% (mycobacteria >60%) and the genome is significantly smaller than most other species in the genus. In addition, initial results of the *M. leprae* Genome Project suggest that *M. leprae* utilizes less than half of its potential genetic coding capacity. This characteristic taken together with its small genome size may explain the severe restriction for growth *in vitro.* Another striking feature of the *M. leprae* genome is its lack of demonstrable strain variants. By comparison, strain variation based on DNA polymorphisms has been relatively easy to demonstrate in *M. tuberculosis.* However, RFLP analysis and DNA sequencing of *M. leprae* has yet to demonstrate significant polymorphisms useful for typing variants for epidemiologic studies.

Results from the *M. leprae* Genome Project are the most intriguing source of new information about *M. leprae.* Sequence analysis of the genome has identified numerous genes falling into at least four important categories useful for future study. These categories include standard housekeeping genes (necessary for understanding intermediary metabolism), stress response genes (possibly involved in intracellular survival), immunogenic proteins (important in defining the immune response to *M. leprae*), and genes already known to be powerful sites for antibiotics. We and others have taken advantage of sequence data for the *rpoB* gene which is associated with the site of action for rifampin. We have identified mutations associated with resistance to rifampin in *M. leprae,* and have configured a DNA-based test to detect these mutations rapidly. We also have successfully applied this approach for detecting rifampin-resistant strains of *M. tuberculosis,* and are developing simple tests for the determination of these genotypes directly from biological samples, obviating the need for cultivating the bacteria.

It is anticipated that as we learn more about the genetic characteristics of *M. leprae* we will be able to understand pathogenesis at the molecular level. In turn, this information will help us to design new approaches for diagnosing, treating and possibly preventing leprosy through immunologic and chemotherapeutic intervention strategies.

Closing Comments

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This was not a consensus conference but we can sum up, in consensus form, some of the things that were said. This is not a complete list and it is subject to some revision. First of all, I believe, as I said at the beginning of the Colloquium, that Carville has over the years made and continues to make a major contribution to Hansen's disease (HD) control and research. Rehabilitation of HD patients remains an important and often neglected aspect of patient care and should receive greater emphasis in the future. HD control programs must be maintained as they are carefully integrated to primary health care, and this need will remain well after the year 2000. Rehabilitation research in HD can markedly benefit HD and other diseases such as diabetes, and such technology transfer can have a major impact in care settings such as community health centers. Psychosocial problems, including the stigma associated with HD and the economic well-being of patients, are important and receive too little attention in

most control efforts. High-quality HD control programs are possible, even under very difficult circumstances, where you have dedicated personnel and government and nongovernmental organizations to support it.

Tuberculosis continues as a major problem in world health, and continued efforts are needed to build and maintain the research capacity to deal with this problem after years of relative neglect. HD and tuberculosis and other mycobacterial research are in many ways tied together, and each can benefit from the others' efforts via technology transfer and, perhaps, more importantly, collaboration. Funding for HD research continues with NIH and WHO but competition for funds has increased. HD researchers will have to take a more activist role in meetings and applications and perhaps politically to continue receiving a significant share of the monies available.

Great progress has been made in our understanding of the immunology of leprosy but much remains to be done, and it is possible that total elimination of the disease could ultimately depend on advances in this area. Progress in HD immunology research can also benefit other diseases. The epidemiology of HD is still not fully understood or even well understood. The study of this problem has become more difficult as the number of cases decrease, thus the need for more effort now.

Perhaps in no area has so much progress occurred from a clinical prospective as with chemotherapy. Curative, much shorter regimens remain a distinct possibility using the newer bactericidal drugs in various combinations, and other potent bactericidal drugs may continue to be found and/or developed. Prospects for improving our understanding of HD and its epidemiology employing molecular biology are good, and this knowledge may ultimately benefit HD control. On the other hand, as Dr. Brennan pointed out, we perhaps need to focus more on the needs of the elimination effort. I also think this is important and that's where much of the effort is probably going to go in the future. What do we need to complete the elimination of leprosy and how can we obtain it?

Finally, I believe we are all agreed that expertise in all aspects of HD control and research should be preserved. Otherwise we risk making some of the same mistakes that were made with tuberculosis and malaria, for example. I sincerely appreciate all of you coming to participate in our program and for your presentations which assured its success. Thank you, I hope your stay here has been a pleasant one, that you have a safe journey home, and that we can meet here again in the years to come to address new problems as they arise.