

James N. Miller Receives Thomas Parran Award

The annual business meeting of the AVDA was held on July 31, 1985, in Brighton, England, as part of the sixth international meeting of the International Society for Sexually Transmitted Diseases Research. At the business meeting, Thomas Fitzgerald, Ph.D., presented the Thomas Parran Award of the American Venereal Disease Association to James N. Miller, Ph.D.:

"It gives me great pleasure to introduce Dr. James N. Miller. He has played a very important role in my scientific career and in the careers of many others. It is difficult for me to put together an introductory message that will place Dr. Miller's contributions into proper perspective. My personal feelings are deep, and whatever I say will sound somewhat shallow. I am sure that this applies to others who have interacted with Jim.

"I first came in contact with Dr. Miller in 1972 and spent two years as a postdoctoral fellow in his laboratory. During this interval I had a chance to learn the techniques and philosophies of treponemal research and to evaluate Jim as a human being. He is a unique person. Most of us are strong in one area and not so strong in other areas. Some of us are very good at research and do a little teaching on the side. Others are strong teachers and do some research on the side. Dr. Miller is outstanding in that he has made equal contributions in both areas.

"Since obtaining his Ph.D. at U.C.L.A. in the 1950s, he has made important contributions in developing basic knowledge about *Treponema pallidum* and host immune responses. His research experiences are broadly based, and I can only briefly mention a few. He started with evaluations of serodiagnostic tests; he characterized polysaccharide antigens; he investigated macrophage activity and phagocytosis; he studied lymphocyte activation by treponemal antigens; and he initiated the first detailed investigations of treponemal attachment to cultured mammalian cells. Currently, he is using the newer molecular technologies of monoclonal antibodies and recombinant DNA to characterize treponemal antigens.

"Without question, Dr. Miller has made major contributions to the field. The most striking, in my opinion, was the development of an effective vaccine that provides total protection against symptomatic and asymptomatic experimental syphilis in rabbits. A number of researchers are currently trying to develop a better vaccine. We can point to Jim's success as a hallmark that demonstrates that a practical and effective vaccine is feasible.

"Dr. Miller's research credentials are impeccable, and we can all hang our hats on whatever he has published. This has become obvious to me in the past 12 years since



Dr. James N. Miller and his wife, Shirley. Dr. Miller is holding the Thomas Parran Award plaque.

leaving his laboratory. I have been most fortunate in being able to continue my collaboration with him.

"Jim's teaching is equally outstanding. It is difficult to attract graduate students into syphilis research, and he has a marvelous track record. Dr. Miller has had seven doctoral students. Fortunately, five of these students have stayed in the field and continue to contribute to our knowledge of *T. pallidum* (Nancy Bishop, Sheila Lukehart, Phil Hanff, Steve Norris, and Darlene Gamboa). This is a direct reflection of Jim's training capabilities. He also has two graduate students who are about to finish their doctoral studies (Dave Blanco and Lee Borenstein); another student is just starting. Over the years, he has trained three postdoctoral fellows (Mike Bharier, Mike Medici, Tom Fitzgerald). No one else in syphilis research has had such an impact. Dr. Miller also gets involved with undergraduate as well as high school students. In the summer he gives these students a project so that they can 'turn on' to science. It does not always work, however. During my stay in Dr. Miller's laboratory, I worked with one of his better high school students, who is now a lawyer in Baltimore. Finally, Jim has been extremely active with other established investigators. With his help and strong encouragement, Mike Norgard, Mike Lovett, and Stu Sell have entered the treponemal field.

"In summary, Dr. Miller's research credentials and teaching capabilities make him a most worthy recipient of the Thomas Parran Award. I would like to make one final comment about my personal opinion of Jim as a human being, and I say this from my heart. Dr. Miller is a role model that all of us can and should emulate. He is a warm, loving, caring individual who has greatly affected many people. My congratulations."

James N. Miller, Ph.D., accepted the Thomas Parran Award and gave the following address entitled "The Future Direction of Treponemal Research."

"Thank you very much, Tom.

"My dear colleagues, family, and friends: It is with a deep sense of honor that I accept this most prestigious award. To my brilliant young graduate students and post-doctoral fellows, past and present, whom I have had the opportunity to train and guide, and with whom I have had the satisfaction of stimulating scientific collaboration and interaction, I offer my thanks. Their continued far-reaching contributions to the field of treponematology provide me with a sense of great pride. Without them, this award would not be possible. Accomplishment by any scientist requires, in large part, an understanding and patient family. To my wife, Shirley, my lover and best friend, thank you for your many years of support, encouragement, and love. My thanks to our marvelous children, Richard and Lynn-Ellen, their spouses, Susan and Steve, and our two grandchildren, Michael and Andrew, for creating that wonderful balance between family love and treponematology that has been so essential to a full and satisfying career.

"My feeling of pride in receiving this award is, in no small measure, related to the greatness of the man after whom it was named. It seems appropriate to recount at least a few of the remarkable accomplishments of Dr. Tom Parran. Thanks to our notable and distinguished historian, Dr. Rudy Kampmeier, I have the pleasure of being able to present you with a capsule summary of a few of his significant achievements excerpted, in large measure, from the memorial to him written in 1970, two years after his death, and which appeared in the Transactions of the Association of American Physicians. The major part of his illustrious career is identified with the U. S. Public Health Service. As Assistant Surgeon General in charge of the Division of Venereal Diseases from 1926 to 1930, State Health Officer for New York from 1930 to 1936, and as Surgeon General of the United States from 1936 to 1948, he inaugurated research programs on syphilis in cooperation with universities. For the first time, an educational program for the public in venereal diseases was dared! Dr. Kampmeier pointed out that in a broadcast on Columbia radio during the 1930s, Dr. Parran used the word *syphilis*—the first time it had been spoken in a public address. His address was promptly shut off in midsentence.

It was said that this angered him and provided him with an even stronger stimulus to educate the public, a goal that he pursued with great vigor. His singular contributions to public and governmental awareness of the venereal diseases and to their prevention and control were extensive, as were his contributions in these areas to medicine in general. He foresaw the need for government participation in medical education and knew that many of his goals could not be attained without government-supported research. He was instrumental in building the National Institutes of Health (NIH) in their modern form. He inaugurated the procedures of research grants to states, individuals, and educational facilities, as well as the modern-day fellowship programs. He was involved in the initial planning of the NIH clinical center, played a significant role in the development of the World Health Organization, and helped launch the Hill-Burton program for construction of the Centers for Disease Control in Atlanta, Georgia. His book, entitled *Shadow on the Land: Syphilis*, published in 1937, did more to familiarize the general public with the impact of syphilis upon the individual and the nation than any event of the time. His "Platform for Action" against this devastating disease remains the basis for the sophisticated control programs recommended and/or in use today.

"If he were alive today, there is no doubt that Dr. Parran would be both proud and excited as he examined the accomplishments and potential for future accomplishments in the field of treponemal research since his time. Yet, he would recognize that there is still much to be done if we are to control the treponematoses with maximal efficiency or eradicate them. Despite past achievements and years of research, the biology of the pathogenic treponemes and the pathogenesis of the complex diseases they produce are poorly understood. We are still unclear as to (1) how to accomplish continuous in-vitro cultivation in a tissue culture system or cell-free medium; (2) the pathogenetic mechanisms (virulence factors) that allow the organisms to establish themselves within the host and produce disease; (3) the extent and nature of the host's contribution to tissue damage via the inflammatory response; (4) the role of immune mechanisms in the healing of early lesions, the maintenance of latency, and the upset in host-treponeme balance that results in tertiary disease; and (5) the location and characteristics of treponemes during latency and the factors that contribute to their survival.

"In my judgment, the importance of resolving these problems cannot be overemphasized. Without a complete understanding of treponemal pathogenicity and pathogenesis, we are restricted in our attempt to develop and properly evaluate our major research goals for control and prevention: more effective diagnostic assays, vaccines, and antimicrobial therapy. The sophisticated classic and molecular technology now available have already en-

abled and will continue to enable treponematologists to accrue newer information directed toward accomplishing these objectives. Knowledge of the nutritional, metabolic, and atmospheric requirements of *T. pallidum* subspecies *pallidum* has already led to limited in-vitro cultivation in tissue culture and significant maintenance of virulent treponemes in a cell-free system. The rational approaches being taken by David Cox and Steve Norris in their respective laboratories may soon lead to success. Let us not underestimate the importance of this research. If serodiagnostic assays and effective vaccines require the use of multiple immunogens in a structural order and arrangement existent only in the intact organisms, in-vitro cultivation will be essential.

“Several laboratories have identified, by SDS-PAGE-Western blot or radio-immunoprecipitation analysis, native specific and cross-reactive polypeptide antigens of *T. pallidum* subspecies *pallidum* potentially important in the pathogenesis of syphilis and as potential serodiagnostic antigens or vaccinogens. It has been possible, through these observations, to postulate a pathogenetic role for specific polypeptide antigens identified by these molecular techniques using both polyclonal and functionally characterized *T. pallidum* subspecies *pallidum*-specific monoclonal antibodies as probes. The elegant molecular studies conducted by Sheila Lukehart and her group have pointed to minor differences in polypeptide antigen content among *T. pallidum* subspecies *pallidum* and *pertenue* that just might account for the differences in the disease and protective immunologic response they produce. Monoclonal antibodies directed against *T. pallidum* subspecies *pallidum*-specific epitopes identifiable by immunoblotting techniques have already been exploited by Sheila Lukehart and Michael Norgard in highly sensitive and specific assays to identify *T. pallidum* subspecies *pallidum* in early lesion exudates and tissues. Considering the limitations of dark-field microscopy and the CSF (cerebrospinal fluid) assays, this methodology represents an exciting approach to diagnosis and is being pursued. Indeed, the use of monoclonal antibodies to purify antigens by affinity chromatography has obvious application in treponematology research. Notwithstanding these important gains, until we isolate, purify, and characterize with respect to their functional properties, significant surface and/or subsurface native or corresponding recombinant antigens, interpretation of such immunoblotting data is limited. The restrictions of both one- and two-dimensional gel electrophoretic analysis, variations in the preparation of treponemal suspensions, lack of standardization with respect to molecular weights of polypeptide antigens, and possible antigen and epitope denaturation by SDS (sodium dodecyl sulfate) solubilization, point to the caution we must exercise. Further, it is conceivable, as I indicated several years ago as a result of my γ -irradiation vaccine

studies, that the significant surface or subsurface antigens associated with pathogenesis and protection may be polysaccharides or polysaccharide complexes. I envision a continuing in-depth approach in the laboratories of Thomas Fitzgerald and Sheila Lukehart and the initiation of detailed studies along these lines in other treponemal laboratories, including our own. Several laboratories, again including the Lovett, Miller, Norris, and Penn laboratories, are currently engaged in studies directed toward the identification, isolation, purification, and/or functional properties of specific and cross-reactive outer membrane and axial filament antigens. The molecular analysis of purified axial filaments from *T. pallidum* subspecies *pallidum* by Penn and his co-workers, and the molecular and functional analysis of cross-reactive axis filament antigens by Radolf and Blanco in our laboratories represent the beginning of concerted efforts to establish the importance of both outer membrane and axial filament structures to the pathogenicity and vaccinogenic capabilities of the organism. Indeed, these studies and those of Axelsen and his co-workers further suggest the potential of specific and/or cross-reactive axial filament antigens for use in immunologically specific serodiagnostic assays.

“It is apparent that we have made and are continuing to make significant contributions to our understanding of treponemal biology and pathogenesis utilizing the strategies I have described. However, the molecular void in our technical approach to these problems has been filled to a great extent with the ability to express cloned genes from *T. pallidum* subspecies *pallidum* in recombinant *E. coli*. Antigens of recombinant *T. pallidum* subspecies *pallidum* have been isolated in the laboratories of Bassford, Lovett, Norgard, and van Embden and are currently under investigation. I should like to stress, however, that in addition to their physicochemical properties, the functional characterization of these molecules and their correspondence to native *T. pallidum* subspecies *pallidum* antigens are critical parameters to be determined. As an illustration, I would like very briefly to present pertinent results of collaborative studies conducted at U.C.L.A. with Dr. Lovett on his recombinant 4D antigen. This is a protease resistant, *T. pallidum*-specific polypeptide with a molecular weight of 190 kdaltons. Extensive proteolysis of the molecule results in a digestion product of 90 kdaltons, which retains antigenicity for syphilitic sera and which is indistinguishable in size, isoelectric point, and antigenicity from a 90-kdalton molecule isolated from *T. pallidum* subspecies *pallidum* after proteolysis. Electron and immunoelectron microscopy reveal, respectively, the 4D antigen as an ordered ring structure located on the surface of *T. pallidum* subspecies *pallidum*.

“With respect to functional analysis, antibody directed against 4D stimulates complement-dependent treponem-icidal activity. Further, in a series of vaccine studies in

the rabbit, we have shown that immunization with 4D, in the presence of adjuvant, stimulates partial protection against intradermal challenge with *T. pallidum* subspecies *pallidum*, Nichols strain, as measured by delays in the incubation period and/or atypical lesions as compared with controls. This achievement with a single molecule of *T. pallidum* subspecies *pallidum* has generated considerable excitement in our laboratories and represents an active area of ongoing study. We also recognize the potential of recombinants as specific antigens in diagnostic assays and as powerful tools for elucidating the role of corresponding native antigens as virulence factors. These objectives are also being explored. I have no doubt that similar investigations are being and will continue to be conducted in those distinguished laboratories devoted to the recombinant DNA approach.

"I believe everyone would agree, then, that the molecular and classical focus upon surface and subsurface antigenic structure and function is a logical approach to our potential understanding of pathogenesis, more effective diagnostic assays, and the development of an effective vaccine. However, we must also concentrate a good share of our efforts on the humoral and cellular immune responses, alone or in combination, that tend to limit or extend these diseases. Their role in disease and latency is being explored in rabbits and/or humans by several of my former students and colleagues, including Fitzgerald and Lukehart, and by Blanco and Borenstein, two graduate students presently working in my laboratory. These studies are also being conducted in inbred hamsters in Schell's laboratory and in inbred guinea pigs in the laboratories of Wicher and Pavia. The advantages provided by each of the experimental animals will no doubt provide meaningful data regarding the immunopathogenesis of the venereal and nonvenereal treponematoses.

"There is much more to say about the future direction of treponemal research but, unfortunately, not enough

time to elaborate in detail. Briefly, let us remember that we are still in search of effective alternative antimicrobial agents to penicillin and, in particular, antibiotics that cross the blood-spinal fluid barrier. The demonstration by Norgard and myself of a cryptic plasmid in *T. pallidum* subspecies *pallidum* points to the potential for antibiotic resistance and further emphasizes the importance of searching for other effective antimicrobial agents. The promise of third-generation cephalosporins has already been demonstrated in the experimental rabbit model and by the effective treatment of a patient with neurosyphilis by Hook, Lukehart, and their co-workers. These agents should be and are being evaluated for all stages of syphilis in well-controlled and detailed studies in humans.

"At present, the focus of research in almost every treponemal laboratory is directed exclusively toward solving the enigma surrounding the acquired treponemal diseases. Little attention is given to congenital syphilis, despite the fact that it is still prevalent in many countries of the world and nothing is known about its pathogenesis. This has been due undoubtedly to the lack of an experimental model in which to conduct these studies. Fitzgerald has now succeeded in producing experimental congenital syphilis in the rabbit, thus opening up new avenues of approach to our understanding of host-treponeme interactions in the fetus and newborn.

"In conclusion, these are exciting times for treponematologists. The combined classical and molecular strategies being used to solve the fundamental problems associated with these diseases will most certainly result in more effective diagnostic and control measures and may possibly result in their eradication. If he were alive, Dr. Parran would look with pride upon the accomplishments already achieved and the planned assault upon the treponematoses.

"Thank you."