VECTOR-BORNE AND ZOONOTIC DISEASES
Volume 8, Number 1, 2008

DOI: 10.1089/vbz.2007.7891.A

Investigator Profile

Interview with Frederick A. Murphy, Ph.D.

Professor of Pathology and McLaughlin Professor in Residence
University of Texas Medical Branch, Galveston

Frederick A. Murphy is Professor, Department of Pathology, University of Texas Medical Branch (UTMB) at Galveston. At UTMB he is also a member of the Institute for Human Infections and Immunity, the Galveston National Laboratory, the Center for Biodefense and Emerging Diseases, and the McLaughlin Endowment Program. Previously, he served as Dean and Distinguished Professor, School of Veterinary Medicine, and Distinguished Professor, Department of Internal Medicine, School of Medicine, University of California Davis. Dr. Murphy received a BS and DVM from Cornell University and a PhD from the University of California, Davis. He served as Chief, Viral Pathology Branch, then Director of the Division of Viral and Rickettsial Diseases and later Director of the National Center for Infectious Diseases, Centers for Disease Control, Atlanta. His honors include elected membership in the Institute of Medicine of the U.S. National Academies of Sciences, the Presidential Rank Award from the U.S. government, membership in the German Academy of Natural Sciences and the USSR Academy of Medical Sciences, the K.F. Meyer Gold Headed Cane, Doctor of Medicine and Surgery honoris causa, University of Turku, Finland, and Doctor of Science honoris causa, University of Guelph, Ontario, Canada. Most recently he has served as a member of the US Department of Health and Human Services Secretary's Council on Public Health Preparedness. He has been a member of the Institute of Medicine Committee on Microbial Threats, co-chair of the National Research Council Committee on Occupational Health and Safety in the Care and Use of Nonhuman Primates, member of the National Academies of Sciences Committee on Public Health, Agriculture, Basic Research, Counter-terrorism and Non-proliferation Activities in Russia, and member of the Institute of Medicine/National Academies of Sciences Committee on Transmissible Spongiform Encephalopathies.

Dr. Murphy, you pioneered the use of electron microscopy (EM) in the field of virology and produced the first electron micrograph of the Ebola virus in 1976. Is microscopy still an important tool in virology today? How has microscopic technology evolved and how can it best be applied to arbovirology research?

It does seem that few young virologists coming into the field of arbovirology are using electron microscopy. I think the Golden Era of electron microscopy in arbovirology came during the years of virus discovery, when "seeing the virus" was a great help in overall virus characterization and taxonomic placement. These days, electron microscopy is more commonly used in the world of viral pathology, and experimental medicine in general, especially using thin sectioning of infected tissues to better understand pathogenesis and pathophysiology. Molecular virologists, focused on the subcellular world, do not seem to benefit as much

from the insight that electron microscopy provides.

Electron microscopy should fit in with other microscopic approaches, such as light microscopic histopathology and immunohistochemistry, along with the tomographic technologies, that is, the microscopic equivalents of CT and MRI scans. Tomographic technologies are amazing in their ability to reveal important aspects of pathologic processes. I only wonder where such technologies will take us in the future.

The images produced today using thin-section electron microscopy look a lot like the ones I took years ago. In this case it is neither the technology nor the image that is the point, but the interpretation of the pathologic changes seen.

Of the newer technologies not involving thin-sectioning, it is frozen purified virus technology coupled with computer graphic modeling of virion substructure that most commonly catches the eye. This has evolved into a cartoon version of traditional electron microscopy—sometimes I wonder if students think viruses really look like the colorful images in textbooks. I recall an amusing experience I had with a producer from the PBS show, "*Nova*," who said that graphic images of viruses are a dime a dozen and that he prefers to see the "real thing" as depicted by negative contrast electron microscopy. That tickled me.

What events and discoveries led to the identification of the Ebola and Marburg viruses and what was your role in those discoveries? Was that the main focus of your research at the time?

Marburg virus was discovered in Germany. I am the only American left who worked on Marburg virus at the time of its discovery in 1967. Only three of us worked on the virus at CDC, Bob Kissling, Robbie Robinson, and myself—exposing so few virologists was the biosafety strategy of the time. In any case, it was a very exciting time. We borrowed a mobile laboratory (housed in an 18-wheeler) from the NIH and set it up in the CDC parking lot. It had never been used before, so getting its systems to work was a challenge. Nevertheless, we did some good work on Marburg virus. That work became the motivation to build "hot labs" at the CDC.

By 1976, when my colleagues Karl Johnson, Patricia Webb, Jim Lange, and myself discovered Ebola virus, biocontainment was much better. The excitement surrounding this discovery was even greater than for Marburg virus, mostly because of the case-fatality rate in Africa. The events surrounding the discovery of Ebola virus and the WHO team's trip to Zaire are well described in Richard Preston's book, "*The Hot Zone*." I have no argument with his story.

At the time of the Ebola hemorrhagic fever outbreaks in Zaire and Sudan in 1976 I was running CDC's Viral Pathology Branch. We took each disease episode and each new virus as they came. Discovery and characterization of new viruses were part and parcel of the prevention and control activities of the CDC—the notion, "know thine enemy," was well entrenched as a key part of the overall mission. I hope this notion is never lost.

One of my favorite criticisms of CDC folklore concerns the nature of the earliest work on a new virus or a new disease. The folklore is that all early investigation is grounded in classical surveillance and epidemiologic outbreak investigation. Not so! Rather, the early work on new zoonotic diseases such as Ebola and Marburg hemorrhagic fevers and their etiologic agents comes under the heading, "basic research"—that is, field-based and laboratory-based research. Those responsible for zoonotic disease prevention and control need to understand this.

How did you become involved in the discovery of the viruses of the family Arenaviridae and the family Bunyaviridae?

The discovery of the arenaviruses began with Marty Hirsch, who was a fellow in my lab at CDC, working on the unique disease in mice caused by lymphocytic choriomeningitis (LCM) virus. Marty was doing great immunopathologic research, so we had infected mouse specimens in which to look for the virus. We found virus particles, but they were so unusual in morphology that I wanted to redo all our work. Meanwhile, Wally Rowe and his colleagues at

NIH published the first images of the virus. Then, Karl Johnson and Patricia Webb, working at the Middle America Research Unit in the Canal Zone, sent me specimens of several other viruses, including the pathogens Machupo and Junin virus, which put LCM at the head of a new family, the *Arenaviridae*. I must say that this work with Karl and Patricia was most enjoyable—great camaraderie, great humor, and great friendships. Later, Jordi Casals, Bob Shope and their colleagues discovered Lassa virus, and when the virus was transferred to CDC for biosafety reasons, Wash Winn and Dave Walker worked on it and other arenaviruses in my lab. Eventually, Tom Monath became the guru for Lassa fever virus, unraveling its natural history and reservoir rodent host in western Africa. This was a gathering of eagles: great scientists, great innovation, and productivity. I always wondered what I was doing among all these brilliant people! We even got to name the family, with Ernie Borden pulling out his old Latin dictionary and suggesting among others the term "arena," meaning sand or sandy, in recognition of the sandlike ribosomes within the interior of the virions.

The work over many years on the viruses that became members of the families *Bunyaviridae* and *Rhabdoviridae* and the genus *Orbivirus* was done mostly with my CDC colleagues Charlie Calisher and Tom Monath, and the great figures at the Yale Arbovirus Research Unit (YARU), Bob Shope, Bob Tesh, Jordi Casals, and their colleagues. This, too, was often dramatic (I am easily caught up in the drama of discovery). For example, I recall the discovery with Bob Shope of the first rabies-like viruses after about 75 years of thinking that rabies virus was unique. In those days much communication was by letter, in this case the letter starting with "Eureka!"

You recently left the University of California at Davis to come to UTMB. What prompted this change?

You could say, "Fred Murphy has never been able to hold a job!" I was at UC-Davis for 15 years, first as Dean of the School of Veterinary Medicine and then as a professor in both the School of Veterinary Medicine and the School of Medicine. But, I had changed jobs several times before; CDC—twice, Colorado State, etc., all with the unfailing support of my wife and family. This cannot go on; next must be some kind of transition to retirement.

Dr. Stan Lemon, director of UTMB's Institute for Human Infections and Immunity, has said, "In the 1980's, when many medical scientists thought infectious diseases had been effectively conquered, Dr. Murphy, as director of the CDC's National Center for Infectious Diseases, helped warn our country of the dangers posed by new, emerging and re-emerging infectious diseases." Your belief was certainly borne out with the subsequent outbreaks of hantavirus pulmonary syndrome, West Nile encephalitis, SARS, and avian influenza. How would you describe the dangers we face today—are we better prepared to predict, recognize, and combat emerging and re-emerging zoonotic diseases?

I don't at all claim to be the inventor of the concept of "new and emerging" infectious diseases (or viral diseases). The people who invented the concept as a way to revitalize the infectious disease sciences were Joshua Lederberg and Stephen Morse. When I first heard their idea I jumped on it. It was so obvious that this should be the flag under which the National Center for Infectious Diseases at CDC would draw the attention of the public to its continuing mission. This was at a time when counter forces were saying that CDC should focus on social sciences and public health aspects of smoking, auto accidents, family violence, etc.

Nature has provided much of the impetus for refocusing some of CDC's resources on infectious diseases. Along with the threat of bioterrorism, natural viral disease emergences are also behind NIAID's growth in support over the past decade. Still, a flag had been needed, and Josh Lederberg and Steve Morse deserve credit for first seeing this. AIDS was the first disease that emerged after the concept was developed. It has been a terrible lesson in the continuing power of infectious diseases to affect human progress. But, so have the emergent arbovirus diseases and the hemorrhagic fevers.

Besides the leadership from within "our citadel" (the infectious disease research, pre-

vention, and control community), exemplified by Josh Lederberg and Steve Morse (and Tony Fauci and many others), leadership from outside has had an important impact. For example, when Bill Gates says that malaria, tuberculosis, and AIDS affect our national security, the message is heard better than if it were to come from us. I recall a senior Congressional staffer saying to me that we must not seem simply to want more money to "continue to play our little games." Unfortunately, such is the opinion of some of our critics, so we must be prepared to turn up the heat when necessary. Dealing with our critics, in the public and in academia, is also part of the purpose of our mantra, "the threat of new, emerging, and reemerging infectious diseases."

Continuing this mantra, I like to remind people that the infectious disease sciences have done more to improve human health and longevity than any other science. I think we are the inheritors of the greatest legacy in all of science—from Pasteur, Koch, Reed, and the other founders—to the incredible effect their followers have had on human and animal mortality and morbidity. As always, our goal must continue to be disease prevention and control, not just the study of the infectious agents and the diseases they cause, *per se*. I hope the youngest arbovirologists and hemorrhagic fever virologists become vaccinated with this notion, just as my generation was.

What are the main challenges and opportunities for improving our readiness to prevent and contain future viral disease outbreaks?

Several things have to happen to deal with today's challenges. One is that the best and brightest young people must continue to come to work in our field, and they must be empowered to pursue their scientific and public health interests to the point of having responsibility for the outcome of their work. Human medicine is in many ways unique in its empowerment of people rather early in their careers. One day a young physician is a trainee and, poof, the next day he or she is fully responsible for a patient's care. In other fields, including many academic sciences, veterinary medicine, and public health, it can take many years for a young scientist to be given such responsibility. I think such empowerment is a key to the future of our field of science. The idea of two-and-three postdocs, for example, is ridiculous.

Additionally, our community of arbovirologists and associated infectious disease scientists must do a much better job of linkage with other sciences, including mainline virology, and the community of public health practitioners. We need a seamless cloth from the sciences supporting basic discovery all the way to the sciences directly underpinning disease control and prevention. There is so much reductionism (my definition: "more and more research on narrower and narrower topics") in our basic sciences today that there is a growing separation from the broader applied sciences underpinning public health practice. We have a long way to go to fix this.

Many of the impediments to disease prevention and control efforts are far outside of scientists' ability to drive change. After 9/11, the impediments to working in the field overseas have become disheartening. After Iraq, the impediments to working in many countries of the world have multiplied. After the Patriot Act, the opportunity for bringing students and fellows from other countries into our labs has become such a burden that some colleagues and some universities have "dropped out." I have no crystal ball to see how this will all play out.

How do you perceive the current threat of bioterrorism and our country's state of public health preparedness?

We are not yet at an impressive state of public health preparedness, but we certainly are further down the road than we were at the time of the anthrax episodes of 2001. I perceive the threat to be very serious. And I worry that more and more of the public's sense of this threat is being subjected to political spin, the purpose of which is to make the government look good. The reality of the anthrax episodes defied spin—only good science, good public health practice, and good public information programs win out in the long haul.

One of the metaphors used at Lawrence Liv-

ermore National Laboratory in its bioterrorism threat detection program is Gretsky's Law: "Skate to where the puck will be, not where it is." We need to be thinking not only of what the last terrorist did, but what the next terrorist might do, if he/she is a better microbiologist or virologist. Even though much of the focus of our country's biodefense programs is on NIAID's "A-B-C list" of bioterrorism agents, I think much more emphasis should be placed on what the next generation of terrorists might be working on. The usual example here is antibiotic-resistant bacterial pathogens as terrorism agents, but what about viruses that defy our diagnostic algorithms or our simplistic public health response plans?

What aspects of your background, education, and training led you to pursue a career in virology?

My decision to pursue a career in virology was not so much serendipitous as just plain happenstance. I enrolled in the College of Agriculture at Cornell because it was free, and I selected microbiology as my major for reasons long lost in my failing memory. Three years later I decided to apply to vet school, again for less than monumental reasons. I was drafted into the U.S. Army Veterinary Corps the day after I graduated from vet school and was assigned to a laboratory at Fort Sam Houston in San Antonio. I did all the rabies diagnostics for the Army in the southwestern states. The consequences of rabies exposure are such that one quickly learns the kind of responsibility and dependability seen in clinical medicine. We also did a lot of other viral diagnostics. After I got out of the Army, I took my new wife and first son to UC-Davis, where I worked toward a Ph.D. in Comparative Pathology. Another wonderful happenstance came when I was about to finish up my thesis: I got a telephone call from Telford Work, then director of the viral diseases program at CDC, offering me a job as chief of a new Viral Pathology Branch. After a 10-minute telephone chat I accepted—no visit to Atlanta; nothing but that telephone call from a grand person. As must be clear by now, my life has been guided by happenstance. I'm not smart enough to have plotted any of this!

Who were some of your mentors and how did they influence you?

This question means a lot to me, in part because I have been asked it before, always with an expectation of a certain canned answer: "I owe it all to that professor back in 19 . . . " I had great mentors along the way, John Osebold at UC-Davis, Telford Work at CDC, Cedric Mims and Frank Fenner at the John Curtin School of Medical Research in Canberra, but I think the early work I did and the responsibility to get that work done played the central role in my professional development. The responsibility I had for rabies diagnosis in the Army and my responsibilities during my first few years at CDC were downright formative, especially given my naïveté.

You have a unique perspective on the history of virology. Is it true that you have been writing your memoirs? Do you plan to have them published?

In fact, I have finished my memoirs. I should explain that the most important thing in my life has been my family, so my memoir is for my family: my four sons, four daughters-in-law, and five grandchildren. My memoirs remind me over-and-over of my dear wife, Irene. Perhaps my memoirs will also be useful after the Alzheimer's sets in, reminding me of my otherwise forgotten grand life. My memoirs also reminds me of my grand friends, the other most important thing in my life. For example, I enjoy being reminded of a favorite quote by Karl Johnson: "Murphy is not really a scientist, he is just a photographer who uses very expensive cameras." (Basically, an electron microscope is a $300,000 camera.) I love pictures, so my memoirs include about 200 pages of pictures (about 800 pictures in all); people, places, viruses, etc. I must say again that I have had great friends over the years, and my memoirs are filled with their stories. I may update all this, especially if some outlandish images become available. Let's leave it at that!

—Interview by Vicki Glaser