This is an interview with Dr. Thomas Waldmann at the Clinical Center at the National Institutes of Health (NIH), Bethesda, Maryland. The interview was held on March 14, 1990. The interviewers are Dennis Rodrigues, Program Analyst, and Dr. Victoria Harden, Director of the NIH Historical Office.

Rodrigues: Could you tell us about your background and professional experiences; when you came to NIH and what you were doing prior to seeing this patient?

Waldmann: I'm chief of the Metabolism Branch of the National Cancer Institute [NCI]. I came to the NIH in 1956 and have been here for thirty-four years. I started out with an interest in the metabolism of the serum proteins, and I admitted patients to find out how the proteins are catabolized and synthesized.

As part of this endeavor, we were studying the metabolism of immunoglobulin molecules. About twenty-five years ago, I turned to patients predominantly with the genetic, hereditary forms of immunodeficiency, but also to those with certain acquired immunodeficiencies. Obviously, there was a different meaning for the term acquired immunodediciency then. It included those who developed immunodeficiency after a period of normal immune function. Although such patients in that era were rare compared to the AIDS situation now, they were of great educational value.

The genetic errors in metabolic pathways taught us a great deal about the role of various biochemical events in some of these patients with immunodeficiency, and a particular genetic or enviromental error told us a lot about what is important for normal immune function. We learned the ways that abnormal function could occur. We discovered that low levels of immunoglobulins could occur by loss of these proteins into the gastrointestinal tract due to endogenous hypercatabolism as well as by nonsynthesis. An array of diseases such as Wiskott-Aldrich's syndrome, ataxia telangiectasia, common variable hypogammaglobulinemia, and Bruton's agammaglobulinemia were very important in defining not only what makes the immune system work normally, but also the consequences to the patient of immune errors. What is the consequence of not being able to make an antibody? What is the consequence of not being able to have normal numbers of T cells? As part of these studies, we had seen hundreds of patients with different forms of immunodeficiency disease.

We were then informed about a patient in New York who attracted our interest in terms of the possibility of learning more about the immune system. What is common now due to AIDS hadn't been well described then. That is, this patient had been well as a child but subsequently developed

profoundly low lymphocyte numbers. We knew profound lymphocytopenia as a genetic congenital error—severe combined immunodeficiency disease, SCID, of infancy—an error in which patients could not make an antibody or cellular immune response. The well-known bubble boy from Texas was such a child. However, in an adult, this had not been well defined or understood.

In this context, we received a referral to the NIH, in June of 1981, of a patient D who, as we shall discuss, turned out to be the first patient seen at NIH with AIDS. To set the stage historically, I believe that the report from the Centers for Disease Control [CDC] concerning five homosexual men with a new immunodeficiency associated with *Pneumocystis* [*carinii*] pneumonia [PCP] appeared in the last week of May or the first week of June 1981. But on referral of our patient, that had not been reported. We were not aware of this unreported condition. The patient, unknown to his family, to us, or to the referring physicians, was a thirty-five year old homosexual man who had been living in New York. He had a particular partner but many other partners as well within the gay community. He had been healthy with the exception of an array of venereal diseases, including syphilis and gonorrhea on a number of occasions, but then he began having lassitude and weakness in February 1981. Weight loss and fever ensued, and he was admitted in April 1981 to the Hartford Hospital where he had *Pneumocystis carinii* pneumonia, lymphocytopenia, cytomegalovirus [CMV] in the blood and urine, herpes simplex II perianaly, *Candida* esophagitis, and *Mycobacterium avium* tuberculosis of the lung, bone marrow, and esophagus. Initially, he was not as ill as you might have suspected from this history. We were presented with an individual who, we felt, would be unable to make T cells.

Harden: Did his physician call you or someone here, or was he in line for a particular protocol? How did the referral work?

Waldmann: Perhaps now would be the time to indicate to you that we do not have the chart available to us anymore. The chart of this patient had been available until the day of his death. But then it has never been seen again. It is conceivable that it was taken for research review by physicians who participated in the patient's care, but it was on the ward where other individuals, the patient's family, for example, might have had access to the chart. The consequence is that I can't refer back to the chart that is unavailable. But unquestionably, we probably had received a call or letter from the hospital caring for the patient. He probably had been admitted onto a protocol, in this case an omnibus Metabolism Branch immunodeficiency disease protocol, 77-C-66 by number. That is a protocol that permits us to

do studies on the blood and relatively simple immunological tests on individuals, including those who are healthy as well as those individuals who have recurrent infections, who thus have evidence of an immunodeficiency state. We were aware that the patient had a low level of lymphocytes, the pivotal cellular component of the immune system, and we saw the combination of events that result as a consequence—*Mycobacterium avium* tuberculosis, *Candida* esophagitis, cytomegalovirus, and *Pneumocystis* infection distributed widely. Even in that era before AIDS, one recognized this pattern of infections as the hallmark of a cell-mediated immune defect. If a patient didn't make antibody, we knew he would have trouble with highly pathogenic bacterial diseases such as pneumococcal pneumonia or meningococcal septicemia.

The pattern that we observed in our patient was the kind of pattern one saw in Hodgkin's disease patients who were profoundly anergic, or in patients with a form of profound immunodeficiency called severe combined immunodeficiency of infancy, where the patient cannot make an effective cellular or antibody immune response. What we were seeing was an acquired form of cell- mediated immunity. In the absence of AIDS, this pattern as an isolated event, without cancer, without chemotherapeutic intervention, was an exceedingly rare observation in adults.

Since we wished to look into the cause of this immunological disarray, the patient was transferred to the NIH in June 1981. We were not aware that the report in which the Centers for Disease Control described the five homosexual males with an immunodeficiency was being published during this time. To better understand the problem, when the patient came to NIH, many individuals from the Metabolism Branch joined forces. In my laboratory, for example, we looked at the ability of the patient's cells to make immunoglobulin molecules *in vitro* in a culture system we had developed in 1974 to study common variable hypogammaglobulinemia. That is another acquired disease whose etiology is undefined, and where some patients have the B-lymphocyte failure and another subgroup has an excessive number of suppressor T cells. This patient could not make immunoglobulins with his cells in tissue culture. These cells in co-culture with my cells inhibited my cells' capacity to make immunoglobulin. Others in the branch studied his cell-mediated immunity. He was unable to make a skin test response to tuberculin, despite the fact that he had widespread *Mycobacterium avium*, nor could he respond to diphtheria and tetanus antigens to which he had been immunized and to which all the rest of us were responsive. These were the *in vivo* evidences in this person of a cellular defect.

Beyond that, the ability of his cells to do specific viral killing were determined by [Dr.] David Nelson and others. At a T-cell and at an antibody level, we were defining the functional abnormalities of the immune system that would be reflected in his disease. The patient developed cytomegalovirus retinitis, mycobacteria of the mesentery, and waxing and waning of an array of infections. The *Mycobacterium avium* couldn't really be controlled as it was not inducing the expected granulomas, but was just growing widely. Many drugs given to him were directed toward the recurrent *Pneumocystis*, cytomegalopneumonia. He had lung pathology, eye pathology, a history of giardiases, *Candida* esophagitis and a terrible problem with pain. He had a rectal problem with herpes.

As these features evolved, we drew together a great number of individuals from the NIH community. We were all groping, trying to understand what was going on. In that era, one couldn't be fatalistic, even when someone was in an apparently irreversible state. One had to assume that somehow one might be able to reverse the immunodeficiency and with that bring into control the infectious disease. The Eye Institute [National Eye Institute, NEI] played a major role. They took many pictures of cytomegalovirus retinitis which was unusual to them at that time. Soon the patient moved from the immedicate care of [Dr.] John Misiti, my medical staff fellow who was intensely involved in day-to-day care, to the care of others in the medical intensive care unit, where great efforts were made to treat this patient. The lymphocyte count was profoundly low in the patient, below 1,000 cells per cubic millimeter. The neurological abnormalities became a major problem as the patient became more and more unable to respond, to rationally deal with things. At autopsy we found massive necrosis, encephalitis, and degeneration of the brain.

Harden: After the autopsy, were pathological specimens maintained for later use? Did anybody go back and verify that this was an infection, once the HIV had been defined?

Waldmann: I don't know. With gene amplification by the polymerase chain reaction [PCR], one could do so. We did keep a serum bank in our branch and it would be possible to look back to see if there were antibodies to HIV. We could not do this in 1981, which was before the etiology of this immune deficiency was recognized. We probably did not maintain viably frozen cells although we do so on certain patient groups.

As I was saying, at the end the patient had massive cerebral necrosis and autolysis. We had a great number of people involved in treating all the different systems. You might have to turn to Dr. Misiti to get the names of

the individuals. Parenthetically, at autopsy he did have a tumor—not Kaposi's sarcoma, but a large-cell lymphoma involving the liver. This feature is common today, but at that time it was not easily recognizable. As we groped to explain the immunodeficiency, we recognized that the patient had used many drugs. To us it seemed that any one of these, including amyl nitrate, which was one of the etiological candidates for AIDS at that time, could have been contaminated or otherwise involved with a toxin that might have impaired the immune system.

His disease continued, and the patient finally died on October 28, 1981, of hypotension and respiratory failure, with multisystem involvement. At this time, an autopsy was permitted, and the wide spectrum of infectious diseases was demonstrated. By the time of the autopsy, we recognized that this patient fit into that category of disease that was being described by the Centers for Disease Control.

Harden: Had other AIDS patients been admitted to the NIH Clinical Center by the time he died in October?

Waldmann: We did not see any other cases on our service. The autopsy on our patient says that "This case represents an example of a recently described syndrome of acquired immunodeficiency in previously healthy young male homosexuals," giving reference there to eight papers. Since one of them is authored by [Dr.] Henry Masur, it might have involved other NIH patients. They viewed this case as having multiple opportunistic infections, especially cytomegalovirus, herpes simplex, *Pneumocystis* pneumonia. That this case did not have Kaposi's sarcoma, but rather malignant lymphoma was most interesting, and this had not been previously reported. The aspects that were unique to the case at the time were the level of involvement of the eyes, the virtual failure of any response to the *Mycobacteriun avium*, and the lymphoma, which at that time had not been described in AIDS patients. There were an array of functional assays done, but we do not know the results in the absence of the chart of this patient.

In terms of sociological issues, the impact of this person's disease, on the one hand, and the revelation that he was a homosexual, on the other, had a devastating effect on his relationships to individuals who had been close to him in the past. From the discussions, it appeared that the family was not aware of the fact that while living away from home in New York, he was an active homosexual. This revelation was a very serious blow to the relationship with his family, and a cause for concern not only in terms of immediate interpersonal interactions, but also in terms of the potential impact that this could have on the social milieu and friends of the family.

The family did, however, continue to see the patient on occasion during his stay at the NIH; they were not here continuously. I gather from discussion with Dr. Nelson that the patient in large measure had been abandoned by his primary partner and other individuals who had been friendly with him in New York, and that no one visited this individual, who was in a critical and life-threatening condition, throughout his whole four-month stay.

Many individuals from clinical pathology began to recognize the importance of this syndrome. In general, they were very intrigued and excited by the intellectual and clinical challenges that this patient provided. John Misiti, as my clinical associate, spent an enormous amount of time with this patient to orchestrate the interaction with other groups. Unquestionably, our patient had AIDS. I appreciate your suggestion to try to validate that diagnosis with at least antibody assays on the serum. Tests of HIV viral integration by PCR on pathological tissues would be interesting.

As this disease became understood in its earliest phases, when it became very likely that it was caused by a retrovirus, but before the mode of spread of this retrovirus was defined, there was a certain level of anxiety in the people who had to deal with his body fluids. This was aggravated by the fact that three of our patients with the genetic, hereditary forms of immunodeficiency developed AIDS as well. Those individuals and this patient—because of his humoral immune deficiency—might not have been able to make antibodies to HIV. Because of their underlying genetic, hereditary immunodeficiency, the possibility of AIDS did not have to be entertained clinically; however it was confirmed by appropriate viral studies. Together these patients caused some concern in the people who dealt day-to-day with their blood. They did not convert at that time, or in succeeding years, to antibody positivity.

Rodrigues: It must have been very interesting for you, having spent so many years working on diseases of aberrations of the immune system, and then seeing these very rare cases. Was it surprising that a disease of immune deficiency could come along that would be a global pandemic?

Waldmann: It certainly was a challenge, and it presented a major question for our laboratory. We had to decide whether to drop everything else that we were studying and study AIDS, or to leave AIDS to others. There was no middle ground. At the time that this patient came, certain unique and dramatic observations were made in our laboratory independent of our study of immunodeficiency. We introduced, for the first time, the study of the rearrangement of the immunoglobulin and T-cell receptor genes for use in the diagnosis and monitoring of therapy of leukemias and lymphomas. Also

we produced an antibody to the interleukin 2 receptor that we used to define the structure of this receptor and to initiate IL-2 receptor-directed therapy. We felt that these unique opportunities would contribute to our understanding of human T-cell lymphotrophic virus I (HTLV-I), which at that time was being defined in another patient within the broad NIH community at the NCI [National Cancer Institute] branch of the Navy Medical Research Center. Using that patient's cells led to the discovery of HTLV-I and the production by our laboratory of the monoclonal antibody to the Il-2 receptor, anti-Tac.

These aspects of T-cell activation are germane to AIDS, but not a direct study of AIDS. I decided to follow them because we were in a unique position in those areas to make a major contribution that would be relevant to retroviruses, malignancy, and immunodeficiency. I felt strongly that the etiology of AIDS would be an infectious agent, perhaps a virus, which was not in our area of expertise. We were not virologists, nor were we the kind of individuals who could make the fundamental AIDS breakthrough. Issues that relate to abnormal cellular interactions in AIDS, the sort of studies that Tony [Dr. Anthony] Fauci or Sam [Dr. Samuel] Broder perform, are very important. Sam Broder, who was my medical staff fellow, went on to do brilliant work in this area using techniques similar to those used on our branch. But I believed that the work that culminated in the demonstration of the HIV retrovirus was beyond our area of expertise and beyond our capacity for viral containment, since our laboratory has only P2 laminar flow hoods. There would have been no safe way for our technicians to have studied a virus that had an undefined mode of spread. The risk to the lab personnel would have been too great. A concern in this regard was expressed by the lab personnel themselves. Furthermore, one of the individuals working in the lab left, albeit to a higher administrative post, but the dominant reason was that we dealt with the virus HTLV-I, which is exceedingly difficult to spread. In contrast to HIV, HTLV-I had not been spread to health-care workers or to laboratory personnel. I don't know of lab personnel that have been infected with this virus.

Harden: In this context, could you talk a little more about how your own thinking about this disease evolved? What was being published in the literature? What was the time frame between the first patient and the issues of concern with viral transmission arose? When you saw this patient, what was your diagnosis and how did this evolve to the understanding of a contagious disease, a retroviral disease?

Waldmann: It would be easy to reconstruct history knowing its outcome. I don't know if I can get a fair picture, especially since we're asking the classical, "What did

you know and when did you know it?" type of question. As the patient came in, we recognized that this patient was of that category that had three decades of normal immune function and then something very critical happened. There are a few causes for that. It is typical of me to not force things into an old, established cause but to try to think about new syndromes. When I started at the NIH, we would find clinical disorders that others could somehow force into a pattern but we would describe as new syndromes. We described the previously undescribed intestinal lymphangiectasia as well as allergic gastroenteropathy. These diseases were defined by us when we forced ourselves to think about them as something new. When our patient entered the NIH, it was known that there is an x-linked immunodeficiency state, essentially in males, that emerges in individuals who have a normal ability to fight infections, but following exposure to Epstein-Barr virus [EBV], develop immunodeficiency. [Drs.] Provisor and Portillo had shown these individuals could die of the virus EBV, which for most of us causes infectious mononucleosis but nothing more. These patients could also develop lymphoid tumors, or could become hypogammaglobulinemic and immunodeficient for the rest of their lives. We were studying the mechanism of the hypogammaglobulinemia of such patients. We knew that when one of us got infectious mononucleosis, our B cells would be infected with EBV and our T cells would react to those B cells and would shut off the B-cell proliferation. That bubble boy in Texas, who lacked T cells developed B cells that were uncontrolled when he received Epstein-Barr virus in a marrow transplant from his sister. The EBV drove the B cells to proliferate, but there were no T cells around to provide a brake on their proliferation. So we had the precedent of EBV being a potential cause of lymphoma and of immunodeficiency after a period of normal function.

Hepatitis virus was also appearing in some of our patients. We were aware that the patient and other homosexual men were using drugs that could conceivably have impaired the immune system. However, drug use as the etiology of AIDS was soon made very unlikely when blood transfusions were shown to cause a similar syndrome. It then appeared that an infectious agent was the cause. There were other infectious agents, such as the one that caused Legionnaire's disease, that were not easy to define, yet were not a retrovirus. It became an issue of whether an infectious cause was present. Early on if we thought it was likely to be a chemical, we might have done further studies of this syndrome, seeking other patients. The fact that we thought it was a virus, and that there were virologists around that would be the ones to discover that and not us, altered our thinking. We did not sense that what was present in five patients at the CDC and one patient at the NIH, was going to be a global problem.

One aspect that affected our decision was the difficulty in taking care of the patient. The medical staff fellows on our service spend 10 percent of any given period of time dealing with patient care and the rest of their time in the laboratory working on cellular immunology, receptor peptides, cloning new genes, etc. To them clinical care obligations, although a learning experience, were onerous. We did not have a cadre of individuals like the medical staff fellows on other services, completely dedicated to patient care over a period of time. If you were in NIAID [National Institute of Allergy and Infectious Disease] or the Medicine Branch of the NCI, physicians had 100 percent of their time dedicated to patient care, let us say, for a year, and then 100 percent of their time, with the exception of their clinics, in the laboratory. We always had shared patient care/laboratory experience. We had for the whole branch about three medical staff fellows a year, so I personally would have one new fellow every other year. One medical staff fellow worked with me. It would have been overwhelming to have even one patient with AIDS. One couldn't do science in the laboratory on the one hand and intense patient care on the other. This affected what we were going to do in the end.

Our first choice concerning etiology was that this was some virus with a pattern that was different from the viruses that had been defined. EBV caused B-cell tumors and B-cell antibody deficiency. AIDS, as exemplified by our patient, had different kinds of infections than those observed with B-cell deficiency. The patient had a low number of lymphocytes, a reduced number of T-cells, and skin anergy, which is a cell-mediated immune defect. There wasn't a counterpart virus known at that time that inhibited cell-mediated immunity. Thus it seemed unlikely to be Epstein-Barr virus or the hepatitis virus.

Obviously, there were retroviruses emerging that had a preference for the T cell. There were individuals, such as Bob [Dr. Robert] Gallo, who recognized that there was an array of retroviruses that could cause both immunodeficiency and malignancy. The human T-cell lymphotrophic virus I (HTLV-I), a virus that we were studying, not only caused adult T-cell leukemia but a profound immunodeficiency as well. It may not be as broadly known as HIV. Patients with adult T-cell leukemia and HTLV-I infection have anergy, delayed hypersensitivity defects, *Pneumocystis* infections of the lungs, an array of infections, and they cannot make antibodies, including antibodies to our monoclonal antibody from the mouse. Thus, they have an array of T-cell abnormalities. This may reflect the action of a lymphokine made by these cells.

One of the candidates for AIDS being presented to the community was HTLV-I, and parallels between patients with HTLV-I and those with AIDS were brought forth. HTLV-I was endemic, one could see transmission of HTLV-I by blood, involvement of CD4 cells, an immunodeficiency leading to infections with this virus.

What was discordant between HTLV-I and AIDS was the regions in which AIDS was appearing. HTLV-I is endemic in Japan, in the Caribbean, including Haiti, and in sub-Saharan Africa. It was not endemic in San Francisco or in New York at the time of the onset of the AIDS epidemic. The Caribbean and sub-Saharan Africa are common to both of these viruses and these diseases. But Japan, at that time, had a great deal of HTLV-I, yet it did not have AIDS at all. It was a problem epidemiologically. It could have reflected variations in the virus. We must recognize there could be differences in responsiveness to a virus related to the HLA groups of infected individuals. Those of us who are immunologists constantly focus on the contribution made by the transplanation antigens to the host response. People who get the neurological disease called tropical spastic paraparesis [TSP] or HAM [HTLV-I associated myelopathy], which is distantly analogous to multiple sclerosis, share an HLA type more frequently than would have been anticipated by chance alone. The observation suggests that this disease is caused by the combination of a virus and perhaps the host's response to that virus. The host T-cell response to that virus unfortunately causes the brain to be the loser, because the T cell proliferates in response to the virus but unfortunately recognizes and damages the neurological tissue. In these patients with AIDS, the issue is if it is due to a virus alone, the combination of certain drugs and the virus, or if there is a connection with the patients' HLA type. Furthermore, early on there were suggestions that Kaposi's sarcoma patients had a predominant HLA type. Now we recognize that one does not need any particular HLA type to get AIDS.

Rodrigues: You talked about the contributions that studying certain types of immune deficiency diseases could have on experiments of nature. Could you give any insights into how this works?

Waldmann: I didn't allow you to ask a question but I'd like to…it may be classic of Washington, give you a particular answer no matter what the question happens to be. That is to try to help you see what was known concerning the immune system when I was going to medical school compared to what is now known—how much insights relevant to AIDS have increased in these thirty years since I went to medical school in the early fifties.

I was recently the president of the Clinical Immunology Society. As part of

my presidential address, I took out my medical school textbooks from the early 1950s. I looked over Rivers' virology textbook, the best hematology textbook, Winthrob, and infectious disease books. I asked, "What did we know about the immune system when these books were written?"

The T cell is the target of the AIDS virus. However, the T cell was not known in 1955; and the role of the thymus in generating small cells that are important to the immune system had not been defined at all. These small cells were virtually unmentioned other than to note that they could become a form of cancer—leukemia. Alternatively, totally aberrant statements were made in these books. It was suggested that lymphocytes might be involved in the catabolism of proteins and that they probably were not involved in carrying lipids to the liver. There was no knowledge whatsoever of their true function. I may not do total justice to people like [Dr. Merrill] Chase and others, but the general scientific community had essentially no knowledge about cellular immunity, T cells versus B cells. These concepts began to emerge in the early 1960s as individuals studying the role of the thymus— or alternatively in birds, another organ called the bursa of fabricius that is the organ for B cells that parallels the thymus in T cells— began to recognize that there are two dominant kinds of cells involved in pathways of the immune system. Incisive people like Bob [Dr. Robert] Good and [Dr.] Max Cooper began to separate the genetic human diseases along errors of the pathways of cellular interaction and cellular maturation, B- or T-cell pathways. In a very wonderful meeting in Sanibel Island, Florida, in about 1963, scientists first began to talk about these diseases in terms of the type of cell and the immune function involved. The tests for T-cell functions emerged from various laboratories, including our own. We were the first to demonstrate suppressor T cells in human beings, and we showed that they could play a role in the immunodeficiency of patients with common variable hypogammaglobulinemia. The T-cell functions were the focus of an early phase of research. The next phase first involved the use of heteroantibodies, then of hybridoma technology and monoclonal antibodies, to define differences in the surface of T cells with different functions. CD4 and CD8 antibodies were defined. CD4, the entry site for HIV, was not known until the late 1970s when Dr. [Pat] Kung of Ortho Scientific, in conjunction with Drs. [Ellis] Reinherz and [Stewart] Schlossman of Harvard and many others, contributed by making monoclonal antibodies to this protein. We used similar monoclonal antibody approaches to define the structure of the IL-2 receptor.

By this time, one could grow B lymphocytes using the Epstein-Barr virus. But there was no way of growing T cells. Drs. [A. Charles] Morgan, [Dr. Francis] Rucetti, and Gallo tried to grow granulocytes, but with a

serendipitous observation presented to their open minds, were able to define T-cell growth factor, now called interleukin 2, that permits the growth of T lymphocytes. Interleukin 2 is very important to me because I focus on the IL-2 receptor as a target for therapy for autoimmunity, malignancy, and graft rejection. IL-2 is the cardinal target of cyclosporin A, the drug so important in graft survival approaches. IL-2 has also been pivotal in studies of AIDS because it permitted the *in vitro* growth of lymphocytes. That in turn permitted [Dr.] Luc Montagnier to identify HIV, and the NIH groups to grow HIV and to develop assays for its cytotoxicity and its diagnosis.

Thus, if we go back nearly thirty years, we can see that we didn't know that certain infections were associated with defects in cellular immunity. We didn't have any functional assays that distinguished between antibody-producing cells (B cells), helper cells (CD4 T cells), and suppressor cells (CD8 and CD4 T cells). We did not have the ability with the antibodies to define the entry receptor utilized by HIV (CD4). We did not have the capacity to grow lymphocytes *in vitro*, a step required for the identification of HIV.

We are all impatient with the pace of AIDS research, but I am impressed with the unbelievable amount that has been learned in the area of clinical immunology. In part this has been due to studies of rare patients with genetic immunodeficiency diseases. I can tell a story on molecular biology as it relates to AIDS. Thirty years ago we had no restriction endonucleases; we didn't have molecular biological tools to identify components of a virus; we couldn't define whether a virus is hypermutable in the way we can identify HIV as hypermutable. The opportunity to put fragments of RNA or DNA into replicating materials for vaccine development was not available. We had had to depend, as with the polio virus, to culture the virus by getting either a dead virus by killing it with formaldehyde or getting virus that was less pathogenic but still immunologically active.

One should look not only to the 1980s and the 1990s for hope. What happened since and before the 1950s set the stage for our being able to have a chance against this plague. Without these advances, it would seem like the plague of the Dark Ages or the influenza epidemic. We are now in a position to think rationally about the AIDS problem. It is very tough problem considering that this virus, HIV, has a great capacity for mutation and thus for alternating its antigenic sites. It presents many difficulties, but I feel that so much has been learned that I'm very encouraged about the future both in terms of treatment and prevention of AIDS.

Rodrigues: Thank you very much.

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