This is an interview with Dr. Kenneth W. Sell, chairman, department of pathology, Emory University School of Medicine, Atlanta, Georgia, November 3, 1988. Dr. Sell was formerly the director of intramural research at the National Institute of Allergy and Infectious Diseases. The interviewer is Victoria A. Harden, director of the National Institutes of Health Historical Office.

Harden: Could you talk about your training in pathology and immunology to help me understand how you and other immunologists thought about AIDS?

Sell: I'm a physician. I trained in pediatrics but later became interested in the importance of the immune system, particularly as it related to immunity and the problems of infection in children. I trained at the University of Cambridge in England with [Dr.] Robin Coombs. At that time I was particularly interested in what was happening on the surface of cells, how cells recognized not only each other throughout the immune system but other cells as well. This led me back to tissue transplantation. The role that transplantation has played in the whole field of immunology is very interesting. At the turn of the century all the people involved, such as [Dr. Paul] Ehrlich and [Dr. Elie] Metchnikoff, looked at the immune system as it related to infectious diseases, which is where my original interest was. Then [Dr.] Alexis Carrel developed techniques for vascular surgery, and later on in the 1950s, the actual transplantation of human kidneys became possible. It then became imperative to understand how the immune system rejected organs. That caused a major spurt in research, investigation, training, and education in immunology. Most of the advances in understanding how the immune system worked were the consequence of pressure by surgeons who transplanted organs and wanted to know why they did or didn't work.

The whole area of tissue type and match ultimately turned out to provide us with knowledge of proteins on the surface of cells which were not meant to be there. They weren't there to recognize an invading kidney graft, but were meant to provide recognition by finding proteins on other cells with which the immune system could interact and could control both the response and the adapting of responses in terms of immunity.

Around the turn of the century, as I've said, immunology developed, first by studying humoral antibody-type reactions. I suppose that was because the technology that related to study of those kinds of antibodies was available. Tissue culture and the isolation of the lymphocytes were necessary before further progress in cellular immunity could be made—the work of [Dr. James] Gowans and others in the early 1950s was especially important. As a result, cellular immunity—the role of lymphocytes and macrophages and all the other specific cells of the immune system—began to be studied.

That was about the time that I got into the field. I was interested in transplantation. I got very involved with how cells worked or didn't work. The whole concept of T cells and cellular immunity, B cells and humoral immunity was developed during the time that I was involved in bone marrow, kidney, and other kinds of transplants. Very quickly then, others became interested and began to recognize how the immune system underwent dysfunction; autoimmunity and other forms of dysregulation were identified. Within NIAID, for instance, we had a program dealing with diseases that were the result of dysregulation of the autoimmune system. Wegener's granulomatosis and various other kinds of autoimmune diseases were studied. We began to understand the problems of the immune system itself and various immunological and genetic deficiencies. That whole area began to develop on a parallel path with the understanding of immunity and transplantation. To be sure, immunity in infectious disease continued to benefit from this kind of knowledge, although the direction of immunological thought developed an entirely new area of research: that was the IgA mucosal immunity system. Sixty to seventy percent of all infections penetrate through the mucosal surface, so mucosal immunity became a separate specialty, if you will, and it still is. All these wide-ranging immunological investigations developed in a parallel fashion.

My own training was in cellular immunology, and I was particularly interested in cell surface markers and how cells interact with one another. That whole area developed during the time that I was in training and doing my own laboratory work. That's my background; I think it answers where I fit in and where the whole field of immunology fit during the 1970s as we were beginning to understand this network of immunity.

Harden: At the same time that there were the great strides in immunology, there was a widespread feeling that infectious diseases were controllable, if not completely curable—in fact, that we had seen the end of infectious diseases. Were you surprised when AIDS appeared as a new infectious disease?

Sell: I was not surprised that a new infectious disease could appear. I never supported the idea that we had really conquered infectious disease. You're absolutely right, however. There was a widely held belief that we had the strength to control bacterial infections and with vaccines, to prevent most of the important viral infections. We were at a stage when certainly there was a de-emphasis of research and attention to infectious disease problems, but the infectious disease problems never really went away. There were many infectious diseases that we obviously couldn't deal with in this country.

We also tended to ignore the vast amount of uncontrolled infectious disease that

occurred all over the world. Take malaria and schistosomiasis, for instance. They caused huge mortality and morbidity throughout the entire world. It was almost as though these weren't important because they were not major issues within our country. They didn't count as a major issue to our scientists, except for those interested in international health in developing countries. I never shared the idea that we had reached a point at which infectious diseases were not important. I agreed that, in general, there was less of an emphasis there, but new diseases popped up all the time. When AIDS appeared, it also popped up as a new disease. It reminded me of all sorts of new diseases in animals and in man that had occurred in the past. The classic one was in animals. The parvovirus that occurred in one species of mink underwent some genetic changes, and all of a sudden it became a disease specific for cats. It underwent more mutations and it became a specific parvo disease in dogs. Each genetic change caused a world-wide epidemic in the new species to which it adapted itself. I don't mean to say that AIDS virus has mutated or jumped from one species to another. All I'm saying is that new diseases can occur, and most often they occur because the etiological agents have left one species and gone into another. When they do this, the disease they cause becomes a rampant epidemic infection before the organism settles down to some sort of equilibrium with its new host. That may even be the case in AIDS. There is speculation that this could be a primate virus that has jumped to man as a new host. The unfortunate thing, if this is true, is that an equilibrium state, in which the organism doesn't kill the host, hasn't yet been reached.

Harden: How would physicians have viewed the disease if it had struck in 1955, before we knew what we now know about the immune system?

Sell: We would have been very bewildered, because in 1955 we were just beginning to understand the cellular aspects of the immune system. We didn't have any of the phenyotypic markers, we didn't really know how T cells interacted with other T cells, or how T cells interacted with B cells. This is the whole basis for our understanding of AIDS. We were able to determine fairly quickly that this virus was interfering with the immune system. Within the first year, we knew which cell was involved—the T-4 helper cell. We knew what the primary attack target was and that the AIDS agent was interfering with all sorts of signals that that this cell provided to the rest of the immune system. In 1955 virtually none of that was known. If the disease had occurred then, we would have seen the infections; we'd have seen the complications of cytomegalovirus and other kinds of opportunistic infections, infections of the lung, but we really would not have known how to ascribe this infection nor would we have known where to focus our attention in terms of the infection because we wouldn't have recognized the disease as it developed. It was that development of our understanding of the immune system, particularly cellular immunity, that allowed the quick focusing of our attention on

the aspects of the immune system that were involved.

Harden: Would you link that to public policy support for basic research?

Sell: Of course. Generally, I feel that basic research has provided the basis for increasing our understanding—not just of the infectious disease area but in every aspect—of understanding and treating disease. Certainly, support of basic research was essential. As we began to understand the immune system, we could understand the pathogenic mechanism in AIDS and the pathogenic mechanism in autoimmune diseases. We could begin to understand how tumor immunity in cancer works. One needs basic research to stimulate new ideas about immune system interactions that may cause or influence disease processes. I think most scientists would agree that you make much less progress when you are disease-focused than when you try to go back and establish some basic understanding of fundamental biochemical, physiological and cell biological reactions.

I also think that almost every investigator, including myself, would agree that basic research is truly serendipitous, because you don't know what direction you're going in. Many great discoveries have been made quite unknowingly, in terms of the original intent of the research. If we had to throw out all knowledge that was discovered accidentally while we were doing experiments, we'd have to throw out most of what we know about the biology of man. Basic research is essential; free-ranging basic research is even more essential. It's good to have aims and objectives, but what really comes out of research often has nothing to do with the original aim or objective of the research. I think the public knows this to some extent, but people really need to know it. I hope Congress knows it, and I hope that NIH continues to push basic research that allows the investigator to pursue the new lines of thought that always come out of basic research. There is a terrible tendency nowadays to focus in on a specific target—to focus in on AIDS or to focus in on cardiovascular disease, for example. Basic research is more likely to bring us new ideas that will solve these problems than is targeted, focused research. It permits examination of the subject with only the knowledge we currently have available, which is never enough.

Harden: The CDC [Centers for Disease Control and Prevention] reported the first cases of AIDS in 1981. Focusing on the years 1981 to 1983, could you please recall when you first learned about the unusual cases that later became called AIDS? How did you first think about the disease? What issues were discussed in the NIAID intramural program? How did your thinking evolve in these early years?

Sell: The first case of AIDS at NIH was admitted on our clinical service—NIAID's 11th floor. The disease was not known as AIDS when the patient was admitted, but he had the unusual combination of infections and the impairment of the immune

system. At first we didn't know what the disease was. Then there were the reports from New York and California. [Dr.] John Fahey's group in California published their findings in several patients. Almost immediately we began to hear at meetings about this group of patients. Similar symptoms were also being recognized in patients in New York. So we had a patient in-house, and we began to hear reports from these two areas. The whole thing proved to be a virtual avalanche of discovery. NIH, of course, has a constant ferment of meetings—everyone comes to sit on the study sections. There were several meetings on the campus that dealt with this unusual infection, and we began site visits. It was just a matter of months until everyone was aware of the fact that there appeared to be a new constellation of illnesses or a new syndrome or new disease. It got publicized very quickly in 1981-82. Almost immediately, the people involved felt that most likely it was an infectious disease, and with all of the epidemiological data collected by CDC, it was thought to be a sexually transmitted infectious disease. Very early on we called a meeting, bringing together people who had dealt with new infectious diseases, with the discovery of new viruses and with vaccine development. We asked [Dr. Albert] Sabin to chair that meeting. We spent time talking about the characteristics of the disease. We also talked about what approach to take if, indeed, it was a new infectious agent, how to identify it. It didn't take very many months of review with various members of the intramural staff and of my own personal review of the problem to realize that it potentially could be anything. Almost every virus that we looked at could cause components of this infection and could mimic some portion of what was happening to the immune system. I previously mentioned parvoviruses in animals. Parvoviruses had caused diseases which had some of the characteristics of AIDS. There were certain minute virus diseases in mice—caused by peculiar CMV [cytomegalovirus] or other viruses—that caused similar diseases. There was a whole range of viruses and even some bacteria that were thought to be related to immunosuppressive illness, and they could possibly have been the basis for what was going on.

We made the decision intramurally to look for every viral and bacterial infectious agent that we possibly could. We excluded retroviruses because we knew that the cancer institute [National Cancer Institute, NCI] had been looking carefully at retroviruses as a cause of tumors and had a very large program with retroviruses. We had a small program with retroviruses. Mal [Dr. Malcom] Martin and Wally [Dr Wallace] Rowe, two brilliant scientists, had been looking at retroviruses in mice, but the scale of our program was much smaller than NCI's. So by convention—not by a formal agreement—we decided we'd look at everything else while NCI would look at retroviruses. We searched everything. We did every kind of technique and culture method we could trying to isolate the culprit.

Harden: Is this the program with which Dr. Richard Wyatt was involved?

Sell: Yes. Richard Wyatt was then brought in to the intramural program of NIAID to coordinate all of these efforts. We also began to set up contracts with people, say for instance, in New York, who were seeing these patients. We set up a repository to collect specimens as well as epidemiological data from the patients and began to examine all types of specimens like urine, blood, and stool to see if we could isolate these viruses. Richard Wyatt was a very experienced infectious disease specialist working in [Dr.] Robert M. Chanock's laboratory. He was called in to coordinate a full program for the intramural NIAID. I think we did a fairly respectable job of looking at all these things. There were many moments of excitement when we thought we had found something new, and many moments when we felt we were really running down nothing but blind alleys. It turned out we were.

Harden: Would you explain to me how the theory of amyl nitrites as a cause of AIDS fit in scientifically and intellectually? I believe that for a brief period it was considered very important.

Sell: The general theory was that an infectious agent could penetrate more easily if there was laxity or expansion of the blood vessel system. This occurs with amyl nitrites, which causes laxity of blood vessels, meaning that an infection could spread more easily once it penetrated. It was thought that populations that used amyl nitrites were more susceptible to the infection than other people. Early on, when we didn't know what the virus was, there was a proposed link with amyl nitrites, but it turned out to be simply a link between amyl nitrite use and the population which was most at risk, the homosexual population. They were the main target of the infection, the main source of transmission to each other, and some ninety plus percent of them apparently used amyl nitrites.

Harden: But amyl nitrites themselves do not cause immune depression?

Sell: There was even some suggestion that there was some modification of immunity by amyl nitrites. It could not sufficiently explain it anyway. There is some potential link between the use of amyl nitrite, however, in the development of Kaposi's sarcoma in AIDS patients once they're infected. I don't know if that's valid or not, but it would make some sense because Kaposi's sarcoma is a disease in which there is blood vessel change and that could be related to the use of agents that cause expansion and laxity in blood vessels. That, however, has not been substantiated. To my knowledge, the effect of these agents on the immune system never was sufficient to explain either susceptibility or spread.

Harden: You've talked about the beginning of the NIAID intramural AIDS program. Could you describe the work of some of your key investigators?

Sell: In those early days, Dr. Anthony Fauci had just been made laboratory chief of the Laboratory of Immunoregulation. The first patient was admitted on his service, and very quickly he began to do some innovative clinical activities like transplanting bone marrow from one normal identical twin to his twin with AIDS. He also entered into several treatment trials, using things that would modify the immune system. We spent several hundred thousand dollars for new immunological agents that were just then becoming available in order to look at things that could modify the immune system in these patients. So he was involved in seeing patients, studying them to confirm the immunological damage that was occurring and then conducting an extensive treatment trial. [Dr.] Clifford Lane was the main person in his laboratory who took care of these patients. There were several Fellows in the laboratory who did a lot of the investigative work, but Lane was intimately involved as a full-time participant in these programs.

We asked people in some of the other laboratories to assist—I already mentioned Richard Wyatt. We asked people in Dr. Chanock's laboratory to look at specimens to see whether or not parvovirus or serum parvo-like viruses were present in the tissues. They were not. Mal Martin is a physician and an infectious disease person, a molecular virologist who had switched his attention to retroviruses. He became interested in AIDS early on. I can remember one conference at which we had a young lady, Dr. Francoise Brun-Vezinet/Barre, who came from Montagnier's lab in France. She had just presented some data at a meeting in New York and then came down to NIH. We had a weekly session in our intramural program, in which we talked about in-house research or invited outside speakers to come in and talk about things that might relate to the AIDS issue. She came and presented her evidence of having isolated the first retrovirus from a patient who didn't have AIDS but who had enlarged lymph nodes. Mal Martin was very interested, and subsequently, he developed the contact with Montagnier's laboratory, which then led Montagnier to provide us with the virus to examine. This was about the same time he was giving the virus to the people at the CDC for them to begin to develop assays and tests with the viruses the French had isolated.

What strikes me as fascinating is that the French, Montagnier's group, wasn't looking for the AIDS virus when they found this virus. They were really interferon people. When they were isolating the virus, they used anti-interferon in their isolation culture, and they happened to use transformed lymphocytes in their culture medium. It turns out that interferon does interfere with this virus and so it potentially makes it more difficult to culture the virus. It turns out also, however, that it takes transformed, not normal, cell cultures to provide the necessary medium on which to grow the virus. Serendipity allowed them to grow that virus, which could not have been grown in any other conventional cultures—that is why

it did not show up in any of our cultures. It was also serendipitous since we were preparing cells from peripherial blood using high-density gradients. We looked at the cells that occurred to see if there were viruses present. We examined them and tried to culture them. This particular virus, however, caused a syntycial reaction that allowed multi-nucleated cells to develop. They were all being lost in the gradient—they all went down as heavy cells in the gradient and didn't show up with the monitor for cell population that we were studying. If we had looked at the whole blood we would have seen these masses of multi-nucleated cells much earlier on and would have recognized the significant abnormality in these patients. In this case new technology, that is gradient technology used to examine mononuclear cells, interfered with the recognition of the abnormality in the peripherial blood.

This latter work of isolation of the virus, of examining the multi-nucleated cells was worked out by Tom [Dr. Thomas] Folks, who at that time was a NIAID postdoctoral fellow. He ran a little laboratory that I had near my office. That, by the way, constituted my one attempt to try to do a little bit of science while doing administration about ninety-nine percent of the time. Tom Folks has now been recruited by CDC. He is running a retrovirus laboratory at CDC, so his career in the field continues. His interest, however, has expanded to include retroviruses that may be important for other diseases. That may turn out to be a very important field in the future. It involves not just the AIDS virus but retroviruses associated with other illnesses, many of which may perhaps be associated with neurological illnesses.

Harden: How were the intramural and extramural efforts at NIAID coordinated? It's been said that NIH's response to AIDS was the classic situation for which the NIH intramural program was set up.

Sell: It was ruled that we could transfer resources to the AIDS problem and so we did, almost immediately. We expanded our intramural program just as fast as we had new ideas. There was no limitation in terms of dollars. We could always reassign or get additional dollars. Our problem was trying to think of new things to do and new people to do them so that we could expand our intramural program.

At the same time, people in the extramural program began to look at things they could do. Most of the things that they identified were in the epidemiological sphere. They were things that to some extent were being done at CDC, but they had more to do with specimen gathering and obtaining information from which the infectious nature from the disease could be more clearly demonstrated. We worked very closely with several of the people in the extramural program and, in fact, helped them develop contracts. Some of the initial contracts involved five centers that studied groups of people who either had the disease or were at risk of

the disease. They examined all sorts of specimens and other data from the participants. We worked together very closely with the extramural people as they developed that program. Within a matter of time, however, the extramural program became very large. They did a lot more on their own, and even though there was a lot of communication back and forth, we were much less involved in the administration of their programs, because we were no longer needed in that capacity.

Harden: I would like you to describe the federal coordinating processes. You've mentioned briefly the relationship between NIAID and NCI. Perhaps you could talk more about that and then about the relationships with other public health service agencies. What are the things that went right and went wrong?

Sell: I was primarily intramural NIAID and so that I didn't have much responsibility for intra-institute interactions or interactions between various agencies. To some extent we participated and when CDC held any kind of a meeting regarding AIDS, we were also invited to attend. I can remember when the whole issue came up regarding the spread of the infection. There were meetings in Atlanta in which we participated. We were invited to participate in every area of new concern that CDC or other institutes became involved and vice versa. Every meeting that was held by an institute at NIH always had representation from all the concerned institutes. The three most commonly concerned institutes at NIH were, of course, NCI and NIAID and then the Heart Institute [National Heart, Lung, and Blood Institute] to some extent because of the blood supply. So we had that kind of a coordination. The CDC was very open, and information went back and forth. I often asked senior people like Walter Dowdle at CDC to serve on the Board of Scientific Counselors for intramural projects at NIAID. They would come up to examine our programs and could see at the time what we were doing. It also allowed us to talk at a very basic scientific level about what was going on in each of the organizations. We had good communication.

Our communications were a little less good with NCI, which was conducting research on retroviruses. That was not coordinated with what NIAID was doing during the early years. In fact, we were somewhat surprised when the first announcement came saying that a virus associated with the disease had been isolated in the U.S. We had not met to discuss the progress toward the identification of that virus.

Harden: Should it have been better?

Sell: You always like to think that institutes, scientists, and agencies will cooperate and communicate particularly when there's a problem of such magnitude and epidemic proportions. Ideally you always want better communication and I certainly would

have liked to see it even better. I'm not sure it would have made a difference in the rapidity of the progress of our understanding of the disease or the quality of our understanding. I don't think that it interfered in any way with what we did.

Harden: That's a very important statement. There have been many criticisms in the press and in books that the response to AIDS was too slow. Many people seemed to express the attitude that scientists should have had instant communications and instant answers. I think it's important that you believe that progress against AIDS was not slow.

Sell: My own view is that from the early days we progressed as fast as anyone had a good idea to support. Ideas that came from the outside in response to our RFPs and RFAs [Request for Proposals; Request for Applications] were funded at a payline level much lower than anything else we were planning at NIH—that is, the scientific merit of these proposals, as judged by the study sections reviewing them, could be much lower than usual grants and still be funded. That decision was an obvious attempt to try to get resources committed to the problem.

I totally disagree with people who say things didn't progress rapidly. Our understanding of the disease, the agent, and the epdemiology developed more rapidly than any other new infection in the history of biomedical sciences. It's a serious epidemic and, therefore, wanting to know all the answers immediately is understandable, but blaming the scientific community for not progressing fast enough is totally irresponsible.

Furthermore, I never saw anyone refraining from the pursuit of this scientific investigation because they thought that the people at risk weren't worth studying. This is another claim that's made sometimes. I certainly never saw that attitude the entire time I worked closely with the problem, and I worked quite a few years at NIAID. It just never came up and was never even hinted at. That isn't to say there isn't a single scientist anywhere who is anti-gay, but I never saw that at NIH.

Harden: Your funding came from Congress, which influenced what you could do with your resources. Do you think that Congress, the administration, and the public understand well enough how biomedical science works, and if not, how can scientists get the message across?

Sell: I think Congress really does understand that basic science is important. The people in Congress that I spoke to understood that it was basic science that allowed us to understand this disease as early as we did. We understood the disease because we knew the immune system. Congress is relatively sophisticated, and even though members like to target money towards pet projects, they understand that basic science—R01 grants, fundamental research—is very

important. I think we need to harp on that constantly, but they have an amazing amount of understanding.

There was an amazing amount of understanding in the public from the very earliest time. I felt there was a lot of responsible reporting about AIDS very early on. Almost weekly we had somebody in the office talking about AIDS, ranging from people at the U.S. television networks to those from newspapers. The vast majority of the reporting was very responsibly done. It's amazing how much good information comes out over the TV and in the press when the media deal with this subject. This responsible reporting has led the majority of the population to understand this particular disease, what's going on and the need for all kinds of research, not just treatment trials.

The people who are afflicted have bombarded the press with the need for instant cures, instant answers, instant vaccines, and immediate access to drugs that haven't been proven yet. The afflicted are the ones who are really driving for things that cannot be done. They are driving for answers that we don't have. They are driving for drugs to be used that aren't available or have not even been adequately tested for safety. It's understandable to do that if you have a disease that's 100 percent fatal. When people with cancer get to a stage that's 100 percent fatal, they do the same thing, just perhaps not so vocally. It's understandable. But I think that the general public understands the disease reasonably well, although it always bothers me when I see kids being ostracized in school because of ignorance in some families. At the same time I see many school districts turning around and welcoming those kids into their schools. Many parents and various school officials do understand. There are always a few misguided, but the understanding of the disease is pretty remarkable.

Harden: Following up on your comments about drugs, I recall a reporter's asking me whether scientists were trying to hold up the release of potential therapeutic drugs from people with AIDS. I replied that I thought it was a regulatory question, that the Congress had decided that the U.S. would not permit people to market drugs without testing for safety and efficacy. Clinical trials, of course, take a long time. Is there any other way rather than having a proper clinical trial to tell if a drug is working?

Sell: Even when you have a proper clinical trial it's often difficult to know what value any particular drug is. I don't think any scientist is holding up anything. The regulatory agency [Food and Drug Administration] wants to be shown that one drug is better than another. It's the safety of the public that's important. There's also a huge financial burden. Take a look at what the federal government has paid for AZT [3'-Azido-2',3'-dideoxythiamidine]. If we didn't have some data indicating it really did some good, it would be an incredible rip-off of society, of

people dying with AIDS.

The primary concern about drugs is the safety of the individual. Even if people with AIDS are dying, that does not mean we should hasten their death or make their existence more unbearable. Even AZT has a huge problem with bone marrow depression and the need for blood transfusions. It's not an innocuous drug, and yet we're talking about using drugs that are more toxic but that we don't know much about. There's tremendous pressure from those who are dying to try anything, and there is pressure from the regulatory agency saying we can't approve everything. We have to have at least some modicum of knowledge about the drug before we let the public use it. I don't think any scientist has held anything back in terms of treatment of patients. In fact, the doctors and the scientists are pushing on the patients' side. They're willing to try almost anything they can get their hands on to help the patients, because they feel just as helpless as the patients do.

Harden: Now that you have been in Emory for three and a half years, how is the academic approach to AIDS different from that of the NIH? What do you see happening here?

Sell: AIDS in Atlanta developed over the three years or so since I've been here. Although it was a problem, it was not as big a problem as it was in New York and San Francisco. The infectious disease physicians, and to some extent the oncologists, took care of those patients. There was not very much to offer them and interestingly, the local physicians were not very interested. This was different from almost all the others centers around the country, which were participating in the clinical treatment programs that were being funded out of NIAID.

The first year there was around $20 million in funds for a large number of centers for new drugs. The physicians here at Emory weren't very interested in that because they couldn't see any new drugs of great interest for the community here. They felt the need was much more in the area of education, in dealing with partners and individuals who were exposed, and in trying to deal with the infection. It was more important to deal with the economics of this situation for the patients who were involved, the tremendously devastating effect on the families and the devastating effect it had on the hospital personnel when it moved from a few cases to ten or twenty on the floor. They were much more concerned about all of these problems. The university research division was much more concerned about precise evaluation of the mechanisms of the disease and not with treatment trials.

Here at Emory, we have a Yerkes Primate Center, and we tumbled into one of the best models for AIDS virus infection in the sooty mangabey monkey. It has an SIV virus which is homologous to HIV-2 It infects these monkeys, but they never

get ill. They live with this virus without problems, and yet when you take blood out of that monkey, the mangabey, and put it into Asian monkeys like the macaques, they exhibit features of the AIDS-related complex (ARC), they develop a full-blown disease like AIDS, and they die of opportunistic infections. This provides us a model to study that is better than a human model. We don't have to inflict our studies on humans, and we can follow in a programmed and planned way a primate model. We had a virus that was living happily and not destroying a group of monkeys. This may have been the situation in Africa with HIV-1, which then moved to man. It was in this area that we submitted most of our research grants. We now have quite a few millions of dollars to study that primate model, so basic research can be done much more precisely, much more planned. The research is quite fascinating, although one disturbing thing has come out of it. One variant of this SIV retrovirus, when put into macaques, is now thought to kill them in a matter of weeks. If, in fact, this is substantiated, then it would suggest that this virus may under some circumstances be modified to become a acutely lethal virus. That's one of things we are currently studying.

It's also allowed us to develop what we think is the first understanding of cell-mediated immunity in AIDS. It's difficult to measure cellular immunity in AIDS. There have been various attempts, more or less satisfactory, using this system to explore many different approaches. We now have what we think is a sensitive and specific cell-mediated immune assay that allows us to replicate it, so that we can take a look at this and other infections in the same animals—cytomegalovirus and other infections—to show specificity. So this model may, in the long run, provide more understanding of the whole AIDS process.

Now in our human populations, of course, we've been impressed, like everybody else has, that there is a tremendous neurological component to AIDS. It may be the first component of AIDS that appears in many of the patients. A lot of our attention has been directed that way. The most recent observation, moreover, is that more and more AIDS cases are occurring in drug addicts. We just happen to have had a program here to look at the effect of drugs on the immune system. We have shown clearly that surface receptors on T lymphocytes are modified by drugs. You can cause them to appear or disappear with various of amounts of cocaine or heroin. In fact, one of our graduate students just did his thesis on that subject in our department. So we're now concerned with drug usage and its effect on the susceptibility of progression of AIDS.

Harden: Thank you, Dr. Sell.

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