This is an interview with Dr. Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID), in his office at the National Institutes of Health (NIH), Bethesda, Maryland, on 29 June 1993. The interviewers are Dr. Victoria A. Harden, Director of NIH Historical Office and the DeWitt Stetten Jr., Museum of Medical Research, and Mr. Dennis Rodrigues, Program Analyst, NIH Historical Office.

Harden: Dr. Fauci, we want to begin in late 1980 or early 1981 and discuss the early cases of what became known as AIDS. When did you first hear about these cases, what was your initial reaction, and how did you approach the initial problem?

Fauci: I first heard about the cases that ultimately turned out to be AIDS from the Centers for Disease Control (CDC) *Morbidity and Mortality Weekly Report*. The cases were those reported in June 1981. I remember very clearly. I picked up the *MMWR* and read of these unusual cases among gay men of a strange immunosuppression associated with opportunistic diseases. I remember looking at the report, thinking first that possibly some sort of a drug that the men had taken was toxic to their immune systems, but in the back of my mind was the question that maybe they were infected with an unusual strain of CMV [cytomegalovirus]. We were very well aware that CMV was an important cause of infection in gay men. I thought maybe there was some mutation of CMV that gave a very virulent course in these individuals and was suppressing their immune systems. But I put the idea to the back of my mind.

Then, when the second report came out later that summer, I started to get a little worried thinking that this might be the emergence of a new disease. Very soon thereafter, still in 1981, towards the early fall, it became clear that IV [intravenous] drug users were getting AIDS. I can remember that I started to get goose pimples. I said, "My goodness. This could be an infection that is transmitted by blood and by sex, and I do not have the foggiest idea of what it is."

We do not usually think of new and emerging microbes as causes of diseases unless we are aware of a new and emerging microbe. We had had a relatively minor experience with Legionnaires' disease. It turned out to be something that was clearly not a public health hazard, though people get it as an opportunistic infection, and some people as a primary non-opportunistic infection. I can remember thinking about AIDS as a potential new disease and saying, "This is something that is really very serious." I called in people in my group, particularly [Dr.] Cliff [Clifford] Lane, who was still a Postdoctoral Fellow in the laboratory, and I went downstairs to talk to [Dr.] Joe [Joseph] Parrillo, who was the head of the ICU, the Medical Intensive Care Unit. I said that we should get some people with this syndrome in to NIH and study them. Our expertise was immunology, and we were interested in immunopathogenesis. We did not have the expertise to isolate viruses, because we were not virologists. Subsequently, we have all become retrovirologists by necessity, but at that time we were looking at it from a

purely immunological standpoint.

Cliff Lane was working on a project about the regulation of the immune system, which was the fundamental area that my laboratory had been involved in since 1968. I asked him, "Cliff, would you be interested in studying a few of these patients?" He said, "It sounds very interesting to me. I want to continue what else I am doing, but maybe I can study some of these patients on the side." I remember saying, "If we bring these patients in, they are going to get very sick, so maybe we should go and talk to Joe Parrillo and find out if Joe would be able to handle the ICU type patients?"

Joe Parrillo was very enthusiastic. Joe was also a former trainee of mine. He was a fellow in my laboratory, and then he went to New York Hospital, Cornell. Later, he came back to NIH. That is how the connection between us and [Dr.] Henry Masur came about. Henry Masur was a medical student at Cornell when I was Chief Resident in Medicine at the New York Cornell Medical Center. We knew that Henry was very interested in AIDS because he had been part of the group in New York that first reported it. It was almost a simultaneous reporting from New York and Los Angeles. I thought that it would be good to get Henry Masur to NIH and get him involved in the research. Sure enough, Henry came to NIH and joined Joe Parrillo.

From there, there was a gradual, and then an accelerated, transition of my laboratory. It had been 100 percent fundamental immunology, predominantly looking at diseases of hyper-reactivity of the immune system, namely the vasculitides, and the hypersensitivity diseases. I made the decision that we would have to switch over to research on this disease [AIDS] because, as every month went by, I became more convinced that we were dealing with something that was going to be a disaster for society. In fact, I wrote an editorial in the *Annals of Internal Medicine* in 1982 making a prediction that this was not something that was going to stay confined to a small group. I discussed it with people like [Dr.] John Gallin, one of my close friends and colleagues, and told him that people might think that I was a little strange switching my laboratory over to the study of a new and strange disease—this is the end of 1981, the beginning of 1982—but it was clear to me that this disease would turn out to be a major public health problem.

When you deal with infections that are sexually transmitted and bloodborne, if you think about it, there is no reason to believe they will stay confined to a small group of people, because sex is a universal thing and people donate blood. We did not even have any idea what it was that we was dealing with. Some people, I remember, were a little—I would say—concerned about me. They said "He has been so successful in what he is doing with fundamental immunology and the

hypersensitivity diseases. Why does he want to switch over to an area where we do not have any idea what the disease is and in which he is not an expert?" But the fact was, nobody was an expert yet.

In those months, from the summer of 1981 through 1982, we put together our small AIDS group. Cliff Lane, although still a trainee, was interested in making that a major part of what he did; I had the commitment and cooperation of Joe Parrillo; and Henry Masur arrived. We decided that we could do the research. You had to have a group in place. You could not admit patients in a vacuum because these people were too sick. Then we started to switch virtually the whole laboratory over to AIDS research. When the virus became recognized as HIV [human immunodeficiency virus], then what we could do with the research exploded in a mushroom fashion.

Harden: I want to ask you one question before we discuss the early patients. Clearly what you did in your research changed when AIDS came along. Where did you think your career might go before that and how has it been different since?

Fauci: I was on a certain research track, and had been for several years. This was 1981. I had been at the NIH since 1968. I had already, I believe, made some impact on the field of human immunobiology, and I was very happy with that because immunology is a very exciting field. My goal was to continue to dissect out the immunoregulatory mechanisms of the immune system. In fact, that is what I am still doing, only I am doing it within the context of HIV and AIDS. I had a vision that I would continue indefinitely to dissect out the immunoregulatory mechanisms of the immune system, and to apply this knowledge to diseases like the vasculitides, the arthritides, and those other diseases of hyper-reactivity of the immune system. I had a very clear vision of what I would be doing for the next however many years.

When AIDS came, it turned my work around, but not as much as it would appear on the surface. The focus was still the regulation of the immune system, and I would be studying AIDS from the context of what the immunoregulatory defects are. That is the reason why we now study immunopathogenesis from a number of different standpoints. Although AIDS is a terrible epidemic, it is an extraordinary model for gaining insights into the immune system, the likes of which cannot be obtained from any experimental *in vitro* or animal model.

Harden: Dr. [Richard] Krause recalled the arrival of what I believe to be the first official NIAID AIDS patient (and the second AIDS patient at the NIH Clinical Center). He said that he was at NIH during a snowstorm when a telephone call came from a physician who was referring someone. He said he thought you would be interested in the case. You were here and took the patient. Can you tell us more

about this patient and about the first group of patients? These people were very sick. What was your initial strategy?

Fauci: The strategy was to do pure clinical observation and the fundamental laboratory tests that we had at our disposal. I can remember that call very clearly, because it was in the middle of a snowstorm. A patient, who was in a hospital locally in the Virginia area, had a strange syndrome. Interestingly, it was someone who was a twin. One of the first AIDS patients at NIH was someone who had a twin. This was the beginning of the twin studies that Dr. Lane and I have been involved in now for well over ten years. We started them in 1982. The other twin was uninfected. I remember saying that we should bring this patient in and see him. That got the ball rolling. We were going to take a look at the patient and study whatever it was that we could study.

Of interest—and this is why science is so beautiful—is that we had been looking for years at the B-cell limb of the immune response, the regulation of human B cells, hyperactivity of B cells, particularly in diseases of hypersensitivity. We were one of the leading laboratories in the world looking at the abnormalities of human B-cell immunoregulation. We found out, in a paradoxical way, that in the immunosuppressed state of these patients, their B cells were inappropriately hyperactive and turned on. The patients were hyperglobulinemic, they were spontaneously making immunoglobulin.

One of the first papers that we ever wrote was about this. We made the observation back in 1982. We reported in *The New England Journal of Medicine* in 1983 the polyclonal activation of B cells in patients with this strange immunosuppressed state, even before the virus was recognized. As it turned out, we know now that aberrant immune activation is one of the most puzzling, but nonetheless relevant, pathogenic events that occurs in an HIV-infected individual. It is paradoxical that as such individuals are becoming immunosuppressed, their immune systems are inappropriately turned on. It may be the persistent immune activation which contributes to the immunopathogenic event. We made that observation without having any idea of what we were dealing with. I think that speaks for sound scientific and clinical observation. You make the observation and you do not know what it means. Then, ten years later, you find out that one of the major pathogenic events of AIDS is hyperactivity of the immune system.

I can remember very clearly making this observation. We were following these patients and doing the whole panel of immune parameters on them. We were doing the study to develop a profile of all the patients' immunological reactivity. I remember going into the laboratory from my office to where Cliff [Lane] was doing the tests. I said, "Look at these patients. They all have hyperactivity of B cells. Isn't that interesting?" This hyperactivity of B cells stood out like a sore

thumb. Our paper on it turned out to be the first paper that reported inappropriate hyperactivation in patients with AIDS.

Harden: Would you discuss the twin study a little more? This is one of the very interesting areas of research that you have continued through time.

Fauci: What happened is that we admitted a patient, and then several patients thereafter, who were identical twins. One of each pair of twins was HIV-infected, or sick with AIDS—we did not know what the infection was at the time—and the other was well. We immediately said that if somebody was immunosuppressed, we should try to see if we could "re-boost" the immune response of the sick person by transfusing what we call syngeneic lymphocytes from the identical twin donor who was uninfected, as well as doing a bone marrow transplantation. It was a simple, clearcut approach.

The difficulty at the time was that the only patients that we had who had AIDS were patients dramatically and drastically ill. We had no way of screening patients, bringing them in early, and studying them the way we do now. In order to become recognized as having the syndrome, a person had to have been sick. Once a person got AIDS—since very little could be done for them—the clinical course of the disease was usually fulminant. I can remember the intensity of those first couple of years when everybody that we admitted to the Clinical Center at NIH was very, very sick. There were no people coming in who were asymptomatic, HIV-positive. It was like living in an intensive care unit all day long. It was very stressful.

Harden: If I recall correctly, when you initially attempted to reconstitute the immune system of a patient, you got a brief response.

Fauci: We got a transient response, and then it went away. We were able to get a little blip in CD4-positive cells; then it disappeared, and the patients continued to deteriorate. We did lymphocyte transfusions, and we did bone marrow transplantations. It was clear that something was destroying the cells that we were reinfusing. That was certainly indirect evidence that we were dealing with an infectious agent. Everybody essentially knew by this time that we were dealing with a transmissible disease. We did not know what the agent was though. Since there was a seemingly selective defect in CD4-positive T cells, there was much speculation that we were dealing with a retrovirus that was T-lymphotropic. This is the reason why people started looking for HTLV-1, or an HTLV-1-like microbe. The original studies that [Dr.] Bob [Robert] Gallo and others did used techniques to look for retroviruses, because the agent was behaving like a retrovirus in that it was selectively destroying CD4-positive T cells.

Harden: Over the years you have continued the twin study. What else have you been able to learn from the twins?

Fauci: We have done a number of transplantations. We recently reported a series of sixteen to eighteen transplants from well donors to their HIV-infected twin brothers. First of all, the transplants have not been dramatically successful, so two things were learned from that. We learned that in order to be able to reconstitute immunity we have to suppress virus replication adequately, because the virus will only re-infect the transplanted cells or the transfused cells.

The other thing that we learned, and this is what we are very actively working on now, is that we have a number of lines of evidence to indicate that the microenvironment of the immune system is destroyed by HIV, not just the CD4-positive cells. We do not have a complete handle on this, but it is the work that we will be doing in 1994 and thereafter. We know it from our work with the lymph nodes, the thymus, and from the stroma of the bone marrow. It is conceivable that, even if you destroy or block all the virus in a person, or even if you try to re-infuse cells, you will not be able adequately to reconstitute the immune system unless you provide a proper microenvironment in which those cells can thrive. That is why we are starting to think in terms of the kinds of therapy, either with cytokines, or even replacing tissue, like thymus implants, that re-establish the lymphoid system microenvironment.

You ask what did the bone marrow transplant studies tell us? They told us, since they were unsuccessful, that we are probably dealing with two things: one is a virus that is still replicating. We know from our lymph node work that there is plenty of virus in the body and it is replicating, even though it appears from looking at the blood that there is not much virus around. That was one of the most important results to come out of our recent studies on the lymph nodes. But also, in addition, it tells us that there is destruction of the milieu that the immune system needs to regenerate and re-establish itself.

Although the data were generally negative, that is, the bone marrow transplantation did not work, I think this work provided extraordinary insight for future experiments that we are conducting now and that I think we will probably be conducting for the next five years.

Harden: Let me follow up on this point. I was fascinated by your recent Dyer Lecture that seemed to take all the findings from the beginning and pull them together into a picture of the pathogenesis of AIDS. As we have been looking through a number of documents, we have come across the names of people in your laboratory whose work contributed to this picture. I thought perhaps you could tell us how your laboratory functioned and which groups were working on which pieces of the

problem.

Fauci: Certainly.

Harden: Let me list a few names: [Dr.] Scott Koenig, [Dr.] Steven Schnittman, [Dr.] Guido Poli, and [Dr.] Tom [Thomas] Folks. Perhaps you could describe how these people interacted.

Fauci: We had a number of individuals, who were predominantly fellows, who were in their training period. I assigned different tasks to each of them, to work in a particular area. I tried to cover, as best as I could, the salient areas that I felt would be important from an immunopathogenic standpoint, because the underlying theme of the laboratory was the immunopathogenic mechanisms of HIV infection.

We had the original work that I have mentioned with Cliff Lane looking at hyperactivity of the immune system and at some of the selective T-cell defects. But then Cliff made a major switch in commitment to doing clinical investigations and clinical trials. He still maintained his interest in basic science, but he has provided an invaluable component to the laboratory now by translating what we do in the laboratory into clinical trials, both immunological reconstitution as well as the antiretroviral work.

At that time Tom Folks was in the laboratory. He had been working formerly as a fellow with [Dr.] Ken [Kenneth] Sell, and when Ken left, he joined me in my laboratory. Tom and I had a very productive interaction in the laboratory where we were involved in establishing permanent HIV-infected cell lines and beginning the work on looking at the role of cytokines in HIV infection.

Tom left and went to the CDC [Centers for Disease Control and Prevention], but in the few years that Tom was with me we collaborated well. There was also an Italian named [Dr.] Guido Poli, who had come from Milan as a postdoctoral fellow. He worked with Tom and me for a year or two. Then, when Tom left, Guido blossomed as the main player in the cytokine work. He has been very productive in delineating the role of TNF [tumor necrosis factor], GM-CSF [granulocyte-macrophage colony-stimulating factor], IL-6 [interleukin 6], IL-1 [interleukin-1], interferon gamma, interferon alpha, and other cytokines in the regulation of HIV expression. In addition, he studied the autocrine and paracrine loop of cytokine regulation of HIV. He continues to do that to this day. He has been with us now for several years and unfortunately, he will be leaving us to return to Italy soon.

In addition, we had [Dr.] Scott Koenig, who, again as a fellow was interested

more in how the body responds to HIV. He did very important work, I think, in delineating the role of cytolytic T cells in clearing HIV. He stayed at NIH for a few years, made some important contributions, and then moved on to MedImmune Corporation.

At the time that Scott was here—I try to stagger my fellows by bringing in new people as others get more senior and leave—a young man from Italy named [Dr.] Giuseppe [Gepi] Pantaleo came into the laboratory. Gepi Pantaleo has been one of the most impressive researchers in the laboratory. He started off as a young fellow and now is making major contributions. At first his area was looking at the cytolytic cells, taking over from Scott Koenig, but then we got very interested in the role of viral burden and replication in the lymph nodes. He is now focused predominantly on that, and he and [Dr.] Cecilia Graziosi are working together on it in the laboratory. So the laboratory has the Guido Poli mini-group that is interested predominantly in the cytokines. It has the mini-group of Gepi Pantaleo and Cecilia Graziosi working on the viral burden in lymph nodes and on viral replication.

Then we had another smaller group that was interested in precursor cells. That was work that was started when [Dr.] Steven Schnittman was a fellow in the laboratory. Steve demonstrated, for the first time that thymocytes, *in vitro*, even the thymocytes that were not expressing CD4 molecules grossly but were so-called "triple negative" cells, were infectable by HIV. He published a very important paper on that, and he also did some of the viral burden work in the peripheral blood. Steve did this work in my laboratory at the time he was getting ready to leave and go to the extramural program. [Dr.] Sharilyn Stanley took over this work when Steve left. Now she is leading that mini-group looking at the effect of HIV on the thymus, the thymic microenvironment, and the bone marrow, and looking at the effect on precursor cells. Hers is another mini-group that is also doing very important work in that regard.

Then we brought in [Dr.] Andy [Andrew] Dayton, who is working with a group on looking at control of viral gene expression, particularly the *rev* axis; so we have a molecular virological approach there.

We also have people who are much more senior and independent who are not predominantly working on AIDS, but who do HIV-related work. [Dr.] Uli Siedenlist, who has been very much involved in cloning and describing the role of the NF-kappa-B transcription activating factor, is fundamentally a molecular biologist. He is now using that expertise to look at how HIV uses the NF-kappa-B access for virus expression and how cytokines use the NF-kappa-B access to induce HIV. Finally, [Dr.] John Kehl is another former fellow of mine who is now a senior independent scientist. He has trained [Dr.] Peter Ruckmann, a

fellow from Germany, to perform some very interesting work on the role of B-cell derived cytokines in the induction of HIV expression.

All of these lines of research are now, I think, synergizing in the laboratory. When a critical mass is created, then all of sudden you can look at the big picture, at everything. You have the cytokine look, the precursor look, the viral burden and lymph node look, the molecular virology look, and the clinical immunological reconstitution look. All of those things create an atmosphere in the laboratory that is perfectly suited for producing the results you heard at the Dyer lecture. I was able to get up and talk about the whole spectrum of HIV pathogenesis. People feed and nourish each other. It is good when there is a critical mass of people all interested in the same general theme, HIV, and how it destroys the body's immune system, with each person investigating it from a slightly different perspective.

Harden: You are in the position of doing basic research, of being very intimately linked to work on AIDS, and, at the same time, you are in the public spotlight as a chief spokesperson for AIDS. Beginning with Peter Duesberg, and most recently in Robert Root Bernstein's book *Rethinking AIDS*, the question has been raised, "Maybe HIV is not the cause of AIDS?" Perhaps you would comment on the value of rethinking AIDS. How many times do we rethink it?

Fauci: I do not think it is a question of totally rethinking AIDS. I think it is a question of keeping an open mind about the mechanisms whereby the virus destroys the body's immune system. There is no question that the primary component of AIDS is the virus. Since there were not complete, precise explanations available of how the virus destroys the body's immune system, some people made an inappropriate leap. They said each and every pathogenic event could not be explained on the basis of the virus killing a cell, because it was perceived that there was not enough virus around or there were other phenomena going on. Then, in a sense, they threw the baby out with the bath water. They said that the virus had nothing to do with it. It was just behavior. People were taking drugs, and people were leading "promiscuous" sexual lives. Behavior itself was causing AIDS.

The epidemiology, in and of itself, completely destroys that argument. But rather than take a very strict unidimensional view, what we do—in my laboratory—is realize that we do not have the complete explanation of how the body's immune system is destroyed. We work on that. We know that without the virus, there is no disease. But if you have the virus, how do you get the disease? Rather than arguing about whether the virus is involved or not, we say, "There is no question the virus is involved; but, how is it damaging the immune system?" That is what I tried to get across in my Dyer lecture in the spring of 1993, and in my plenary lecture in Berlin at the International AIDS Conference. I spoke about the multifactorial, multiphasic components of the immunopathogenesis and viral

pathogenesis of AIDS and how that would give us insight into the design of therapeutic strategies.

We can now look at a prototypical HIV-infected individual and the different phases of HIV disease. It is not the small window that we saw in 1981, where a person would come in who was drastically ill, and the only thing that we saw was someone who had no T4 cells and was very sick. But if someone is watched from the beginning to the end of their illness, we see that there are multifactorial components of HIV disease. There is the virus itself, there is activation of the immune system. There are other indirect mechanisms like inappropriate cell triggering, probably apoptosis to a certain degree, cytokine secretion, regulation of HIV expression, a disrupted microenvironment, and the profound immunosuppressed state. These are all complex issues that need to be dissected out. We must keep an open mind because everything cannot be explained by a single unidimensional approach. Without the virus, nothing happens; however, the virus of itself does not explain everything directly. That is the critical issue. That is how I handle it when people say, "No, it is not the virus. Just throw it out."

It is interesting because there are many diseases whose pathogenesis we do not understand, but nobody questions what causes those diseases. For example, we do not have a very good idea of why people who have tuberculosis get granuloma. Why does caseation occur? Why do we get cavitation? People will say, wait a minute, sometimes if you look at the caseating lesion in someone with tuberculosis you may not see very many microbes. Does that mean that the tubercle bacillus is not responsible for the pathology? No, the mechanisms are the induction of a variety of inflammatory and necrotic processes. Just because each and every pathogenic event in AIDS cannot be precisely explained is not a reason to say that HIV is not the primary mover in AIDS.

Harden: Thank you. When you began your research, you did not know what you were dealing with. How did you approach the biohazard problem? Were you worried about your own safety, and your colleagues' safety?

Fauci: No. From the beginning we took the approach that we would be as careful as we possibly could without being hysterical about it. There was really no substantial fear. Maybe there should have been, but there was not. Certainly there was no fear in taking care of patients. We had been trained from the time we were in medical school that it is our responsibility to take care of sick people. If someone does not want the responsibility then he or she should go do something else. There was never a question in my mind, or in Cliff Lane's mind, or in the minds of the people who came after us, that this was what we had to do. We decided we wanted to do it.

If the people who were working in the laboratory were afraid, then we would find something else for them to do. We would not begrudge them their fear, but we would find something else for them to do. There was never a situation where there was a lot of concern about getting infected from an unknown cause, because it was clear from very early on that this disease was not spread casually. All we wanted was to make sure that when we handled material we handled it in a careful way. This is what we still do.

Harden: As I recall, your wife is a nurse who deals with AIDS patients. Have either of you had any personal repercussions? One nurse told us that her children did not want to tell people that their mother worked with AIDS patients.

Fauci: I have had no personal repercussions at all. My wife, Christine Grady, was specifically involved, not only in taking care of AIDS patients, but in teaching other nurses the special problems that are associated with the nursing care of HIV-infected individuals. She was, and still is, totally committed to AIDS research and AIDS nursing. We have never had any repercussions from outside or within the family. We have the same attitude. This is what we do with our lives. This is our job. We are just trying to do it as best as we can. Not doing it was never even a consideration.

People would sometimes raise their eyebrows because we have three young children and my wife took care of AIDS patients throughout the entire three pregnancies. She worked from the very beginning of her pregnancy with our first daughter, who is now almost seven years old. She would take off a couple of months after the pregnancy and then come right back to taking care of HIV-infected individuals.

Rodrigues: I have a follow-up question on your recognition early on that AIDS was caused by an infectious agent and that AIDS was something new, that it was an emerging disease. Many of the materials that I have read describe how AIDS took everyone by surprise, how it was unexpected. But many other people were saying that the microbial world cannot be taken for granted.

Fauci: If the question is was I surprised, the answer is that I was not surprised at all. In fact, from my earliest editorial in 1982, I was singing the tune that this could turn out to be a global disaster. You do not fool around with infectious diseases, particularly those that are transmitted by a mechanism, sexual interaction, that virtually everybody in the world does sooner or later. It was foolish for people to think that this disease, being an infection, was not going to explode into a global pandemic.

Harden: When you wrote your 1982 editorial, had you heard about the infections in Africa and other places?

Fauci: No. My editorial was still related to gay men and intravenous drug users in the United States.

Harden: Do you have anything else that you would like to say about your own laboratory research before we move into a discussion of your duties as an administrator?

Fauci: One of the things to note is the spirit that permeates the laboratory. I have had two interesting and unusual perspectives working in the area of basic research in immunology and immunopathogenesis. First, I have worked on diseases that were important but were not of major public health significance. They were fruitful areas of basic research that in and of themselves were very exciting. Second, I have worked on AIDS. When you superimpose upon exciting basic research the fact that AIDS is a major pandemic of extraordinary public health proportions, the excitement that this creates in the laboratory is extraordinary. It is an indescribable experience knowing that what you are doing will have an impact on the lives of tens, if not hundreds, of millions of people. That gives you a lot of energy to do what you are doing.

Rodrigues: From your perspective as the Director of NIAID, do you think that there is now more public support for basic research in order to be prepared for other emerging diseases?

Fauci: I think that, unfortunately, given the constraints on resources not only for AIDS but for other diseases that are deserving of support, it is very difficult to get people to appreciate a vague concept of the next emerging microbe. I have been working very closely with the Institute of Medicine, with people like [Dr.] Joshua Lederburg, who is a staunch advocate of making the public more aware of the possibility of emerging microbes, and with Dick Krause, who is still very much involved in this area in his position at the Fogarty International Center, to make sure that the science base in microbiology, infectious diseases, and immunology is prepared for the next emerging microbe.

In fact, because of the competition for resources related to problems that are now ongoing, it is very difficult to convince people that an extra investment for emerging microbes is needed. We are not going to give up though. There are a group of us around that are pretty dogged about that. There is a hard-core group that is trying very hard to keep the public perception of the importance of support of biomedical research for the next emerging microbe very high.

The difficulty is that this is being carried out in a situation where the resources are

limited because of budgetary constraints. I do not think the American public is willing to support throwing a lot of money into basic research for the next emerging microbe. They are too worried right now about AIDS, cancer, and all those other diseases they perceive as a threat to them. The potential threat of a microbe that they have never heard of is very vague and nondescript, even though the lessons of AIDS are part of their generation.

Back in 1918, when influenza wiped out twenty to fifty million people worldwide and hundreds and thousands of people in the United States, the people who lived through that, I think, had a good idea of what an emerging microbe might do. But then as the decades went by, they forgot it. Here we are with AIDS and people still have not had the foresight to understand that this can happen again. We are not even half over with this yet.

Harden: By 1984, you were deeply into your AIDS research. You were a successful laboratory chief. Suddenly the opportunity to become Director of NIAID arose. You did not give up your laboratory position; you just added another on. People still marvel at how you get everything done that you get done. Why did you decide to accept the job as Director?

Fauci: There were a couple of reasons. Certainly one of the conditions in my own mind and that I put forward in my discussions with Dr. [James B.] Wyngaarden and [Dr.] Ed [Edward] Brandt, who was Assistant Secretary [for Health and Human Services] at the time, was that I would maintain a heavy commitment to my laboratory. I would just have to work harder, put in more hours, and be more efficient. Fortunately, this has worked out very well. My work, in many respects, has trained me to do that. My perception of what I wanted to do at that stage in my career was to have a broader impact on the field of immunology and infectious diseases. However, I wanted to do it from a scientist's vantage point and not necessarily from a fundamental administrative standpoint. I wanted to bring a much more scientific flavor into it.

I had administered a laboratory, but that is nothing like administering an institute. But I quickly learned how to do it and found out—I did not know this before—that I have administrative skills. This is fortunate because it is not only making my job easier, but it is allowing me to continue to do my research. My goal was to have a broader impact on the field, not only of AIDS, but of all the infectious diseases and immunology, and only if I can do that in the context of continuing to be a very actively practicing scientist. Fortunately for me, I have been able to do it.

Harden: With regard to work on AIDS, what did you find when you became Director? What was bequeathed to you in the way of an overall AIDS program?

Fauci: We did not have much of an AIDS program. However, what Dick Krause had done, which showed, I think, great foresight, was to establish the Multicenter AIDS Cohort Study, to look prospectively at 5,000 gay men and to follow them over years. We are still following that cohort in 1993, which is about ten years from the time the project was established by Dick Krause. But we did not have an overall AIDS program. There was AIDS research going on. There was myself and my laboratory but not very many other people involved in the intramural program. There was some modest—small to modest—support for AIDS extramurally.

When I, someone who was very interested in AIDS, became Director of NIAID at the same time that the epidemic was taking off in an exponential fashion, it became clear to me that we would need to have a big push in AIDS research. I did something that was considered very bold at the time. I went to Jim Wyngaarden with a budget that would seem outlandish. I wanted to quadruple the amount that we were doing in AIDS research in one year. I explained to him that this increase was necessary because the AIDS epidemic was going to explode in our faces. We had to be out front, ahead of it. Jim agreed, and I am very grateful to him for that because he allowed the Institute to put a budget forward requesting a substantial increase.

Then it became clear that the administrative structure was not in place to handle the exploding amount of research that was being done on HIV and AIDS. At that point, I established the Division of AIDS within NIAID. I got a lot of resistance about that from the classic and traditional infectious disease people and from immunologists, not only in the institute, but outside. "Why are you having a special division of AIDS? Why not have a special division for every infectious disease?" My response to them, with all due respect to the importance of other infectious diseases, was "Right now in our era there is going to be nothing like AIDS, and so we need a separate division." The Division now has turned into one of the largest divisions, if not the largest, that NIAID has.

Harden: When I talked to [Dr.] Jim [James] Hill early on in our interview process, he told us—perhaps this is the same budget that you are referring to—that NIAID actually was the first institute that pressed strongly for a large increase in AIDS funds. Once a larger budget had been approved by Congress, other institutes jumped on the bandwagon. Do you recall if you felt you were being courageous in view of the political climate at the time?

Fauci: It is obviously difficult to respond to such a question about being courageous.

Harden: I realize that.

Fauci: I think it did take some guts on my part because I went out on a limb. I was, in many respects, like the Lone Ranger out there. I can remember very clearly, sitting in my library, right over here, with Mike [Michael] Goldrich, with Jim Hill, and one or two of the younger staff, and I said, "I am going to surprise you, but I am going to ask for a budget that will make your hair stand on end." They looked at me and said, "Do you think we will be able to get it through?" I said, "I do not think we have any choice. We have to get it through. I think we would be negligent if we did not stand up and be counted and say we must have major growth in our effort on AIDS."

Harden: You were, in effect, taking a risk. The administration's policy had been that if an institute wanted to do more AIDS research, the money should be taken from somewhere else in the budget.

Fauci: That was the great concern of the immunologists and the infectious disease people. They said, "Tony, be careful. If you go out and ask for it, they may tell you to do the research but they might not give you the money for it.

Harden: But, as I recall, under your proposed budget, if they had said that, everything else in NIAID would have folded up.

Fauci: We would have been in serious trouble. It was a big chance. But I knew I was going to win. The reason I knew this was because I knew I would have the support of the Congress, and Jim Wyngaarden was the first step. He allowed me to ask for the increased budget. Ed Brandt was very sympathetic to it. Then after that, the Congress even piled more money on it. But I do not think the Congress would have done that if we had not come in asking for an outlandish amount. This was the time when Congress always put more money in than the administration asked for, unlike today when resources are so constricted. But I knew if I could get the budget past the administration and have the Director of NIH and the Assistant Secretary go along with my request, that the Congress would come in and help out even more. That is exactly what happened.

Harden: This was the 1986 fiscal year budget that you would have been asking for in early 1985. When we graphed budget figures for AIDS research, it was clear that fiscal year 86 was the year in which AIDS budgets began increasing dramatically.

Fauci: That is exactly what happened.

Harden: My recollection is that Rock Hudson died of AIDS about this time. Perhaps that was another factor persuading Congress and the administration to increase the AIDS budget. I do not recall whether the budget hearings were before or after that

event.

Fauci: We got our first boost before Rock Hudson died. Certainly Rock Hudson's illness and death had nothing at all to do with our assessment of what was needed. I believe that Rock Hudson died after the Congress was already aware of the need for increased AIDS research funds.

Harden: Had Congress already agreed to support your budget?

Fauci: Yes.

Harden: We discussed with Dr. John Gallin the expansion of AIDS research in the NIAID Intramural Program. He suggested also that you were instrumental in assisting that expansion, especially in acquiring the Twinbrook Facility. Would you talk about that?

Fauci: We have a superb intramural research program apart from AIDS. We had it prior to AIDS. We have people whom we have to support and allow to grow—young people coming up, and established investigators. You are very well aware of the history of the program. It is a sensational program. It was also clear to me that we needed to expand AIDS research intramurally. One of the great strengths of the intramural program is that we are able to move quickly in certain areas and do high risk types of research. We had people there who were willing to do that.

Now in order to do that, we needed to expand. But I did not want to expand at the expense of the other established non-AIDS investigators; therefore, we acquired the Twinbrook facility to provide space. We got money from the Congress, and we started to get people who had not been previously involved in AIDS research get involved all of a sudden. There was [Dr.] Bernard Moss, [Dr.] Malcolm Martin, and others, and the expansion of my own group. We had a number of people who were peripherally involved in AIDS research, but fundamentally it was Malcolm Martin, Bernie Moss, and myself, and then a few other people. [Dr.] Tom [Thomas] Kindt started his rabbit model and a few other people were doing some part-time, less intense, but nonetheless qualitatively quite good science in AIDS.

In order to accomplish this we had to expand the intramural program, because the science in the non-AIDS area was too good to phase out all of a sudden just so that AIDS research could grow.

Harden: I understand that justifying and acquiring the Twinbrook Facility was quite a coup?

Fauci: Yes, it was.

Harden: Do you want to talk more about that?

Fauci: It involved a lot of very aggressive negotiation, aggressive in a good sense. We had to be very persuasive that this was what we needed. Thanks, I think, to the insight of Jim Wyngaarden we were allowed to have that space. I had a very good relationship with Jim. Although many people look upon him as a very staid, conservative person, he is brilliant, but he is also very flexible in many ways. I remember sitting down with him. He is the kind of man who is not very animated in discussion. You have to know him; he listens to what you say and then he says yes or no. When we went in there, Mike [Michael] Goldrich handled it from his side with the Executive Office and I handled it one-on-one with Jim Wyngaarden. Jim said, "Okay, go with it. It is yours."

Harden: One other budget question. We graphed the extramural budget data, which I am sure you are familiar with, and in the projected figures for 1994 we see AIDS research outstripping everything else. As NIAID Director, do you think that is wise?

Fauci: Actually, that is not the way I wanted it. But I think that money on AIDS research will be very well spent. What happened is that because the resources are very restricted, AIDS was targeted in the 1994 budget by the new Clinton Administration to be an investment area. The budget was built from the top down instead of from the bottom up. What I wanted to do was to have the non-AIDS area grow proportionately while still increasing AIDS research. I still feel that way. As it turned out, AIDS research got a major increase, 18 percent from 1993 to 1994 for NIAID; the problem was that the non-AIDS areas, because there was not enough money around, plateaued. Support even dropped by as much as 7.5 percent in some areas. That is something I was very concerned about and objected to, to Dr. [Bernadine] Healy.

What happened was that the streamlining or cuts that all the institutes underwent were done on a formula with which I disagreed. The formula was that the amount of cut that the Administration wanted to effect across the institutes would be proportional to how big an institute was. NIAID's cut was based on $1.065 billion dollars, which was the 1994 budget, but the cut would be taken only out of the non-AIDS research. The amount of cut taken would be based on the totality of the institute's budget, but since they wanted to protect AIDS, all of the cut would come out of non-AIDS research.

As much as I am, have been, and will always continue to be an AIDS advocate, I thought that this was not an appropriate way to make the cuts. In fact, the

Congress agreed with us on that. However, they were not able to correct it as much as I would had liked to have seen it corrected. So the reason that the budget graphs criss-crossed is that non-AIDS research took the hit while support for AIDS research went up. The gospel that I keep preaching to the American public, to the Congress, and to the Administration when they will listen is that we must make a major commitment to all of biomedical research. What now is AIDS was non-AIDS awhile ago. We would not have had the basis for immunology, for molecular biology, for microbiology, for retrovirology, if we had not done basic science in those areas. My concern is that we need to correct this problem. We need to have a little correction in midstream here and make sure that non-AIDS research grows proportionately to the opportunities.

Clearly, the scientific opportunities in AIDS research are there and the money is well spent. In fact, scientific opportunities are greater than the resources we have in AIDS. But opportunities are also greater than the resources we have in non-AIDS research.

Harden: I was talking with one of your staff members in the Division of AIDS at one point, and he remarked to me, "AIDS has changed the way we do business at NIH." Would you comment on this statement with particular reference to the involvement of activist groups?

Fauci: I do not think there is any question about it. What has happened is that the devastating public health catastrophe of AIDS disproportionately—initially selectively—affected a certain population, gay men. Gay men had just emerged within the last couple of decades in their empowerment and identities, and they are articulate, for the most part very well organized, and politically savvy. They became very interested in what we did with the money that we got both for clinical trials and for basic research. I think a major part of my work in this epidemic has been opening the doors and breaking down the barriers between the activist groups and the scientific community. I took a big chance in doing that because I received much criticism from the scientific community. However, it allows us to see the impact of the disease at the grassroots level.

You never want to compromise the integrity of the science that you do, but, quite frankly, the way we approached clinical trials had a degree of rigidity in it. Some flexibility was needed and has now been installed. You could have a pristine clinical trial that was so user-unfriendly that no one would participate in it. Patients with AIDS would get drugs in the guerilla clinics, as it were, or get them in a manner that was not standard. They would also be on all different types of drugs. By changing the way that we do business at NIH, the constituency which has the disease for which you are scientifically responsible has some positive, productive, contributory input to some of the elements of how you do the

science—not all, but some.

When the gay activists were demonstrating, predominantly against the FDA but also against the NIH, and being very strident in their criticism, I challenged them. I said, "Okay, come on in, sit down, and let's talk about it. What is it that you want?" That was when we developed relationships with them that are now very productive. We have activists who are important members of our advisory councils. We consult back and forth with them all the time. AIDS changed the way we do business at NIH in that, when appropriate, the constituencies play a major role in some of the policy and decision-making processes. You cannot just cave in and let people tell you how to do science the wrong way, but there is a lot you can learn from understanding how the disease is affecting a particular population, somewhat removed from the bench, and removed from the "ivory towers" that we have here.

Harden: Let us follow up with the case study of AZT [3'-azido-2', 3'-dideoxythymidine]. The trial of the drug, as I understand it, was halted perhaps too soon because of activist demands that, "It looks good, let's go with it." Is this a morality tale?

Fauci: No, actually it is difficult to say what was the right or wrong thing to do. It was a situation where there was only one drug available—it was not like trying out one amongst many antibiotics—and the activist community and the constituents were suffering. They demanded that they have access to anything that could give them even a little hope. Pressure was put on the FDA. They responded appropriately for rapid expedited approval of AZT, making drugs available that normally would not have been available for years and years.

Harden: Do you think this delayed understanding of AZT?

Fauci: I do not think it delayed understanding of AZT. I will tell you the reason why. The studies of AZT went on after the approval. First of all AZT was approved, and we should get this historically correct as long as this is a historical document. AZT was approved first for HIV infection with AIDS and ARC [AIDS-related complex]. Everybody agrees—all of the studies—that there is benefit from AZT, which is unequivocal, if you are sick with HIV disease. The debate is over whether there is any lasting benefit if you start treatment very early, namely at 500 T4 cells or fewer, as opposed to waiting until somebody gets symptoms.

We knew from our trial that if the drug was started early and the results compared to those from a placebo, the people who were getting AZT did better, at least for the first year. It was at that point that the pressure to approve AZT for people with early HIV disease built up on the grounds, that, "It is unethical to continue the study. There is a benefit. Approve the drug—which was already approved for

AIDS—change the package insert and say the drug is now usable for people who have fewer than 500 CD4+ cells, even if they do not have symptoms."

What subsequent studies have shown is that, if these people were followed for three years, the initial benefit, which looked as though it was going to be significant, disappeared after that time and there was no real long-term benefit. After the recent June 1993 state-of-the-art conference looking at the data from the Concorde Study, which was the U.K./French study, and at a number of other studies, the recommendation now is that AZT should still be given if someone is symptomatic, no matter what the T4 count is. However, if a patient is without symptoms and has between 200 and 500 CD4-positive T cells per cubic millimeter [(mm^3)], it is not an absolute recommendation to treat that person with AZT. The physician and the patients have the option of deciding between themselves whether they want to have the "possible" benefit of AZT. There is no long-term benefit on the average, but there are some patients who will benefit. The "possible" benefit is a better quality of life for a year or so weighed against the cost and the potential toxicity of the drug. This is a change from the previous recommendation to treat everyone with CD4-positive T-cell counts less than 500 per cubic millimeter [(mm^3)], even those who are without symptoms.

The approval of the early use of AZT was, in fact, particularly influenced by the great pressures exerted in the country by constituency groups to make drugs available very rapidly.

The British were able to carry out a study that we would never have been able to do in the United States. There are different styles in different countries. There is virtually no chance in the U.S.A. that a study that shows some early benefit could have gone on without giving drug to the placebo group, and that is the reason why the study was stopped. We are pleased that the British were able to keep their study going. We have now modified the recommendation somewhat, but not dramatically. The bottom line in all of this—we might as well get it out in the open—is that we need better drugs than AZT and ddI and ddC. Certainly there is a benefit to these drugs that is discernible, and significant, after someone gets sick. But when someone is well, we do not have a drug that will prolong the disease-free state and the life of an individual significantly enough that we could make the statement that everybody should be on the drug as soon as they are infected.

The pathogenesis work that we did in the lymph node studies showed that one can detect virus burden and replication very early in the asymptomatic stage of HIV disease. Thus, we have the scientific basis when safe and truly effective drugs are available to treat a patient as soon as possible, from the moment it is known that he or she is HIV-infected. That rationale is sound. What we do not have, in 1993,

are drugs good enough to justify treating somebody that early. What we need to do is to develop better drugs, and to work with the combinations of drugs that we already have, to determine whether if, in fact, someone is treated early, their disease-free state is prolonged significantly.

Harden: I have two or three questions about the development of these drugs and treatments. First: The idea of using supercomputers and other technologies to do designer drugs has not yet resulted in a useful drug. Do you think it is possible? Second: Is there great promise from cytokine regulation as possible therapeutic interventions?
Third: Would you describe what NIAID is doing about these and any other approaches?

Fauci: With reference to the first question, targeted antiviral therapy is certainly the way of the future, and even the way of the present because it is being done already. You could computerize the design of a drug by finding out what the structure of the molecule that you are trying to block is, and then getting a computer analysis of what the right conformation of a molecule to block that molecule would be. That is very much akin to what we are doing in taking highly purified components of the virus, getting the crystallographic structure, and determining what small peptide would block the conformation or the function of something like protease or TAT. Those agents are already in clinical trials. We do not have any information right now, in June of 1993, about whether or not these agents will turn out to be effective, but they hold promise because they are very specific for the virus. That responds to your first question.

The second question relates to our work back in the mid-1980s on cytokines. It is clear that cytokines play a major role in the regulation of HIV expression. In the test tube you can block cytokines and block virus expression. Therefore, the rationale exists to test drugs *in vivo* that have an impact on cytokine production and cytokine induction of HIV expression. There are ongoing clinical trials with substances like pentoxiphylline, thalidomide, IL-1 receptor antagonists, and a number of other drugs, that can block cytokine expression.

Harden: Is NIAID supporting both of these kinds of research?

Fauci: Both intramurally and extramurally, the NIAID is supporting them.

Harden: Do you have a hunch as to what might be most successful?

Fauci: I think that the modification of cytokine expression will be an important part of the ultimate armamentarium of HIV therapy. I think that therapy for HIV disease will ultimately consist of a combination of blocking the virus, interfering with

inappropriate immune activation, blocking cytokine induction of HIV expression, and ultimately reconstituting the immune response either by tissue transplants or by cytokines which actually can build up the immune response.

Harden: I have one more question. As you have been in the public eye so much you have had to conduct your affairs under more intense scrutiny perhaps than any other scientist/administrator ever has. How do you handle this? How do you decompress? I read things on occasion and I note in the margin, "This is Fauci-bashing." How do you personally handle the potshots?

Fauci: You have to keep your eye on the ball, and never forget what it is you are trying to do, what the goal is and what is your scientific pathway to that goal. You also have to adopt an attitude. I borrow the line from *The Godfather*—it is in both the book and the movie—"It's nothing personal. It's strictly business." You have to understand that even though frustrated people who are in pain attack you, it is because you are a visible person. If I reach out to them, they see me, they hear me, I am there. I am not off in a closet somewhere.

When someone is in pain and suffering, he or she needs—and it is almost an instinctual need—to blame or to attack someone for the lack of speed or success of the scientific enterprise. The person who is most visible out there becomes the target. I learned very early on in this epidemic that as I became more of a spokesman, as I became someone who was leading the charge, as it were, that I was going to be the target. Once you accept that that will happen, and if you do not take it personally, then you can go on with your work and you are able to function.

Harden: I recall that when you talked to the NIH Alumni Association you mentioned the function that your sister serves in keeping you in touch with the public's views on AIDS. Can you comment more on that?

Fauci: I have a sister, Denise, who is three years older than I. She is a well-educated woman, a college graduate, a former schoolteacher, who left her profession to raise her family. She represents what I would consider the middle class, the upper-middle class, intelligent person in America. There are many misperceptions about HIV, such as the ones seen in the newspapers that are media-driven misperceptions, the ones that are scientist-driven misperceptions, things that inevitably will be misinterpreted. I get a good handle on how the general public is interpreting information by my sister's response to me and to anything else that is in the newspapers on HIV.

For example, I knew that people were wondering seriously about whether HIV was the cause of AIDS, when [Peter] Duesberg was campaigning intensively

trying to convince people that HIV was not the cause of AIDS, because my sister would call me up and say, "Anthony"—she is one of the few people besides my father who calls me Anthony now—are you sure that HIV causes AIDS?" When she calls and asks me that, I know that the general public is wondering about that.

When there was talk about incidents like some of the scares we have had about children getting AIDS in school, and whether they can get it from their classmates, I would say, "No. All the data show that a child would not get it from his or her classmates." My sister would call and say, "I am worried about my grandson, or my granddaughter, who is in kindergarten. Can they get AIDS from someone who has a cut?" If she is worried about this, then so is the rest of country. Denise has served as a nice barometer for me of what people are sometimes afraid to say, but what they really worry about.

Harden: One more question. What about your own family? When someone makes a threat against you or your family, how do you handle that?

Fauci: The days of the overt threats are over. One thing I can say about ACT UP is that ACT UP has never personally, physically threatened me or my family. They have insulted me, and one activist in particular, Larry Kramer, who has, in fact, become a very good friend, wrote an article that insulted my wife. He had never even met her. He just said awful things about her out of anger and frustration. He felt so guilty about that that he is still very contrite about it. Incidentally, my wife and Larry Kramer have since become friends with mutual respect.

I do not really worry, but if I am concerned about anything, it is not about the avowed activists, because they do it to get your attention. The thing that is of some subliminal concern is the real wacko who wants to go after a public figure, because I am a public figure. As a scientist, generally you are not a public figure. There are advantages and exciting things to being a public figure, but there are also burdens. I am a very recognizable face on television and so on. If I have any concern, it is not about someone who is an activist seriously trying to gain my attention about something because activists know they have an open door with me. It is about the person who goes crazy and decides he or she wants to take somebody out or harm someone's family. Obviously, the chances of that happening are very small, but it is still within the realm of possibility.

Harden: Do you have anything else to add before we move to more general questions?

Fauci: No. That is fine.

Harden: I would like to discuss your third role at NIH, that of being the Associate Director for AIDS. It is an even larger public role than the NIAID directorship. You

initially accepted the positions of NIH coordinator on AIDS and chaired the AIDS Executive Committee. At that point you were faced with trying to get cooperation among all the institutes. What was your initial strategy?

Fauci: My initial strategy was to get everyone to appreciate—and they did very readily—that we all had a common goal and that was to conquer this epidemic. It was also to use whatever expertise we had—individual institutes had different levels of, and qualitatively different, expertise—and to get people not necessarily to work together, which was important, but to make sure we covered all the bases. We had to check that there was not a gross overlap of people doing exactly the same thing in exactly the same way. There is complementation, and duplication is sometimes very productive, but we also wanted to make sure that there were no big gaps. That was the major charge of the Coordinator of AIDS Research at the NIH, which is what I do at that level.

Harden: Were there any particular obstacles such as people who did not want to cooperate?

Fauci: No. The group was very collegial. Obviously, when there are resources available, people will try to grab as many as they can. When you make recommendations for the allocations of budget requests, it sometimes becomes difficult. The Congress does whatever it wants. Usually they do it within the realm of the recommendations. But the initial budget that goes forward has to be built from the institutes up. Obviously, there are people, who have good and honorable intentions, jockeying to get more, trying to do what they can to get the most resources. In that respect sometimes you have to disappoint people because you have to make the initial request meet a certain level of funding that you got from the NIH Director, or the Assistant Secretary, or the Secretary [of Health and Human Services], and fit in the relative priorities of what that request should be.

Harden: Would you comment on your experiences in meeting with Vice President, and later President, George Bush, and with President Ronald Reagan when they came to NIH. What did they, as presidents, want to know about AIDS, and what did you tell them?

Fauci: Vice President, and then President, Bush clearly got much more involved in AIDS than did President Reagan. Though President Reagan was sympathetic, AIDS certainly was not in the forefront of his attention or interest. He did, however, have a department to handle it. Bush and Reagan wanted to know the extent of the disease, the projections for the epidemic, where we were going with the science, and whether we had as much funding as we needed to perform the science adequately. They were very concerned about getting the right momentum going scientifically.

Bush took much more of a personal interest, and that is how I developed a personal friendship with him. When he came to the NIH, I gave him a briefing of a couple of hours, showed him the wards and some patients, and showed him our laboratory. I thought that was going to be the end of it. But, subsequently, he called me up a couple of times and asked me some thoughtful questions about AIDS. I was very flattered that the Vice President of the United States would do that. He did it not infrequently. As Vice President, he would call me down to a meeting at the White House, ask me to brief him, or if he had someone who was an important person, a foreign dignitary who wanted to know something about AIDS, the Vice President would just get on the phone and ask me to come down there.

I started to get to know him very well. He was kind and generous to me socially, inviting me to the Vice President's mansion for private dinners, Christmas receptions, and occasions like that. As you can see, I was very fortunate.

When he became president, we continued our relationship, and he was very good at listening to what I had to say. He tried, I believe, as best as he could within the constraints of his administration, to do some of the things that he has been criticized for not doing. It is very easy to criticize the Bush Administration, but the man really cared about the country and about HIV-infected individuals. He did much more than he was given credit for. The problem was that some of the measures I would recommend were very difficult for him ultimately to enact or execute because he knew the resistance that he was going to get from the more conservative elements in his administration and in the Congress. It was not a secret, that he was, and is, a moderate person. But I think he was realistic enough to know that he would not be able to get certain programs through.

People who criticize Bush say that he should have exerted more explicit leadership in trying to get programs through. But it is interesting, and paradoxical, that even now President Clinton, who has very noble intentions about getting certain things done vis-a-vis policies for HIV, is running into resistance from some of the same people who would have given Bush resistance. It is surprising that even some of his own people are being resistant to these policies. What that tells us is that there are many other forces besides the President that ultimately determine what is going to get done in this country.

I think Bush's record of supporting biomedical research from the standpoint of resources is very good. So far Clinton has done a good job of highlighting AIDS and the need for more resources for AIDS. I think that both of them have been very good about it, and each of them has gotten unjustified bad press. Bush has gotten unjustified bad press because his administration, in general, was a much more conservative administration than that of Clinton, which is now just in its

first six months. President Clinton, who is trying very hard to do the right thing by HIV, has met unexpected resistance from certain elements which have not allowed him to execute what he otherwise would have. Now he is being criticized for not getting it done. It is very easy to criticize the person at the top. I guess the historic bottom line lesson of this for me is that AIDS is a very complex issue, and it is very easy to criticize the people at the top. That is the reason why I think Bush got a lot of unjustified criticism and Clinton has already gotten unjustified criticism.

Harden: We all remember that George Bush, when asked to name an American hero, named Dr. Anthony Fauci and thus brought honor to you, to the NIH, and, by extension, to all biomedical scientists and physicians. He also invited you to the White House and put some pressure, I believe, on you to accept the NIH directorship. Do you want to talk about that?

Fauci: I was very flattered and surprised that he listed me as one of his heroes. I knew him pretty well at that point. I was very gratified and pleased. I did not hear the Presidential debate in which he called me his hero. I had been on a trip, and as I walked into the elevator at the NIH when I came back, people said, "You must feel terrific." I said, "What happened? What are you talking about?" I finally got to my office and they told me about it.

With regard to the NIH directorship, I am very grateful to President Bush for understanding why I did not want to be NIH Director. I wrote to him early on when my name was being sent down to the President from the Secretary as the top choice for the NIH Director's job. I wrote to President Bush when he went up to Kennebunkport [Maine], and I sent him a message through some people I knew at the White House that I was going to turn the offer down. I wanted him to understand that it had nothing to do with my admiration for, and friendship with, him. It is not an easy thing to say no to a President who offers you such a prestigious job. But I explained to him the reasons why I wanted to turn it down, which were my science and my commitment to AIDS and to the NIAID.

Bush wrote me a beautiful letter back saying that his respect and admiration for me was even increased by understanding how devoted I was to the cause, and that he was looking forward to continuing to work with me. I was afraid that he would say, "Get out of here. You are insulting me by not saying yes." That was the first time. The second time was even more anxiety provoking. [Dr.] Jim [James] Mason, the Assistant Secretary [for HHS], asked me if I wanted to take the job. This was after I had written to the President and said no the first time. Several months went by and we still did not have a Director at NIH following the departure of Jim Wyngaarden. Jim Mason asked me if I wanted the job, and I said I did not for the same reasons as before. People thought that it was because of the

fetal tissue issue. It had nothing to do with fetal tissue. No one ever made any conditions to me about fetal tissue. That never even came up in the conversation. It was purely my not wanting to be in any way dissociated from my laboratory, my science, and the AIDS research at the NIAID. Jim Mason said, "You will have to say no to somebody higher than me." I said, "Jim, don't do this to me." He said, "You will have to talk to Lou Sullivan." Secretary Louis Sullivan called and said "Tony, what do you think? Would you like to do it?" I said, "Lou, I do not want to do it. Please do not put me in a position to create any embarrassment." He said, "All right. Fine."

About a week, two weeks, went by and Lou got on the phone and said, "We are going to the White House." I replied, "Oh my goodness, what are you doing to me?" He said, "I am sorry, Tony. You are going to have to say no to the President. We have spoken to [John] Sununu, and we have spoken to the domestic policy people. They do not think you are going to say no to the President."

I remember that I went into the White House and I was waiting outside the Oval Office. John Sununu came over to me and said, "You are not going to say no to the President, are you?" I said, "Governor, I am very sorry, but I am going have to do it, because nothing has changed. I think that the President will understand that." He said, "But nobody says no to the President in the Oval Office." I said, "Well, I do not think it is a macho thing to do. I am just very uncomfortable about being here. I am only here because Lou Sullivan asked me to be here."

I figured this was the end. This would really get the President upset. I walked into the Oval Office and sat down next to the President, who said, "Well, Tony, do you want to revisit this?" I replied, "Mr. President, everything I said before goes in spades. I have a great deal of admiration for you. I am very proud to serve in your administration. But what I do best is what I am doing now. I think I would contribute more to you and to the country if, in fact, I were able to continue my job."

I told the President that the same reasons governed my thinking as when I had spoken and written to him the previous time. I wanted to stay very closely involved with the science. He paused for a moment, and he looked at me. Then he said, "Is there anything that we can do to create a situation where you would want to do the job? How about if you do it for two years then you go back to being the Director of NIAID? Or we will give you enough administrative help that you could continue to run your laboratory and you could continue to do the AIDS research? You can do anything you want, AIDS, laboratory, OAR [Office of AIDS Research], everything you want to do." I said, "Mr. President, this is very painful for me, but, with all due respect, I will serve you much better if I stay

where I am."

I thought, "This is the end. I have tried the man's patience." But Bush is such a wonderful human being that he looked up at me and said, "Tony, once again I keep having more and more admiration for you. Good luck to you. If there is anything I can do to help you, just give me a call." And he actually gave to me his secretary's private number. "Just call me. I want to talk to you right up front if you have anything that I can help you with."

I figured that he was just saying that and that now he would be angry with me. As we walked out of the Oval Office, Governor Sununu said to me. "I cannot believe you did that." Sununu was not upset with me. He was actually very friendly. I had good relations with him too.

That was it. After a while, I guess it was a few weeks to a month, I thought that this would be it because Bush would go off and find someone else who would be his favorite medical person, as it were. But, sure enough, he gave me a call about a month later and asked me a question that was of some importance. Then, two months later, he invited me to the White House for a small dinner so we continued our friendship. I have always felt very fortunate that I was able to act the way I believed I should act, namely, turn the President down, without having him feel that I was turning him down personally. As it turned out, it served to make our relationship even stronger right up until the end of his presidency. I hope it will continue even now if I get the opportunity to deal with him.

Harden: Dr. Bernadine Healy became the NIH Director instead. Would you comment on her tenure as Director, especially with regard to AIDS research. What kind of relationship have you as head of the NIH AIDS effort had with her as the NIH Director?

Fauci: She has been very supportive of AIDS research. There is no question about that, if you look at the record. Unfortunately, she came in at a time when the NIH budget was very constricted in its growth. If you look at the two years she was Director the resources were very constricted. That was not her fault; that was just the way it was. Moreover, the exponential growth of AIDS was beginning to plateau. Although AIDS did not do very well during the couple of years that Dr. Healy was Director, it was not because she did not try to get more for AIDS. She was very much in favor of full support for AIDS research. It was just that she happened to be Director at a time when the resources were much more constrained than they had been previously.

Harden: Some people seem to think that we will make greater scientific progress if we have a so-called AIDS research czar. We have had two things happen recently,

one is the new NIH Reauthorization Bill, which if I read it correctly, says that new AIDS monies will have to go through the OAR [Office of AIDS Research]. Please comment first on the bill in terms of whether this is just another layer of bureaucracy, and then I want to come back and talk about the AIDS czar, Ms. [Kristine] Gebbie, who has been appointed.

Fauci: The institute directors, including myself, were from the very beginning against the legislation to have the money go first to the OAR and then be distributed. We thought it might be a layer of bureaucracy that would interfere with getting the money to the people who execute the science. However, all things considered, the Administration and the Secretary wanted to go with it. We will do everything we can to make it work and not, in any manner or form, be obstructionist about it. There is a concern that we expressed in an official letter to Dr. Healy, which was then sent to the HHS Secretary, but that is water under the bridge. The law has passed and we will live with the law and make the best of it.

Harden: Let me clarify. Is this law only for extramural funds, or is it for intramural ones as well?

Fauci: All the money goes to the OAR, and then it gets redistributed to the institutes. The institutes ultimately get the money, but it stops in the Office first.

Harden: But grant applications will not come to the OAR; they will still come to the institutes?

Fauci: Yes. They will still come to the institutes. The OAR is the place where the money goes first and then it gets distributed, with the rationale that that Office will have the flexibility, if things change rapidly, of redistributing the money. But things do not happen that way in science. You could accomplish that with a small discretionary fund.

Harden: With reference to Ms. Gebbie, who has been appointed as the White House AIDS Policy Coordinator, she will not, as I understand it, have a great deal of line power, so the term AIDS "czar" may not be appropriate.

Fauci: She is not an AIDS czar. President Clinton has not called her that; she is AIDS Policy Coordinator. "AIDS czar" is an unfortunate term.

Harden: What would her relationship be to biomedical research? She is not a scientist.

Fauci: No. But the Policy Coordinator will have the responsibility of coordinating policy across agency lines. The AIDS epidemic has an impact on virtually every government agency. The purpose of an AIDS Policy Coordinator is to see that the

interactions among the agencies are unified and conform to a broad national plan for AIDS. That is one of her major responsibilities, to develop a broad national plan.

Since the Department of Health and Human Services, and the NIH as a component of the Department of Health and Human Services, is a major player in the AIDS epidemic, we will obviously be a major part of the things that need to be coordinated with the other agencies. But there will be no directives telling an agency what to do. It will go through the individual secretaries. There is no anticipation that Kristine Gebbie will be telling the NIH Director, or myself, or anyone, what to do scientifically. Policies will be broadly coordinated across agencies, but it will be done through the secretary of that agency.

Harden: Scientists are always interested in serendipity. I have spotted a couple of results from research on AIDS that had applications in other places. Are there any that you would like to highlight?

Fauci: Certainly. What we know about the immune system has grown exponentially in the last ten years on the basis of having an unfortunate, but nonetheless extraordinary model of the destruction of the immune system. We have learned what components of the immune system are needed for the system to function properly, how they interact or rely on each other, particularly the focal nature of the CD4-positive T cell. It has markedly enhanced our understanding of the immune system.

Secondly, it has given us insights into the whole area of drug development and vaccinology, because right now targeted drug development has gotten a great boost with HIV and AIDS. Diagnostics, the use of the polymerase chain reaction as a diagnostic tool for other infectious diseases, and the understanding of the role of activators and enhancers of gene function have had major spinoffs from looking at, and dissecting with such great scrutiny, the regulation of the HIV genes. There are many areas that, even in such a short period of time, have benefited from the research on AIDS. I would expect that twenty or thirty years from now we will see spinoffs from the research that we could not possibly imagine, in the same way that spinoffs from the war on cancer were unpredictable twenty years ago. For instance, the entire field of retrovirology emanated out of the war on cancer. In addition, much of the molecular biology that we know today has emanated out of the war on cancer as well as out of the study of microorganisms. I think there will be an extraordinary benefit for all of science.

Harden: Do you think we will have a vaccine or a therapy first for AIDS?

Fauci: We already have a therapy for AIDS. It is not a very good therapy, but we have

one. Are we going to find a cure? I do not think that we will have a cure in the classic sense. I think we will have a combination of drugs that will suppress the virus so efficiently that an infected person could have a much greater prolongation of a disease-free state than we have with the currently available therapies. The nature of the virus may not allow us completely to eliminate all of the virus from the body. You would have to suppress chronically virus replication. The goal is to have a combination of drugs which, when administered early in the course of infection, would be able safely to extend the disease-free state to ten, twenty, thirty, or more years.

Vaccines probably will be more of a problem because this is a virus that is transmitted by cells, as well as cell-free virus. You would have to protect against both. Whether or not that is feasible is unclear; I am hopeful that it will be. I am operating with the guarded optimism that we will have a vaccine by the end of this decade, but I cannot guarantee that.

Harden: The National Research Council recently released a report predicting that AIDS will sink into the inner cities, and that the middle class will not have an epidemic in the United States. In that case, because people in the inner city are often not active politically, the prediction is that AIDS will become a political non-issue and research will stop. What is your response to this?

Fauci: I think that the way that was "spun," as it were, to the public was unfortunate. Although I do not believe that the virus is going to be spread homogeneously throughout the population in the U.S.A., and it will be more focused in certain groups, cities, and areas, I do not believe that it will be as marginalized as the National Research Council report indicated. Take a look at the reports that came out two months ago that, in sixty-four cities in the United States, the leading cause of death among people between the ages of twenty-five and forty-four is AIDS. That goes beyond marginalization, I think. AIDS is not going be spread homogeneously, but it will not be a forgotten marginalized disease. I do not think there is any question about that. The data already tell us that.

If I were, out of nowhere, to tell you that there is a single communicable disease that is the leading cause of death in sixty-four major cities in this country between the ages of twenty-five and forty-four, what would you consider that? I would consider it a public health catastrophe.

Harden: What about on the larger, worldwide scale? What is our obligation to Thailand, let us say?

Fauci: What is our obligation? You are talking about a social-politico-ethical issue on which I am certainly not qualified to give a definitive statement. But our

obligation exists only insofar as we have an obligation to our brothers and sisters throughout the world. You can make the same case for malaria, from which two to three million people a year die; for tuberculosis, from which three million people die; and for parasitic diseases, from which millions of people die. We have the same obligation, I guess, to worry about them as we do about people who are HIV-infected. I think we do have an obligation insofar as our resources, or neighborliness, enable us to execute those obligations. But I do not see how we can possibly be responsible for the entire world, given the fact that we are in somewhat of an economic crisis here in the United States.

Harden: Given our economic limitations, do you think we are doing what we ought to be doing?

Fauci: Absolutely. We have very good collaborations and cooperation with international scientists, public health ministers, and public health officials throughout the world.

Harden: Thank you very much, Dr. Fauci, for talking with us.

###