This is an interview with Dr. John I. Gallin of the National Institute of Allergy and Infectious Diseases on 23 June 1993 in Dr. Gallin's office in the NIH Clinical Center. The interviewers are Dr. Victoria A. Harden, Director, NIH Historical Office, and Mr. Dennis Rodrigues, Program Analyst, NIH Historical Office. Dr. Gallin was provided with a list of questions in advance of the interview. MaryAnn Guerra, Chief, Administrative Management Branch, for the NIAID intramural program, participated in a portion of the interview.

Harden: Let us begin by asking you to give us some information about your background. I ask physicians what influenced them to go into medicine and, in your case, into medical research as well. Please trace your life briefly up to coming to your present position.

Gallin: I was born in New York City on 25 March 1943. My father was an attorney, my mother was a housewife. I was the second of two children. My older brother subsequently entered dentistry. Throughout my youth, I had a strong interest in science, which was directed towards clinical science. When I was a tenth grader, my mother became acutely ill with severe hemoptysis. I woke up and saw the blood on the rug. She was wheeled to the ambulance. I was very impressed by this and, following that event, wanted to become a doctor. I went to Amherst College, where I graduated *cum laude*. In college, I became more involved in research. I was introduced to the laboratory in the summer of 1964, after my junior year, when I worked with Dr. Paul J. Van De Mark at Cornell University, Ithaca, New York. At college I majored in biology and did a thesis with Dr. Edward R. Leadbetter. At Amherst also I fell in love with Elaine Klimerman [Gallin], who subsequently received a Ph.D. and became my closest colleague, best friend, and wife now for almost 26 years. I published a number of papers as a college student and actually applied for admission to several Ph.D. programs.

One day in my senior year at Amherst, after I had been accepted into several graduate programs, my father came and had lunch with me. He said, "Why don't you go to medical school? You can then do whatever you want, but you will have more influence and more flexibility in what you pursue." I listened to him and went to medical school (Cornell University Medical School). I was an intern and a resident at Bellevue [Hospital, New York]. I came to the NIH in my first appointment in 1971 as a clinical associate. After three years in the Laboratory of Clinical Investigation, of which Dr. Sheldon M. Wolff was the laboratory chief, I went back to Bellevue Hospital as their senior chief resident in medicine. I returned to NIH as a senior investigator.

Harden: When you were at Cornell, did you meet Dr. [Anthony] Fauci?

Gallin: No.

Harden: You met him at the NIH?

Gallin: I met him here. I will tell you about that shortly.

Harden: Fine.

Gallin: At Cornell, I continued my research interests. In the summers, I worked in several laboratories. One of these, when I was at an earlier stage of my student life, was run by Dr. William M. O'Leary, who was a microbiologist. Later, in my last year, I worked in the Division of Infectious Diseases in the Department of Medicine at Cornell, which was then headed by Dr. Edward Hook. It was an outstanding division. Within it were Dr. Donald Kaye, who is now Chief of Medicine at the Medical College of Pennsylvania, and Ed Hook, who subsequently became Chief of Medicine at the University of Virginia at Charlottesville. The fellows under them at that time were Drs. Gerald L. Mandell, current President of the Infectious Diseases Society of America, Merle A. Sande, immediate Past President of the Infectious Diseases Society of America, and Glen Cobbs, all of whom were my mentors as a student. They had a big impact on my pursuing a career in infectious diseases.

Other people also had a big influence that senior year. They included Dr. Walsh McDermott at Cornell, Dr. James Hirsch of Rockefeller University, and also [Dr.] René Dubos. Dr. Hook organized Friday luncheons with these people and these meetings had an enormous influence on me in terms of my recognizing the subspeciality of infectious diseases as one that I wanted to pursue. My years at medical school were very happy. I got married, we had our first child, and I wrote two papers that were published in *The New England Journal of Medicine*.

When I was at Bellevue, I was very impressed by the flexibility and freedom that we had as interns and residents. I was greatly influenced there by several other people. [Dr.] Saul J. Farber, who was Chairman of Medicine and is still Chairman of Medicine there, became a mentor who instilled the importance of maintaining a clinical presence throughout my career; [Dr.] H. Sherwood Lawrence, who discovered transfer factor, which in its time was a very exciting discovery in infectious diseases, and who served as an example of doing clinical research and busy medical service; and [Dr.] Gerald Weissmann, who was a leader of neutrophil biology; all contributed to my development. Dr. Weissmann had a major influence on my interest in phagocytic cells, a research area which I have pursued subsequently. It was at NYU that I met a fellow medical resident, the late [Dr.] Ira M. Goldstein, with whom I subsequently edited the first two editions of *Inflammation: Basic Principles and Clinical Correlates*.

When I came to NIH, I went to work with [Dr.] Harry R. Kimball in the Laboratory of Clinical Investigation. He was interested in phagocytic cells, but, in

the middle of my first year, after I had been assigned to him, he decided to leave NIH and go into private practice in Yakima, Washington. He subsequently has had an illustrious career and is now President of the American Board of Internal Medicine. His leaving NIH provided a great opportunity for me, because everybody who was interested in phagocytic cells seems to have left that year and I was all by myself. Dr. Wolff asked me, "What do you want to do?" I said, "I will continue doing what I am doing." He gave me a little space and a few resources, and he said, "Have fun." That is what I did, and it worked out well.

At the beginning of my second year, which would have been around 1 July 1972, when Harry Kimball left, there was a vacant laboratory which had two modules, 500 square feet, and one office. On that day, 1 July, Tony [Dr. Anthony S.] Fauci came back to NIH, having finished his chief residency at the New York Hospital. He was across the hall from where I worked. Dr. Fauci's laboratory was a total mess, because people had raided it while he was gone and stolen all of the equipment. It looked like a pigsty. He was very upset because he thought he was coming into this well-equipped new facility that was going to be really clean, and it was a disaster. I remember walking over there, introducing myself to him, and saying "Would you like some help?" We cleaned up his laboratory, and that was the beginning of a long-lasting friendship. I was always impressed because no matter when I came in to work, Tony Fauci was in that tiny little office or in his laboratory doing his work. We often had long conversations on Saturdays and Sundays about many things.

Harden: You and Dr. Fauci are close personal friends, as well as colleagues, I believe.

Gallin: Right. We talk about our research, we play tennis, and we do some fishing together. It is very nice.

Harden: Could you elaborate a little about your research? Did you remain in the laboratory?

Gallin: I remained in the laboratory. As a clinical associate, I was very lucky because I was adopted by all the senior staff, and I felt totally free to interact with all of them. What I did was to get into a lot of projects utilizing what I thought were the talents of the various senior people and learning from them. Also, because I had some backgound in the laboratory before I came to NIH, I was able to conceive and design my own projects. I was very fortunate in getting into a position of independence very early in my career. My wife and I also worked and published together. I had the support of my senior mentors.

Harden: You were doing research on infectious diseases, but you must also have been involved in that wave of new developments in immunology that happened in the 1970s.

Gallin: Yes, I was different though because nobody ever really understood what I was doing. I can still remember a colleague saying to me, "Why are you doing that work on neutrophils? You are never going to do anything that is clinically relevant." I also remember my interview before coming to NIH as a clinical associate. I interviewed at two laboratories: [Dr.] Shelly Wolff's laboratory and [Dr.] Donald Fredrickson's laboratory. Dr. Fredrickson was then chief of the Laboratory of Molecular Diseases of the Heart Institute [National Heart, Lung, and Blood Institute] with Dr. [Robert I.] Levy. The reason I interviewed with Fredrickson and Levy was because I had published some papers on the effect of infections on serum lipids in *The New England Journal of Medicine* as a student. I can still remember that Don Fredrickson looked at me and said, "Why would you pursue a career in infectious diseases? It has all been done. We have the antibiotics." I said, "Gee, I do not think so." I have subsequently reminded him of that interview. He denied it completely and claimed, "I never said that," but he did. You do not forget interviews when you are at that junior level.

Harden: Could you comment on the thrust of your research in this period?

Gallin: My work at that time was very much on how phagocytic cells crawled out of the bloodstream and into the tissues. There they are the first element of the host defense system against infection. What Shelly Wolff did that I thought was most outstanding was recognizing the importance of the host defense system in infectious diseases. He correctly predicted that the future in this area would be in learning to understand, and then control, the host defense components. He earmarked several areas in the field which should be developed. One was phagocytic cells; one was complement systems; one was cellular immunity, which subsequently became Tony Fauci's area; and then there were several other interrelated areas.

So Shelly Wolff collected young people interested in these areas. My own group of clinical associates was quite amazing. There were seven of us. One was [Dr.] John Atkinson, who is now chairman of medicine at Washington University, St. Louis, and quite an accomplished investigator in complement; there was myself; there was [Dr.] Peter E. Lipsky, the current editor of the *Journal of Immunology*, who has done very well; there was [Dr.] Charles Dinarello, who basically discovered interleukin-1 and all of its ramifications; and then there was a fellow named [Dr.] Jim [James] Pennington, who is now a senior executive at one of the pharmaceutical companies. Two of the members of our group went into private practice. It was a very exciting group. There was a lot of interaction and a lot of fun.

I pursued my interests in phagocytic cells and then the research was interrupted when I went back to Bellevue to complete my clinical training as a chief resident.

I came back to NIH and continued to work on phagocytic cells. I was made a section chief in 1978. I worked on the population of patients with chronic granulomatous disease of childhood. These patients' phagocytes are not capable of producing hydrogen peroxide.

When [Dr.] Robert Good described these patients in the late 1960s, he thought there was one enzyme linked to the disease and that it would be a very simple thing to understand. He believed that in a few years we would have treatment for it. What we have learned over a span of twenty years is that it is not so simple. It is a spectrum of diseases with disorders of oxidation metabolism, and we have now defined four genes that can lead to this disease. It is an abnormality of any one of the four genes. We are in the midst of trying to correct the disease through gene therapy right now. It has been an exciting story, but it is a whole other story than AIDS.

Harden: It would be fascinating to discuss that other research.

Gallin: I can tell you a little more about my appointment as Director of the Intramural Research Program for NIAID.

Harden: Please do.

Gallin: That occurred in 1985, following Dr. Kenneth Sell's departure. Dr. Fauci first selected Bill [Dr. William E.] Paul to be the Intramural Director of the Institute, and he agreed to do it. He did it for about seven days and then he quit. He decided he did not want to do it. You can ask him why, but he had a very short tenure as the Scientific Director. Then Tony Fauci conducted another search and asked me if I was interested. I said yes. We had a long discussion about whether it was the best thing for me and my career. One day in August we were eating fish with our wives on Tilghman Island and Tony asked me whether I wanted to take the job. I said yes.

Harden: Have you ever regretted it?

Gallin: No, I have never regretted it. It has been a lot of fun.

Harden: Let us go back now to the early 1980s, and talk about AIDS, when it first emerged into people's consciousnesses, before you became an administrator and before you were actually working on it. Can you remember when you first heard about the disease and describe your initial thoughts?

Gallin: I think I first read about it in the CDC [Centers for Disease Control and Prevention] *Morbidity and Mortality Weekly Report*, or maybe I actually heard about it earlier. There were stories in the *New York Times* or the *Washington Post*

about some unusual patients. But the first serious discussion was on one of those Saturday or Sunday mornings when I came in and was talking to Tony Fauci. I can still remember him saying that this was going to be a disaster. He picked it up right from the very beginning. He immediately recognized that this ailment was in his area of research because it was clear that all the things in the immune system that he had been studying were defective in the patients. You could tell by the kinds of infections the patients were having. Very early on, Tony Fauci said that it was going to be horrible and that he was going to study the problem. There was no hesitation on his part. I was astonished at how quickly he recognized the seriousness of the potential of this infection.

Harden: Did he already think of it as an infection rather than as a toxin or something else?

Gallin: I do not know if he knew immediately it was an infection. He knew it was a mysterious illness with all these infectious diseases associated with it. He knew immediately it was in his area of research. You will have to ask him about when he thought of it as an infection. He probably told you when he first figured it out. It was very early and I was very impressed at how quickly he recognized that this illness was going to be a disaster.

Harden: For the world, yes, indeed. Now even though you were not involved directly with the early period of AIDS research, what else do you recall about other people who might have got involved with, or commented on, the illness as it became fairly clear that it was an infection and that it had the potential to be a disaster? What kinds of things were happening within the intramural laboratories besides Dr. Fauci's work?

Gallin: You mean before I was Scientific Director?

Harden: Yes, in the early years. Is there anything else you recall?

Gallin: No one else seemed to jump on the problem right away. Not those people I was talking to anyway. They were the people on the eleventh floor of Building 10. I looked at this new disease, and it was clearly not something that I was going to place a lot of work on. I do not know if Bill Paul recognized it then. If he did, he did not seem to jump on it at all. But Tony Fauci began bringing in some patients, and it became "his thing" very quickly.

People began looking for ways to study these patients as it became obvious that there was an infectious agent involved. For example, we did a relatively early collaborative project [with Dr. Fauci] describing some abnormalities of phagocyte chemotaxis in AIDS. This chemotaxis project was started by one of my fellows at the time, [Dr.] Philip [M.] Murphy, who just got tenure last month. At the time he was a clinical associate on the floor.

We also studied some patients who were getting IL-2 [interleukin-2]. Some of Dr. Steven Rosenberg's patients who were getting IL-2 for other purposes were having serious staphylococcal infections. We knew about them because we were the infectious disease consultants for the hospital. Many patients receiving IL-2 intravenously were getting staphylococcal infections. Something was wrong. We looked at the phagocytic cell functioning and picked up an abnormality in the patients on IL-2. But many of the patients had AIDS. It was not clear whether AIDS or the IL-2 caused the phagocyte abnormality, so we had to sort that out. We found that that IL-2 can cause abnormal phagocyte functions. Steve Rosenberg said he could treat the infections and was more worried about the cancer, so he was not too concerned about the IL-2 effect. It was also true that in AIDS patients there was some measurable compromise in phagocyte function.

Harden: Do you recall the various ideas relating to the etiology of AIDS? I have asked this question of many people trying to see how ideas on causes developed.

Gallin: I think everybody thought that something like a virus was causing the disease, but no one knew what it was.

Harden: Yes, until more research revealed it. When you became Scientific Director, you inherited, by my count, something like sixteen major intramural research projects in 1983 and 1984. When you walked into your office and started reviewing the intramural program of the Institute, how did you evaluate the whole thing?

Gallin: You mean with regard to AIDS?

Harden: Yes. AIDS and AIDS versus other projects. I see this as an interesting problem for an administrator. You came on in 1985 and my memory is that it was not until 1986 or later that AIDS budgets started increasing.

Gallin: Right, that is what your charts show.

Harden: Yet, as the new Scientific Director, you had multiple responsibilities.

Gallin: In 1983 and 1984, we had not begun the computerization of the budgetary process and the monitoring of the FTEs [full-time equivalents], so tracking the budget was a much more difficult process than tracking the resources today. Before he left Dr. Sell had introduced the first IBM word processing system, but it was primitive by today's standards. As a matter of fact I thought, "There is no way I am going to do this. If tracing all this information by hand is what I have to do, I am not going to survive on the job." It was very laborious and it was not clear to me that it was working optimally. That is the kindest way I can put it. It was very difficult to see exactly how the resources were being distributed to some of these emerging

areas of scientific interest.

Laboratory chiefs had been asked to provide some information that Dr. [Richard] Krause could use to raise money for AIDS research. They compiled a wish list. But very little was actually being done in the laboratories, except in Dr. Fauci's laboratory. He was the first NIAID investigator to pursue AIDS in a major way and to pursue the pathogenesis of HIV. Mal [Dr. Malcolm] Martin was just beginning to do his work on the retrovirus, and [Dr.] Bernard Moss was pursuing his studies of vaccinia. No resources then had been added, so people were redirecting their funds. But not everybody was convinced of the severity of AIDS or whether they were going to be motivated suddenly to stop what they were doing and move into this area because they thought there was both an exciting intellectual project to pursue, as well as a crying need to pursue it.

It became apparent that there was an urgent need to apply modern computer technology to the NIAID infrastructure. In collaboration with the NIAID Executive Officer, [Mr.] Michael Goldrich, and with the support of Dr. Fauci, we developed an NIAID-wide network. We developed the first local area computer network on the NIH campus and it has been wonderful. I do not think we could have handled the incredible increase in resources that the intramural program required in the mid-1980s in any kind of efficient way without that. It was an important development. [Dr.] David Wise, Alan Graeff, and a committee of interested NIAID staff deserve the credit for its development.

Subsequently, nobody could live without this system. I refer to the communications of scientists with each other and with the administrators and so on. All NIAID components, including the Rocky Mountain Laboratories, are linked together. It is unbelievable how fast it has advanced and how much better it is getting. Plus there is the linkage to all the hardware, so that all the scientists' data is now transmitted electronically, sometimes from very remote places, a topic which we can discuss in a minute. It was very fortunate that computerization technology was available with the unfolding of the AIDS crisis.

One of the big problems that I faced was that each year, in 1986 and 1987, we had to go and present to Dr. Fauci what we thought our requirements were for HIV and what kind of increases we could handle. What was so astonishing is that we always did as well or better with financial appropriations than we had anticipated, even in our wildest fantasies. Then we had to use the resources. That was not so easy. If somebody gives you millions of dollars, it is an awesome responsibility. We were not given space nor personnel initially, just dollars. That produced quite a dilemma. I could not embarrass Dr. Fauci and say we could not spend the money. What we did and what proved to be in the long run, for reasons I can tell you later, a very fortunate thing is that we started using the contract mechanism in a major way. It is a quick way to create support services and to expand the

capacity of the intramural program, without requiring new space, and without acquiring personnel, which always lag behind the budget.

We set up contracts in Frederick [Maryland], and at that time we were very fortunate in that [Dr.] Norman P. Salzman was the chief of the Laboratory of the Biology of Viruses, a very important laboratory here which trained, amongst others, Drs. Bernie Moss, Mal Martin, and Michael Bishop, who subsequently won the Nobel Prize with Dr. Harold Varmus. Norm [Salzman] was at the point in his career where he was ready to contemplate retiring from NIH, but he did not want to leave science. We were very fortunate that, through a complex series of mechanisms, he decided to step out of the intramural program and apply in a competitive way for a new contract that we were setting up to grow the HIV virus from our patient populations. Salzman moved down to Georgetown University, where he became a professor of microbiology, and he received the contract. He became a critical component of [Dr.] Cliff [Clifford] Lane's (the current Clinical Director of NIAID) and Tony Fauci's programs for cultivating clinical isolates of HIV.

At the same time we had a big contract set up at the NCI cancer facility in Frederick managed by Program Resources Inc. PRI performed clinical immunology monitoring studies of our patients. The NIAID network was tied into the PRI facility rendering data management easy. Dr. Lane worked with [Dr.] Henry Masur (Clinical Center Chief of Critical Medicine) and together they interacted with Tony Fauci. Thus, the increased use of the computer in the last eight years has been a major change in the manner of doing the business of science. Currently, virtually every NIAID scientist has his/her own personal computer, which is more powerful than the big computers used to be fifteen years ago.

Harden: I think you are the first person to point this out. We forget how recently these machines came into our lives.

Gallin: Many of the institutes do not even have them yet.

Harden: I got one of NIAID's first PC's in 1985, when I was working on my Rocky Mountain spotted fever book. I had an original PC and had to install a ten megabyte hard card. At that time it seemed like more disk space than I would ever use.

Rodrigues: Who, within the institute, had the foresight to move ahead with setting up the local area computer network?

Gallin: I was very excited about the potential of computers. Michael Goldrich, who is the NIAID Executive Officer, and Tony Fauci were willing to let us do it. I was

particularly excited because I had seen on the eleventh floor of the Clinical Center the computer David [W.] Alling, who was our biostatistician, had set up. He had the first Wang computer system and had us all wired together so that we could do our statistics at our desks essentially through a machine he had in his office. We thought that was very nice and that if we could do that sort of thing in a major way it would be great.

I can still remember that when I was in college a friend of mine, who was a wizard at these sorts of things, said, "One day you are going to be able to type a paper you see on a TV screen, change it, press a button, and apply it to paper." I said, "No, that will never happen." My college friend was right.

What we did about computers at NIAID was different, I think, from what many of the other institutes did. Instead of hiring a contractor to set us up, we did it ourselves. We were very lucky that there were a few people in our institute who knew computers. One was Jim [Dr. James A.] Dvorak, one was Tom [Dr. Thomas M.] Chused, and there were several others. David Wise, in Mike Goldrich's group, became the leader of the program. We assembled a committee of those who wanted to become users and said, "What do you want?" Then we were very lucky, to find a very talented young fellow who made it work. That was Alan S. Graeff, a technician in [Dr.] Warren Stroeber's laboratory at the time. He was not happy with what he was doing in the laboratory, as he was really a "computer jock." But he knew and appreciated the requirements of scientists. He came in, worked twenty-four hours a day, and made it happen.

The reason it happened was because there was the NIAID administrative/financial support from Mike Goldrich and Tony Fauci. There was a committee that spent about a year designing what they thought we needed, and they were correct on most of the things; and then there was someone to implement it. David Wise oversees the entire system while Al Graeff now runs the system for the Division of Intramural Research and has assisted other NIH components to set up their systems. AIDS resources helped to bring about the network at NIAID and indirectly at NIH. That is one example of the huge impact of AIDS on NIH.

Harden: Can you think of any other things like the computer that had an impact on NIAID's AIDS research?

Gallin: I think the effects of computerization, which I could go on and on about, ranging from e-mail to documents, had the most important managerial impact. All our personnel, procurement, technology transfer papers are now handled through the computer.

Prior to NIAID's computerization, the Clinical Center, through the then Director of the Clinical Center, Dr. Philip Gordon, and later Drs. Griff T. Ross, and

Mortimer Lipsett in the 1970s to 1980s, also envisioned the importance of computerization. They brought the Medical Information System [MIS], to the Clinical Center.

Harden: Why don't we talk now about the NIAID intramural AIDS program. I identified a group of areas in which NIAID worked, including epidemiology, pathogenesis, antiviral and immunological therapy, vaccine work, molecular biology, and animal models. What did I leave out?

Gallin: There were a few things you left out about those early days. One is the work of [Dr.] Tom [Thomas M.] Folks, now at the Centers for Disease Control, who was working initially with Mal Martin and with Tony Fauci. Tom was a very important person in helping to appreciate [Dr. Robert] Gallo's observation, to relate it to the patient, and to the beginning of looking at what cells became infected.

The other thing that was going on in parallel, which was also very important and which you touched upon, was Project SIDA in Zaire. That was a unique interaction among a number of agencies in the government: the CDC, the NIAID, and later Walter Reed [Army Medical Center]. It was actually international. People from Belgium played a major role in it and also some people from Germany. The Germans set up a modern blood banking facility in Kinshasa in Zaire, which I have visited. Kinshasa is a third or fourth world setting. It is very primitive. The people from Belgium had set up an infrastructure for interacting with the health care delivery system that existed in Zaire. But it was the CDC and their people, together with NIAID, that set up a modern investigative research effort in this environment. Drs. Thomas Quinn and Skip [Henry L.] Francis, working with Ms. MaryAnn Guerra, played a major role setting up the NIAID research component at Project SIDA. It was amazing to me how all the events related to AIDS that occurred in Africa turned out to be an incredible predictor of what was going to happen in the United States. It was sort of a preview as to what was going to happen here with us. You could look over there and say, "We know that in the next four or five years we are going to have this problem," and it happened.

Harden: That was very early on, was it not? People keep saying that there were other people who had connections with what was happening in Africa. It took a while before we found out who they were.

Gallin: You have them. Tom [Dr. Thomas] Quinn was also a major person. [Dr.] Chris [Christopher] Brown was also over there.

[MaryAnn Guerra joins the interview at this point.]

Harden: We were interested in the information on budget and FTEs that you gave us. We looked into it in some detail, and I came up with a graph on FTEs. I was trying to figure out what was happening with the budget and when Congress started to appropriate additional money for AIDS. I knew that at some point there was a quantum leap in the budget for AIDS. I was interested in how you remember this event and what kind of impact it had on the intramural program?

Gallin: Let me start and then MaryAnn [Guerra] can fill in. Your graph shows that fiscal year 1986 is when the tremendous influx of resources started. I can still remember the fears that MaryAnn and I had at that time as to how we were going to spend all this money and where were we going to find the space to put the people. An interesting thing happened. I hired a technician, Lee Tiffany, who had worked at the Smithsonian out at a place called Twinbrook in Rockville. He told Cliff Lane—he did not tell me initially—that space was becoming available there because the Smithsonian was moving to a new location. Dr. John Gerin, who was managing a Georgetown University contract we had on our hepatitis research that was located at Twinbrook, also notified me about the availability of the Smithsonian laboratories at Twinbrook.

It never occurred to me that we could get it, but I went to Tony Fauci and said, "Tony, we need some space. There is 50 thousand square feet of space in this building. It has a greenhouse on the top which would make a great cafeteria." Tony said, "Let me see what I can do." To make a long story short, what he did, through whatever magic he had, and I do not know how he did it exactly, was to convince Senator [Lowell] Weicker that we had to have this resource to tackle the AIDS mission. Virtually singlehandedly, I am told, Weicker made it possible for us to have the budget that made the resources available to the institute and the budget to renovate the building. We were able to acquire this space from the Smithsonian. MaryAnn and I had some great visits out there looking at pre-Revolutionary era pianos and all sorts of things the Smithsonian had stored there. We undertook a massive renovation which was done at an unusually rapid rate through a contract we had with Georgetown University. I think from beginning to first phase, it was only months.

Guerra: We procured the renovations through the Georgetown contracting who did Phase 1 for us very quickly. After NIH acquired the direct lease of the entire building NIH Division of Engineering Services did the renovations for the next phases. We used a contract mechanism that we already had in place and moved the project forward rapidly.

Gallin: We had two things then. We had this space and we had some money. We had to decide what to do with it. There was one very important memo that I received from [Dr.] Bob [Robert] Chanock. The subject of this memo was "Areas of Research in the NIAID AIDS Program Which Require Immediate Increase and

Support." He wrote me pleading that we rapidly establish an SIV [simian immunodeficiency virus] program within the institute. He said that everybody has now at this point heard about the AIDS virus, and everybody is trying to get a quick fix to make a vaccine. He said that it will never work. It did not work in polio, and it is not going to work now. He said, "You have to go back to the ABCs," which means you have to have an animal model. You have to evaluate systematically a model of the disease to develop a vaccine. Then, from those lessons, you learn to develop the human vaccine. I can still remember going to Tony Fauci at that time and we had an exciting discussion about Bob Chanock's proposal. We decided that we would be foolish not to proceed with his proposal.

Originally with [Dr.] Bob [Robert] Purcell, who was a section chief in Bob Chanock's laboratory, and Bob Chanock, we set up an SIV model. We also set up a feline immunodeficiency virus model out at Twinbrook. That was one of the first uses of Twinbrook. A young investigator named [Dr.] Phil [Philip] Johnson was brought in. He very rapidly emerged as a real mover and shaker and took charge of that model. Bob Purcell, after setting it up, gradually went back to his hepatitis work and drifted out. Phil Johnson stayed until he became a professor at Ohio State. [Dr.] Vanessa Hirsch, who was working with him, is now overseeing, with Bob Chanock, the SIV model, which has been very successful. This intramural program is one of the few centers in the country that is pursuing that model. Dr. Harry Ginsberg, an emeritus professor from Columbia University, is now an expert on this group.

At the time of the setting up of this Twinbrook facility, we had to figure out whom else to move there. At first we had a virologist, [Dr.] Niza Frenkel, a full professor from the University of Chicago who had joined Bernie Moss. Initially she thought she might work on HIV, so she came to work with Bernie Moss's group but was stationed at Twinbrook. Then we recruited two viral immunologists from the Wistar Institute, [Dr.] Jack Bennink, and [Dr.] Jonathan Yewdell. We began to have a nucleus of virologists and viral immunologists with an interest in AIDS. Bernie Moss decided to relocate another adenovirus person who had an interest in the potential use of adenoviruses as vectors to transmit genes that might render cells resistant to HIV infection. This was [Dr.] Jim [James] Rose and he moved out to Twinbrook too. That was the nucleus initially.

Then it became very clear that Bernie Moss was having a lot of trouble with some of his people being out at Twinbrook and some of his people being in Bethesda. He did not like that. I was very sympathetic to his wanting everybody under one roof, so we brought all of Bernie Moss's people back to Bethesda. We decided to move a whole laboratory out to Twinbrook, and the choice was [Dr.] Tom [Thomas] Kindt's [laboratory]. The rationale was that Tom Kindt was developing a rabbit model for AIDS, so we decided to have all our animal models for AIDS at the Rockville Twinbrook facility. Kindt needed to interact more with the

virologists. We thought that with Vanessa Hirsh and Bob Chanock there, they would have a very sensible proximity interaction and that indeed has happened. That has been a positive move. Tom Kindt has no desire to move back. He is now my Associate Director for Twinbrook operations. So Twinbrook has been developing nicely since then, and other scientists have been recruited.

About that same time—around 1986 or 1987 as all this was happening—it became clear that we needed to be thinking about the whole AIDS effort, about what the entire intramural program was doing in some sort of coordinated and logical way. If, for no other reason, than to be able to explain to Congress and to other people what we were doing with all the money that was beginning to come in. It was in those circumstances that we decided to create, at least on paper, what we call the AIDS Vaccine Development and Treatment Center. The NIAID intramural activity was still at that point an intramural program. Subsequently, as we grew intramurally, it became a Division. The growth of the NIAID intramural program illustrates one of the impacts of AIDS. Our budget increased from about 53 million to 119 million dollars in less than six years.

The Vaccine Development and Treatment Center plan outlined the interaction of the various elements of the intramural activities for AIDS. By then, more and more laboratories were doing something in AIDS. Now, in virtually every laboratory in the institute someone had a project on AIDS. In some laboratories it was 100 percent, or nearly 100 percent, and in some less. Overall, our activity is about 50 percent on AIDS for the intramural program in 1993. You can see we have a molecular microbiology group, which included [Dr.] Bruce [W.] Chesebro and Mal Martin; a clinical immunology group, which was led by Tony Fauci and Cliff Lane; an antiviral agent group, which was led by Cliff Lane and Mal Martin; a vector development unit, which was led by Bernie Moss and which focused on his vaccinia work.

More recently, Bernie Moss has worked with [Dr.] Ira [H.] Pastan of NCI [National Cancer Institute] to develop an antiviral agent using a CD4 *Pseudomonas* exotoxin. This was really the idea of Dr. Ed [Edward] Berger, who was a tenure-track scientist in Bernie Moss's laboratory. Ira Pastan had the technology to couple the various elements like CD4 to *Pseudomonas* exotoxin, which he had been using in chemotherapy for cancer. He wanted to target therapies to cancer cells and he had this marvelous toxin, *Pseudomonas* exotoxin. Bernie Moss suggested that we could use the same approach to annihilate cells that were infected with HIV and that express CD4. That is now under clinical evaluation.

During this period [Dr. Herbert] Sandy Morse developed a mouse model which has been very interesting. It is called mouse acquired immunodeficiency syndrome [MAIDS], which initially we thought was going to be a great model for

HIV. It is caused by a different retrovirus, but one somewhat related to AIDS. Sandy Morse developed this together with [Dr.] Janet Hartley. She had worked very closely with [Dr.] Wally [Wallace P.] Rowe, who made some of the initially important studies on retroviruses. The mouse model is teaching us many lessons about the pathogenesis of retroviral infections, but is probably not a good model for human AIDS.

Harden: I believe that only Bruce Chesebro from NIAID's Rocky Mountain Laboratories [RML] was listed as working on AIDS. Is anyone else there doing AIDS research?

Gallin: There is another group at RML that works on AIDS. It is led by Dr. Seth Pincus, who works in the Laboratory of Microbial Structure and Function. [Dr.] John L. Swanson is the laboratory Chief. Dr. Pincus is a senior staff fellow who has been working on antibodies against AIDS, as well as on some HIV immunotoxins. This is somewhat related to what Bernie Moss and Ira Pastan were doing. Dr. Pincus has done some nice work there.

Guerra: Dr. Pincus's research was funded through the AIDS targeted antiviral program.

Gallin: That has been a important program for our Institute. Initially we were very skeptical when Building 1 [the NIH Office of the Director] received AIDS targeted monies to distribute to institutes. I was very nervous because I feared that we would get programs started with Building 1 soft dollars, but we would not have institute dollars to continue them. Building 1 dollars might disappear one day, and then what would we do with all these people and their projects? So far that has not happened. In actual fact we have been able to nourish a lot of young programs and to bring them to a point of importance. That has worked out well.

Harden: You are talking now about young people who are just beginning their careers. I would also like to know about your senior people who might have looked into how their research might be related to AIDS. I would guess that they would spend a year or two working on it and then say that they had done all they could. That would be the end of it. Did you have many people like that?

Gallin: We had a few. One pair was Jack Bennink and Jonathan Yewdell. When they arrived at NIH they intended to work on AIDS, but subsequently their science led them to other areas. Bob Purcell was very interested in setting up this SIV program out at Twinbrook, but once it was set up, he felt that his priorities were back in hepatitis. He let the Twinbrook program take its own course. Niza Frenkel first came here saying that she was going to do some work on HIV, but it never panned out. She, in the meanwhile, discovered a new virus, human herpes virus 6, which turns out to be the cause of roseola, a childhood infection. Instead of HIV, she pursued that virus, which has turned out to be extremely important.

She subsequently moved to Israel.

Guerra: There is also [Dr. Herbert] Sandy Morse.

Gallin: He continued his work on the mouse immunodeficiency syndrome, but it has not panned out as an AIDS targeted program. There are other examples of that in the institute. The main people who have obviously stuck with AIDS and continually have made relevant and extremely important observations are Dr. Fauci and his team, Malcolm Martin and his laboratory, and Bruce Chesebro, who started with a percentage of his effort in AIDS, and continues to have a percentage of his effort in AIDS. His primary area of interest is slow viruses. He works on scrapie and other slow viral diseases. He continually makes important observations on AIDS out at the Rocky Mountain Laboratories.

Tom Kindt's rabbit model has received a lot of criticism in terms of its relevance to human disease and how important it is. Despite that criticism, Dr. Kindt continues to have confidence in it. He has put in much effort and made many advances in just the last few years. He believes the rabbit will prove to be an important model of HIV.

Guerra: What about Bernie Moss's vaccinia work?

Harden: Where does that stand at this point?

Gallin: In relation to HIV?

Harden: Yes.

Gallin: It keeps waxing and waning. I think the principles of the technology, of being able to package a variety of genes in a virus which can be shown to be immunogenic, are obviously important. Dr. Moss's work has broad implications for a childhood vaccine and potentially for HIV. For details of that project, I think you should speak to Dr. Moss.

Harden: We need to speak to many individuals for details of these developments.

Gallin: On your list, here are the people I would recommend for you to meet. You should meet with Tom Quinn to get a perspective on the Zaire project, Project SIDA. He knows that better than anyone. I think you should meet with Bernie Moss. I think you should meet with Mal Martin for sure. If you can get out to RML, or do it through our teleconferencing system, I think you would get a very interesting perspective from Bruce Chesebro.

Guerra: How about Cliff Lane regarding the Clinical Center program?

Harden: We have already talked to Dr. Lane, and we will be talking to Dr. Fauci for the second time next week.

Gallin: The other money matter that we should mention, and one that was a major event on your list, is this building we are sitting in [A-wing addition to the NIH Clinical Center]. I will tell you how it came about in 1988.

We needed more space for AIDS. We needed it on this campus. The Cancer Institute was getting more, and so Dr. Fauci spun his magic again. He went back to his friend Senator Weicker and asked him to help us. There was apparently some drama in this. If you want to understand administrative drama in terms of getting something through Congress for something like this building you should speak to Mike Goldrich [the Executive Officer of NIAID]. What he tells us, and I believe him, is that while everybody was out at a cocktail party one night, he was told to stay late and work up a justification for an AIDS wing to the Clinical Center. He stayed until midnight doing it, and they hurried the justification down to Senator Weicker, right before he was to give a major statement about NIH needs in the Senate. Apparently Weicker's influence helped to get us this new building, the A wing to Building 10.

A third of the space is for administrative support, two thirds for research. The space is shared with NCI and the Clinical Center. What we decided to do was to move the administrative limb of the intramural program, the bulk of the Scientific Director's Office, and the Administrative Management Branch down here and thereby free up additional laboratory space, which we desperately needed, on the eleventh floor of Building 10. We have done this and are now in the process of a complex round robin providing laboratory space up on the eleventh floor.

In addition to that there is a floor of this building that is devoted exclusively to AIDS. It has some high containment facilities for safely handling the AIDS virus. The NIAID component of that is shared between two laboratories, the Laboratory of Immunoregulation, Tony Fauci's laboratory, and the Laboratory of Molecular Microbiology, Mal Martin's laboratory. There is some space set aside there, for people who may need access to a safe place to handle the AIDS virus from other laboratories. They can go in there and work for a short period of time.

Harden: Do you have any tuberculosis work going on here?

Gallin: The tuberculosis effort is something that I would like to touch on because it is clearly related to AIDS. The biggest public health threat today with regard to tuberculosis is multiple-drug-resistant tuberculosis (MDR-TB), which probably had its origin in the AIDS epidemic. AIDS patients provided a perfect culture medium for growing this infectious agent. It is extremely difficult to determine if

these patients have tuberculosis because they do not get an immunologic reaction to infection. MDR-TB first was seen in the inner cities, places like New York City. MDR-TB is of major concern because it is transmitted by the aerosol route. It has a high mortality.

Intramurally, we had no tuberculosis work at all prior to about a year and a half ago. There are three things we have done that I think will be significant. We have convinced the NIH community that we need to resurrect a high containment facility, Building 41T. We were able to convince Dr. [Bernadine] Healy to appropriate from the Gallo-French-American AIDS royalty fund some dollars to make it possible to redo that facility. NIAID is going to be the lead institute to manage the research in that facility, which will be shared by intramural and extramural colleagues.

We are setting up a similar facility in Montana, but a less elaborate one. My objective would be to have a facility there to serve the West Coast.

Four units are being set up in the Clinical Center to make it possible safely to bring patients with tuberculosis to NIH. We have received some funding from Congress to start investigations of tuberculosis. Several laboratories are pursuing basic bacteriology and bacterial pathogenesis.

The clinical program is also pursuing the tuberculosis effort. The major project to date is an extension of work that my own laboratory did in patients with chronic granulomatous disease (CGD), showing that gamma interferon protected CGD patients from infections by boosting the immune system. We have also been able to show that in patients who have a disease related to tuberculosis, atypical mycobacterium infection. We identified a group of patients who had highly drug resistant atypical mycobacterium infection and demonstrated that gamma interferon had dramatic effects on the clinical course in those patients. We hope that this will provide a precedent for applying this drug to tuberculosis.

Harden: Do you have to deal also with the danger to staff working with drug-resistant tuberculosis?

Gallin: Yes, and the major emphasis on their safety originates with me. When I was a house officer at Bellevue, I decided to work on tuberculosis and I got tuberculosis. Fifteen years later, I had to have a thoracectomy because I had tuberculosis. I got it because I was not, at the time, working in a good environment. I will not have my staff working with the organism unless the conditions are right. That is why we are setting up Building 41T, why we are setting up this facility in Montana, and why we are having units built in Building 10 for patients.

Harden: Let me follow up with one more question relating to safety issues. Some of the

people we have talked to have indicated that they have had personal fall-out from working on AIDS. Their children did not like to tell their friends that their parents worked with AIDS patients, or dealt with AIDS in some way, because then the friends would not want to play with them. Have you experienced any personal consequences like this?

Gallin: No. I have had people ask questions, but it is just a matter of education.

Harden: Maybe we should talk a little more about some of the budget and FTE questions that we had. When you say that you had X number of FTEs devoted to AIDS or non-AIDS, and when you state that some people had a portion of their projects devoted to AIDS, I would like to know how you came up with the numbers. I also want to know whether the numbers include clerical and other non-scientific staff.

Guerra: When we first got the additional FTEs for AIDS, we found out who needed to have extra FTEs on projects. When we gave out FTEs, we gave them per laboratory and we tracked them per laboratory, giving them an AIDS allocation and a non-AIDS allocation. We have done that over time. Actually, our automated computer system calculated our AIDS FTE usage. We were very careful when we gave out our AIDS FTEs. When we used them administratively, there had to be a reason for it. For example, when the budget doubled, obviously the procurement side of things increased dramatically. A number of FTEs went to procurement people to improve the processing and ordering time. And the HOPE Amendment—that is one thing in the budget I would like to touch upon—came along in 1988 and 1989. Through it we got about six million dollars one year, and that drove our budget up. It had an incredible impact on the clinical side of our program and on FTEs.

Harden: Maybe you could explain about the HOPE Amendment. What did HOPE mean?

Gallin: I forget what HOPE stands for, but it is the 1988 legislation mandating AIDS Clinical Evaluation Units at the Clinical Center. It resulted in an infusion of money to expand the outpatient clinical activities at NIH, and it mandated that there be a certain amount of clinical space for AIDS. That was a major event because there was no space in the Clinical Center available for this. Ultimately it required the action of the Director of NIH, Dr. James Wyngaarden, to identify space for the new AIDS clinic. That was the first time, to my knowledge, that a Director of NIH had actually stepped in and reassigned a significant amount of space in the Clinical Center.

Guerra: The space had been used by the National Institute for Child Health and Human Development but they were not using it for clinical space. I think they were using it for office space.

Gallin: But they claimed they had plans to use it. Anyway, they were relocated very quickly.

Harden: We have read some of the Medical Board Minutes about that, and they did a lot of negotiating.

Gallin: This AIDS Clinic was critical for us to carry out the drug trials that Cliff Lane and Tony Fauci wanted to do. It remains a very dominant part of the program. In fact one of the things that is happening over this period of time is that the use of the Clinical Center is shifting from primarily inpatient use to primarily outpatient use.

Guerra: This shift had a dramatic impact on the resources too. When we increased the number of outpatients, then we had to have research nurses and medical technicians' support. Some AIDS FTEs were devoted to that. I think we also had an administrative position to help do some of the administration related to that whole new effort. So the administrative positions coincided with the projects that were approved. John [Gallin] decided if projects warranted the administrative infrastructure to go along with the scientific support. Those decisions are made bit by bit as you can actually see. We used to keep a tracking system where we would show the date that things were added and whether they were AIDS or non-AIDS FTEs. You can see how very delicate decisions were made. They were not just made in a vacuum. They were very thoughtful processes.

The other interesting thing that happened, occurred at Frederick [Maryland], when the clinical program expanded. AIDS had a big impact in terms of budget for our clinical management fund. Part of the dollars that we got supported the clinical program, both inpatient and outpatient. But the clinical support required for the program—immunology support and neurology support—we did through contracts. That was because of the FTE and space limitations and competition. We could not hire everybody to do everything that needed to be done. We initiated some big contracts to support the clinical program, one at Georgetown and one up at Frederick. We utilized the contract mechanism to renovate a building at Frederick. There was an under-utilized building there that had basically been a freezer repository, and we got the money to renovate it. We were able to convert it into a laboratory building that ended up supporting the clinical program through an expanded contract.

Gallin: I would like to elaborate on that freezer repository, which people had initially called Ken [Dr. Kenneth] Sell's white elephant. We thought this gigantic freezer repository was just ridiculous at the time because it seemed like an endless amount of space to preserve specimens. But it turned out to be a visionary and correct thing for Dr. Sell to do. As soon as we started seeing all these AIDS patients, and with the beginning of Project SIDA, all these materials started being sent to us and we needed to freeze them. It has turned out to be a marvelous

freezer facility, which has been completely consumed. We have had to expand it. That resource was a very valuable and important contribution to support our programs.

Guerra: It was a good idea, but basically it was used for storage. We gave two floors to storage, and then we used the rest for other work.

Gallin: Now that whole building [Building 469] is in a high-containment level so everybody has to wear a gown, gloves, masks, and so on to do everything all day long. That is the way the research is done in that building.

Harden: Who has to worry about making sure that the power does not go off and cause you to lose the frozen specimens?

Gallin: The freezer does not require power. It works off liquid nitrogen. You have a long protective period but there are also all sorts of alarms, and there is policing.

Guerra: That is a rule. You have to have a back-up system. As soon as one element goes down, another kicks in.

Gallin: We have another freezer repository that is part of the infrastructure of our institute, and a very complex backup system is in place with people who police it twenty-four hours a day to make sure it is working right.

Harden: I want to come back later on to further discussion of the stored samples. But I would like to get through a few more of these questions first. My question is that Dr. Fauci is, of course, an intramural investigator as well as the director of the institute. Both you and he doubtless understand that this could cause the appearance of a conflict of interest. How do you decide, when the director wants something for his intramural laboratory, how to allocate the potentially scarce resources?

Gallin: It is simply because I have known Dr. Fauci so long and so well. There is an element of trust between us that has worked to each person's advantage. But we made it very clear from the beginning that, if I were going to be the Scientific Director, in that capacity he worked under me as a laboratory chief. He has never once in eight years challenged me when I have made a decision about resources for his laboratory. If I must turn him down, I say, "I am sorry. We are not going to do that." That is how it has worked. I think if it had not been that way, I would have left a long time ago.

It has worked because he has wanted it to work. He has been very sensitive to the fact that he is a very visible person. He knows very well that there are many people who would love to take pot shots at him. The last thing he wants is to have

anything happen to his intramural research activity. I think ultimately, that Dr. Fauci's intramural laboratory is the most important thing in his professional life. If he had to give things up, research is the last thing he would ever want to give up. He is not going to compromise that and he never has.

Guerra: He has specifically said that if anything he asks for seems inappropriate for us to tell him. We have had an open door. I can say things to him that nobody else would say to him in terms of intramural administrative decisions, because he wants to make sure that he is protected and that the things are right or done right.

Harden: He wears so many hats. We will pursue some more of those in detail when we talk to him again. But this situation with his laboratory is his one major intramural connection at NIH, and I wanted to ask you about it.

Gallin: It is a major connection because he is the major person in the intramural program involved in clinical activities who is pursuing AIDS. I do not think that you would find an investigator in our intramural program who feels that he or she has ever been denied a resource for AIDS-related activities. This means that Dr. Fauci has never ordered anything at the expense of anybody else.

Harden: It is good, MaryAnn, that you are here because I think you also do the technology transfer for the Institute. I was curious about the development of the first experimental AIDS vaccine manufactured by MicroGeneSys.

Gallin: GP160.

Harden: I wondered what legal arrangements there were between the institute and that company. Was a CRADA [Cooperative Research and Development Agreement] involved? Tell me about it.

Guerra: There is a lot of history in terms of the relationship between MicroGeneSys and the Institute. Mal Martin initially worked with MicroGeneSys with a CRADA, and there was an exchange of materials. One of the materials that Mal provided to them ended up being used in one of their diagnostic kits. That related to gp160 and eventually to the vaccine that came out of it. There is ongoing discussion as to whether the MicroGeneSys patent may be based on an NIAID invention, or using an NIAID material as part of the vaccine.

It is an interesting story and Mal [Martin] can share it with you but it came about after the recent article in *Science* on whether MicroGeneSys was cooperating with the institutes. We have been trying to get MicroGeneSys to license Mal's patent because they were selling the test kit. They said they wanted to license it and that they had submitted the paper work but the license was never executed. An issue arose about whether Mal's patent was valid because of some mistakes made by the

patent branch. MicroGeneSys backed off and would not license anything from us. Mal got nothing from that, and the institute got nothing from that. In one of our conversations, I said, "Mal, it sounds as though you might be an inventor of this vaccine." We had our patent attorneys look into the situation, and if they are right, although we may have lost Mal's original patent, Mal may be an inventor on MicroGeneSys's patent. We have not got a resolution on that. We worked off and on with MicroGeneSys.

Cliff Lane also had a very active relationship with the gp160 research, in terms of the clinical trials that were done. He can give you the details on that. I prefer not to. That work was not done under a CRADA. Mal's work was done under a CRADA. The clinical trial work was just done independently, as we do a lot of clinical trials, where we use their drug and we do the trials [no agreement in place]. We have been getting more sophisticated over time in developing formal agreements so that misunderstandings do not occur.

Gallin: One of the things you might pursue, if you want more information on cooperative work, is the negotiation for use of large chimpanzees that MicroGeneSys initially had their vaccine injected into. You could get interesting discussion from Bob Purcell, Cliff Lane, and Mal Martin, in terms of what should be done with these chimpanzees, which have been immunized and which are very expensive to maintain, at NIAID's expense. For a long time, MicroGeneSys was reluctant to let us challenge the animals to see whether the immunization worked. Their argument, which, at the time, I think was a valid argument, was that they might not have achieved maximal immunity. They keep wanting to boost the chimpanzees and get more of an immunologic response. We have finally reached the point where we have decided that we will immunize the animals on our own to a stable level of antibody response. Then they are going to be challenged with HIV to see if there is any protection.

Harden: Wasn't it 1986 when the Technology Transfer Act was passed? This was something new happening that you may not have had to deal with before.

Guerra: It was interesting because I think the act was signed in 1985. I can remember the CRADA with MicroGeneSys. It was early on.

Gallin: No. The CRADA with MicroGeneSys maybe antedated the act.

Guerra: It was really a one-page CRADA.

Gallin: The act did not initiate all these rules and regulations. What the act did was to give permission to federal employees to reap some benefits from technology transfer and thereby to encourage technology transfer.

Harden: Has the act inhibited the work of the intramural scientist in any way? For example, industry sometimes wants to protect information.

Gallin: There are certain examples of where it has been a problem.

Guerra: They always ask for everything to be protected. You go into one of these agreements and, in your first negotiation, they say that everything that is generated through the CRADA is proprietary information. Then you go back and agree that you will let it be proprietary information until a patent application is filed, or until you have an IND [investigative new drug] approval. You will limit how long you will keep the information confidential. In general, they will agree to that. I would not say that our collaboration with MicroGeneSys is a shining example of a government-industry relationship. We have gotten better ones as time has gone on and CRADAs have become more customary. That was one of the first ones. Now we have many CRADAs that are really benefiting intramural scientists. Think of the work of Bob Purcell and Wyeth-Ayerst.

Gallin: Wyeth helps support our chimpanzee program for the development of hepatitis and respiratory virus vaccines.

Guerra: Some of the CRADAs have been terrific in many respects for carrying out the next stage of intramural research. The MicroGeneSys one was just one of the first ones. Mal Martin has not had any other CRADAs since then. Cliff Lane has a couple of CRADAs that he is working on now in terms of some of the AIDS research.

Harden: What have we not touched on that you would like to talk about in relation to NIAID intramural AIDS activities?

Gallin: You have not covered some of the clinical things: one is material that Dr. Fauci covered in his recent [G. Burroughs] Mider lecture on the pathogenesis of HIV and the fact that HIV is not a latent virus. He showed that HIV infection is a continuum of events which you cannot see because it is in the lymphatic system for a long time. When the lymphatic system becomes exhausted, and HIV breaks through that system of containment, then invariably you get total destruction of the immune system. Understanding the fine detail of immune destruction in AIDS has major implications in terms of identifying where therapeutic intervention is appropriate.

Dr. Fauci and his colleagues showed that AIDS does not have a latent phase. In patients infected with HIV, HIV is constantly active, and if you look in the right place you will find the virus. HIV is contained in the lymphatic system for a number of years, but eventually it explodes out of that system, goes everywhere, and kills the person. I believe the paper published in *Nature* just a few weeks ago

is a landmark paper.

Harden: It certainly has implications for therapy, does it not?

Gallin: In terms of therapeutics, I think the use of immuno-stimulants in this disease is emerging as a very exciting area that you are going to read about in the next few months. In particular, I am excited about Cliff Lane's current studies suggesting interleukin-2 is capable of reconstituting CD4 cell numbers in patients with AIDS. These cells are the principal ones attacked by HIV, and when they drop below a certain number the patient becomes highly susceptible to opportunistic infections like *Pneumocystis*. What Dr. Lane has found is that if you give patients IL-2 in the right way—it is very critical thing what the right way is—the fall in CD4 T-cell counts is reversed. I think the use of IL-2 and other immune cytokines, such as gamma interferon, IL-10, or IL-12, in the management of patients with AIDS and other immune disorders is going to be very exciting in the next few years. It will have broad implications beyond AIDS.

Harden: It seems to me that research on AIDS has been a particular example of the unique opportunities in NIH intramural programs.

Gallin: When you think of that, you have to go back to the experiments of Dr. Wallace Rowe and Bob [Dr. Robert] Hubner and the people who early on recognized that retroviruses were important in human disease or had the potential to be of great importance. These were the people who set the foundation for others like Bob Gallo to jump in immediately and to relate retroviruses to disease. That is the unique thing about the intramural program. It allows people to do what sometimes seems like "way out," high-risk, long-term research.

Harden: I am going to ask one more question before I wind up. You have been very kind to talk at such length. Looking at my FTE chart, it appears that, in the beginning, the first burst of AIDS activity came out of the hide of the non-AIDS work. Have your people who do not work in AIDS felt as though their work has suffered from all the money going to AIDS?

Gallin: First of all, saying that the initial burst came out of the hide of non-AIDS work is an unfair statement. What that represented was people voluntarily shifting their directions. You had people like Tony Fauci and Mal Martin deciding to make major changes in the way their laboratory efforts were going. They went from non-AIDS work to AIDS, because of the intellectual opportunity and their own motivation. There was obviously a great concern during that period, and this is one of the effects of this whole era, that Congress would say targeted research is a must—"refocus what you are doing or we will not give you the resources." That never happened, not in our institute. In our institute if you look at the actual dollars available for the non-AIDS work, and the rate of increase of the non-AIDS

dollars, although it maybe lagged a little behind some of the other institutes, it was never dramatically behind. If you think of the fact that many of the intramural scientists have voluntarily redirected their activities towards AIDS. As a research institution, we are, in a sense, the beneficiaries of this public health disaster.

Harden: What is going to happen now under the new NIH Reauthorization Act? If I understand it correctly, the new funds for AIDS will be administered by the Office of AIDS Research rather than going to individual institutes. Is that correct? Does that mean that you have to apply to that office for funds?

Gallin: I have not had the opportunity to read the law, so I do not know exactly what it says. You should get that from someone who is an expert like Tony Fauci. Anything that I would say is secondhand. The one thing I could comment on is that one of the impacts of the whole AIDS crisis is that it has clearly enhanced the visibility and the scrutiny of science everywhere, including that of the intramural program. Doing science is more and more like being in a fish bowl. People are watching everything that you do. There is a real consciousness that somebody is looking at what you are doing, and a concern that you cannot do anything wrong. That sometimes can be a potential impediment to work.

Harden: Has the intramural program had much pressure from AIDS activist groups, for example, the way Dr. Fauci and the extramural program have had people questioning decisions? I refer to the activists' questioning of large-scale clinical trials.

Gallin: There has been a little pressure for some of the intramural investigators, but it has not been a major problem. Tony Fauci has really absorbed most of that himself. Two other diseases have been the source of major ACT UP-like activities: one is Lyme disease and one is chronic fatigue syndrome. These are other issues that historically would represent very interesting things to look into at some point. It is amazing how much of the outside pressure Tony Fauci has been able to absorb.

Harden: I have one final question and then Dennis may have some more before we leave. A recent National Research Council report says that AIDS, as far as the Council can see, will sink into the inner cities, into the drug-abuse population and the minority populations, most of whom do not vote. Does that mean that ten years from now there will be no political constituency for research on AIDS, and we will start to see the money dry up?

Gallin: I do not agree with that. I think that at first, some people believed that it would just be the homosexuals who had the disease. They were all going to die and then we would not have a problem. That did not happen. Now some people think it is going to be the drug abusers, but what we are learning is that AIDS is continuing to spread. I guess that, as long as there is sex and as long as people have sexual

desires, there is a threat of AIDS just like with syphilis. I think it will be a major blow for the inner cities. But, unfortunately, I do not think AIDS is going to burn itself out in the near future.

Harden: I am coming back to what you said earlier about Africa because the National Research Council report is fairly narrowly focused on the United States. But in Thailand and in Africa AIDS is spreading rapidly through heterosexual sex.

Gallin: I do not know enough about the sexual habits of people there or the social structure of those places. I know that in Zaire the situation is very different from here. In Zaire a middle-class, or an upper middle-class male, will normally have multiple sexual partners in a year, many more than in this country. This perpetuates the problem.

Rodrigues: One question I had is about how the political activism has affected the way things operate in the intramural program. I think you have already touched on that by talking about the fish bowl effect, of feeling that you are under a magnifying glass. But another question that occurred to me goes back to the comment you made about Dr. Frederickson, when you first came here, and his feeling that infectious diseases were a dead end street for research.

Gallin: I think the point of his statement was that, as we then had a mechanism for containing infectious diseases with marvelous antibiotics, did we think that this area needed intense research effort? I can see why someone might, around 1969, have thought that there was not an emerging epidemic. We had gone through a so-called "era of the antibiotic." Antibiotics had not been around for all that long, there were new ones coming on, and resistance had not yet emerged as a major problem, although it has subsequently become a problem. But Dr. Richard Krause, the former NIAID Director, very clearly predicted the future emergence of new infectious diseases in his book, *The Restless Tide*. He applied history to envision what was going to happen. That really was not a novel statement, but it was a nice twist, it was refreshing, it was timely. It needed to be stated.

Rodrigues: Some scientists say that AIDS was such a surprise that it took them totally off guard. They never expected this sort of disease problem. But, there are other voices saying that you can almost expect this to happen in the microbial world.

Gallin: Right, and we are seeing it today. These problems have not stopped and are not going to stop until we outsmart the bugs. Consider multiple-drug-resistant tuberculosis (MDR-TB). I do not think we can outsmart evolution. That is not likely to happen, not in our lifetime.

Rodrigues: But do you think the concept of having to be on guard for the emergence of totally new types of problem has changed the focus of research in the intramural program

at NIH?

Gallin: I do not think it has changed the focus of research in the intramural program. I think it has changed the sensitivity of our benefactors, and who knows how long that will last? It is hard to predict the future. But I do not think that intramural scientists have changed their directions of research to a course of understanding emerging microbes and how that happens. Maybe we should. It is an interesting question. But I have not seen that happen. What pressures may cause a microbial change that may create new diseases resistant to therapy has not been approached. It is an interesting question, a very broad and very fundamental question that maybe we should start looking at.

Rodrigues: At one point when we were doing some research, I tried to identify people who are actually on the area of emerging diseases. I could not find many people who had tried to look at the common features of new diseases.

Gallin: This will probably come, I predict, as a fallout of the Human Genome Project. As we understand more about the human genome or any genome—animal genome, microbial genomes—we will understand what the weak points are in the genetic code, so to speak, that predispose the host to mutations, to change.

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

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