

This is an oral history interview with Dr. Robert Yarchoan on the NIH response to AIDS. The date is 30 April 1998, and the interview is being held at the National Institutes of Health. The interviewers are Dr. Victoria A. Harden, NIH Historian, and Dr. Caroline Hannaway, Historical Consultant.

Harden: Dr. Yarchoan, I would like to begin with your background, with where you grew up and where you went to college, and with what influenced you to go to medical school.

Yarchoan: I grew up in Oceanside, Long Island, New York, and I went to Amherst College where I majored in biophysics. I had a sense from a young age that I would become a physician. But then in college I started to wonder whether I should instead get a Ph.D. I finally decided that it would be better to first understand how the whole body worked and then focus on a particular area, rather than start off specializing on a particular biochemical pathway. Then, after going to medical school at the University of Pennsylvania, I debated between research and practice. I decided to settle on research, and after doing an internship and residency, came to the NIH.

Harden: Did you have any physicians or nurses in your family, or any other medical background?

Yarchoan: I had a great uncle who was a physician. My father was a dentist, and my mother was a nurse, so I was exposed to various aspects of medicine growing up.

Harden: Tell us a little more about coming to the NIH as a clinical associate. How did you get here? Why here? Why not somewhere else? And what was the attraction?

Yarchoan: The real attraction was NIH was a place to learn to do high-quality research.

Harden: How did you know about it?

Yarchoan: Everyone knew about the NIH. From the time I was in medical school, NIH was seen as a mecca where high-quality science was done. Then, during my residency, [Dr. Robert] Bob Howe, a hematologist who had trained in the Metabolism Branch at the National Cancer Institute, and I were talking about possible places to go. He called up [Dr. Thomas] Tom Waldmann and said that he had a good candidate, and did they have any possible openings in the Metabolism Branch. Tom said yes. So I came here and interviewed, and wound up joining the Metabolism Branch.

Harden: Were you interested in cancer research already at that point?

Yarchoan: I was debating between oncology, hematology, and immunology—I wanted something to do with cells and cellular interaction. Scientifically, I was fascinated by immunology. The idea that a branch in the NIH was doing immunology research and connecting it with cancer was very attractive to me at the time.

Harden: What about patients? You are in a clinical field, so you did not opt for purely bench research.

Yarchoan: Right.

Harden: You wanted to continue seeing patients.

Yarchoan: Yes. I saw that there were very highly qualified Ph.D.'s, and some M.D.'s, who wanted to get away from patients completely. For me, the attraction was seeing things in the clinic, doing things in the laboratory, and making the connection. Really from the get-go, I have tried to position myself at that interface.

Hannaway: We talked a little about your earlier research when you first came to the NIH, and we have seen that you have publications on influenza and other viruses. You were obviously interested in this aspect of immunology. Could you describe a little about the research you were doing?

Yarchoan: Yes. Once I got here and settled down, I started working with [Drs.] Warren Strober and [David] Dave Nelson in the Metabolism Branch. At that time, the people in the Metabolism Branch had their focus on dissecting the immune system, particularly the human immune system, and studying a variety of immunodeficiency diseases. The Metabolism Branch had an inpatient ward and a clinic where they saw people who had immunodeficiency diseases or tumors of the immune system.

We were interested in trying to develop a system for looking at specific antibody responses. At the time, Dave Nelson had a friend, [Dr.] Brian Murphy, who is still on campus in NIAID, in [Dr. Robert] Bob Chanock's group. Brian and Dave had developed an ELISA for antibodies to influenza virus for use as part of their vaccine program.

We thought we might be able to use that ELISA to look at antibody production in the test tube. So we started looking at people who were being vaccinated with a cold-adapted influenza vaccine that Brian Murphy was testing, and then we switched over and started to use influenza to stimulate the immune system—peripheral blood mononuclear cells and so on—in the test tube. I spent some time with Dave Nelson trying to pick that system apart and understand the regulation of it.

Later, we found that we could measure the antibody from one particular precursor B cell, and I became interested in looking at the individual precursor B cells and how they were regulated and whether they produced one or two classes of antibody and so on.

Hannaway: Would you also comment on your experience in being a young investigator in the NIH intramural program. What was unique about this?

Yarchoan: I had been at elite schools and postgraduate medical training. But this was the most intimidating and intense place I had ever studied or worked. The Metabolism Branch at that time was an absolutely wonderful place. There were a lot of very bright people, many of who have gone on to high positions. Even the hall conversations, which ranged from science to casual topics, were invigorating. But also, the transition from being a practicing physician in a residency program to doing laboratory research involved basically starting from square one again.

In college, I had done some laboratory research as part of a thesis, and I was able to draw on that experience and the methodology taught there. But even so, it was quite challenging going from a medical residency, where I felt fairly competent, to this. But in retrospect, it was an incredible learning experience.

Hannaway: Were there machines or technologies or such about which you had no idea how they operated?

Yarchoan: Yes, just about everything was new for me.

Hannaway: Were there any limitations in your experience or any major frustrations of being a researcher at the NIH?

Yarchoan: I think the major limitations were just how quickly you could learn and how much time and energy you had to do things in a limited space. As a young clinical associate, you were basically doing your own work. There was enough bench space to do your own little project. For the type of work I was doing, the resources were adequate.

What I found was that there was nothing like a big project that you could suddenly plug into and grab a part of it. You had to create your own project and then move it forward. So it was a little harder to get going at the beginning, but once you got going, it was very nice because you had done all the work and it was yours.

It was also nice because you could get help from people. One thing I remember was that we were starting with this ELISA and we wanted a way to quantitate it. There was no mathematical model as to how to do that. It seemed to me that the curves were similar to the curves that you had with

radioimmunoassays, and I found one of [Dr. David] Dave Rodbard's old articles on the modeling of radio immunoassays. But there was not a way to calculate, experimentally, the upper asymptote. So I wrote a little program in Basic [computer language] on the one shared computer we had in the Metabolism Branch to do that. The program used brute force to try a series of numbers and see which one gave the best- fitting curve.

Then we sent the paper out to an immunologic journal. One of the reviewers critiqued our mathematics. I tracked down Dave Rodbard and asked him to look at what we did and compare it to the programs he was developing to look at ELISAs. He was very generous in helping us. He said what we were doing was fine. So we wrote back to the journal about his response, and they accepted the article. So that was very exciting, actually, finding that we were able to link up with the world's expert in this area who was just a few floors up and a couple of wings over.

Hannaway: Having people available that you could readily talk to.

Yarchoan: Right.

Harden: Was this different, qualitatively, from what was available at a university? Can you comment on that?

Yarchoan: This is the place where I have really learned to do research and have done it, so it is a little hard for me to compare. I think what you have here that is unique is such a critical mass of people, literally, within walking distance on one campus. I do not think that you would find that in many places in the world.

Hannaway: Some people have commented on the balance that is given, say, to laboratory research versus clinical research at the NIH, and you were interested in being a clinical investigator. Did you feel that people at the NIH valued laboratory research more, or did you have any impressions about this?

Yarchoan: I think laboratory research is certainly highly valued here. Where the optimal line should be drawn is hard to say. It seems that in the last five or six years there has been some thought given to swinging the pendulum more towards basic research. The impression I get is that people feel that if you swing it too far in either direction, you will lose something, and that you need to have a spectrum. It sounds like the NIH is moving forward and keeping that sort of spectrum going.

Hannaway: Why did you decide to stay at the NIH? We can see that you found the environment for science and research attractive. But were there any particular things that influenced you?

Yarchoan: At the end of 1982-83, my wife, who also was doing research, and I

needed to try to find a more permanent home for ourselves. We were both looking around here and there, and we went out and interviewed. Also, at about that same time, 1981 or 1982, [Dr. Vincent] Vince DeVita asked [Dr. Samuel] Sam Broder to form and head up the NCI's AIDS therapy program. As I understand it, DeVita basically told Sam to form a small program and see what he could do with it. Also about that same time—I do not know if these were simultaneous announcements or if they came within a short space of time—Sam became the Associate Director of what was then the Clinical Oncology Program, which was a layer of administration, which we no longer have, between the division and the branches. Dr. Broder also became the Associate Clinical Director of the Cancer Institute. More or less, this is the position that [Dr. Gregory] Greg Curt has today.

Sam had a laboratory up on the thirteenth floor of the Clinical Center, and he was one of the people that I spoke to about possibly staying on and doing additional work. That seemed very exciting to me at the time. My wife had a job offer in what is now called CBER [Center for Biologics Evaluation and Research, part of the Food and Drug Administration] doing research and some regulatory work. So it seemed attractive to both of us, and I moved up to work with Sam Broder.

Hannaway: Is that when you first met him?

Yarchoan: No. Sam had been in the Metabolism Branch at the time I came and had basically been working next door to me for the last several years. So I knew him well from talking and sparring with him on a variety of subjects in the halls, discussing scientific observations.

Harden: Let us go back, then, since you have us at the beginning of a new program on AIDS, and let us start discussing AIDS here. Can you recall when you first heard about this new disease, before you were ever involved with research on it, and what you thought about it?

Yarchoan: Yes. One of the things that the Metabolism Branch did was to get a number of patient referrals from all over the country with immunodeficiency diseases, either defined or undefined. There was a protocol that Tom Waldmann and the Branch had in which these patients were admitted and studied. The clinical researchers in the Branch would also try to help find the best therapy for the patient. My best recollection is that around May or so of 1981, a patient was referred from New York City with an undefined immunodeficiency disease. As I recall, this patient was gay, had been to Haiti, and had a male lover in Haiti who had died of a tuberculosis-like illness. He was admitted with severe immunodeficiency, and I think he had *Candida*. And, as I recall, soon after he came here, he got CMV [cytomegalovirus] retinitis.

Harden: That was the first AIDS patient.

Yarchoan: That was at least the first that I had seen.

Harden: We know about this patient.

Yarchoan: Okay.

Harden: But go ahead.

Yarchoan: After this patient came, we became aware that the CDC [Centers for Disease Control and Prevention] had become aware of several cases similar to this, especially in New York City and Los Angeles. So we figured out that, whatever this disease was, this patient seemed to fit the mold. In retrospect, he was a textbook case of AIDS. As I recall, Tom Waldmann tried doing some studies of him, and basically the patient just did not have any peripheral blood T-cell lymphocytes to study. Then the patient wound up getting one opportunistic infection after another. I think he may have gotten *Pneumocystis* pneumonia. He was a young, previously healthy man, and we had no idea what the disease was. There were heroic efforts to keep him alive and treat him, and nothing really worked. I think that several months after he came to the NIH, he finally expired.

Harden: But were you intimately involved in his care, or were you one of the group? We have had several people describe coming in to see this patient.

Yarchoan: I was one of the fellows that covered on that ward, but I was not the person primarily responsible for him. But we cross-covered on him and we often discussed what to do about him. So I was one of the people involved in that sense.

Harden: But this was probably too early for panic to have set in among the staff. Were there any special precautions that you remember?

Yarchoan: No. This was just another immunodeficiency patient who came in.

Hannaway: But you did regard this person as extraordinary.

Yarchoan: It was pretty wild, seeing someone who had been healthy and who then came down with such profound cellular immunodeficiency. We were all struck by it. I remember that one of the clinical associates, [Dr.] John Missiti, got very interested in him. John went up to Baltimore to try to learn what recreational drugs were being used in the gay community there. He tried testing the drugs in the laboratory to see if one of them was causing the T-cell deficiency. One of the theories being considered was that some drug being used by this population could be causing this T-cell

deficiency.

Harden: Do you remember when the idea that it might be caused by some sort of a virus or an infectious agent first came up? Was it early on or was it after you got more patients that you could see a pattern?

Yarchoan: What was apparent early on was that this was occurring in the gay population. An infectious agent was always a possibility, but I think the first real evidence was when a report came out—I am going to say a few months later, but it was probably six months or so—that the disease appeared to be spread by blood transfusion. That was the real indication that it could be spread by some sort of transmissible agent. There was a lot of concern at that time about this.

I also remember that my wife, [Dr. Giovanna Tosato], had heard from her mentor, [Dr. Michael] Mike Blaese, that there seemed to be some children in Newark with a new immunodeficiency. She had gotten some blood from these patients through Mike and she had been trying to study the immune function of the cells. In retrospect, this was pediatric AIDS, but we didn't know it at the time because the disease had not been described. No one used any gloves working with these patients, and there were no other special precautions taken at that time, because we didn't think of the disease as infectious.

Harden: We will come back to that question, too. In this early period, were you interacting with people like Dr. Robert Gallo as the move towards understanding the cause began? My recollection is that it was late June 1982 when the hemophiliac cases and the transfusion cases came to light. So it was later that year that Dr. Gallo started working on this problem. Were you at all involved in his work?

Yarchoan: I really was not. I did a lot of thinking about it. But I had my own project going on at the time. There was also a sense early on that it was tough to study this as an immunologic disease because the immune system was so wiped out in the patients who had what we now call AIDS that it was hard to isolate T cells from the peripheral blood.

Harden: So you did not think of yourself as an AIDS researcher or get involved until the point you were talking about earlier, when Dr. Broder was going to set up an AIDS therapy unit around 1983 or 1984, after the virus was discovered?

Yarchoan: Setting up a unit makes it sound like a bigger deal than it was at that time. I think he had just been appointed as head of the Clinical Oncology Program, but he still had only a single module. Then he moved up to the thirteenth floor in the Clinical Center, probably sometime in late 1982 or early 1983, and I joined him around January of 1984.

Harden: To do AIDS work?

Yarchoan: To do work on retroviruses and AIDS. The problem that he faced was that without a causal agent to work with, it was hard to develop rational AIDS therapy. There was a lot of interest in Sam's laboratory at the time looking at HTLV-1. Remember, the first human retrovirus, HTLV-1, had been discovered just a few years earlier in Gallo's lab, and soon after that the second human retrovirus was discovered by him. This was a very exciting period. And HTLV-1 seemed to be a way of studying immunodeficiency caused by an infectious agent that you could get your hands on. There was good evidence that people with HTLV-1 infection did have some sort of immunodeficiency. Also, other animal retroviruses caused immunodeficiency. So we spent part of our time trying to study how HTLV-1 caused immunodeficiency, thinking that this might provide some sort of model for what was going on with HIV.

Harden: I have two more questions along this same line. First, did you have any sense of urgency or frustration with the people, the activist community, the press, saying, "We have to have a treatment?" Did you have any sense that you should be trying to find something?

Yarchoan: No, I do not think so. I was pretty isolated from such outside criticism.

Harden: At that time. Okay.

Yarchoan: I remember at the time that there was more of a sense that we needed to first understand what on earth this thing was before we could effectively work on treatment.

Harden: My other question comes back to what you said a minute ago about it just being fantastic that you had these human retroviruses. It has been pointed out by other people that it was almost mystical that the first human retrovirus was identified in 1979 and 1980, and then we have this epidemic caused by one in 1981. Do you have any comments on that?

Yarchoan: Yes. It was a very exciting time. On one hand, the discovery of the retroviruses opened up a number of avenues of research. But AIDS showed us that something that no one ever worried about before suddenly could become a major problem for the country and for mankind. It was as though there was a whole new area that opened up, and at the same time had to be opened up, in order to address a new public health problem.

Harden: But perhaps you knew enough about animal retroviruses so that it was not a totally foreign concept.

Yarchoan: Correct. Remember, Bob Gallo's group had been looking for human

retroviruses for years and years.

Harden: Of course. But they had not actually been able to demonstrate one.

Yarchoan: They had not been able to demonstrate one, and then suddenly you had several retroviruses to study.

Hannaway: This next question is a more general question to lead into the question of treatment. I wonder if you would comment on NCI's drug discovery program as it existed about the time that AIDS appeared. Was this seen as a valuable program by NCI's administrators and scientists? What was the status of the drug discovery program?

Yarchoan: Which drug discovery program are you particularly describing?

Hannaway: The one that Dr. Broder had been involved with.

Yarchoan: I first need to clarify something. During much of that time, I dealt with Sam and Sam dealt with the rest of NCI. I did not deal directly with Vince DeVita very much. The impression I got was that Sam was given some resources to start an effort, and he was given additional support when he asked for it for a specific step in the research. Sam often described our group as a SWAT team, by which he meant a small, very focused group of people, rather than a large, bureaucratic program. I never figured out whether the SWAT team existed because it was the way Sam wanted to work or because the institution provided relatively few resources at that time. But the impression I have is that things were moving very quickly, that there was not a set program. It takes time to get a program in place. A lot of the effort at that time was made by individual scientists who were interested and who felt that there was a public health crisis that they wanted to help address. Sam would be the best one to speak with about the specifics. I did not get a sense that there was overwhelming institutional support for what he was doing initially.

Hannaway: He expressed the view to us that he felt that the National Cancer Institute and others were naïve about the process of drug discovery. How do you find out if drugs work in particular instances?

Harden: And yet the National Cancer Institute had a historic commitment to drug discovery. It was the only institute that did.

Yarchoan: Yes, but it was focused on cancer drug discovery. Actually, cancer drug discovery and antiviral drug discovery are very similar, but they are also, in many ways, very different. You could find out a lot more about anti-infective and antiviral drugs before they went into humans than you could about cancer drugs, at least at that time. In that era, cancer drug discovery was relatively primitive. If something seemed to selectively kill certain

cancer cells more than it did normal cells, that was often a rationale to consider further testing as a cancer drug. But with a virus, you can get a substantially better sense of how selective the agent is before you put it into people if you have a good *in vitro* testing process. So initially there were just a few people testing therapies, but there were no large, established efforts to develop therapies or drugs for AIDS.

Hannaway: What were your views about the possibility of treating retroviruses. Some scientists thought that they were not going to be treatable. Can you remember how you thought at the outset? Did you think that you were liable to have any success in searching for treatments?

Yarchoan: The easy answer is that I did not have a clue. But it seemed worth trying. It seemed a possibility if there was a virus causing AIDS. We did a certain amount of brainstorming. My best recollection of the events is that [Dr. Luc] Montagnier's paper, which described a virus he was calling LAV at the time, came out around November of 1983. I may be off by a month or two. In the same issue of *Science* was a paper—I think [Dr. Edward] Ed Gelman was one of the co-authors with Bob Gallo—in which they were describing the possibility of HTLV-1, or a variant of it, causing AIDS. Even though Montagnier turned out to be correct, it was hard to get a sense of whether LAV was the cause of AIDS from that initial paper, and there continued to be ideas put forward about possible causative agents. There was even an article several months after that suggesting that some type of cyclosporin A analog caused by a fungus might be causing AIDS. So, in the period of time from November of 1983 until about May of 1984, we continued to focus on HTLV-1, because it was not clear what was causing AIDS, and at least we had a good model to study.

Then the series of four papers came out from Bob Gallo's group. Sam had heard first from Bob Gallo that he had something exciting; then we got the embargoed copies of the galley proofs of those papers and were able to read them just before they came out. When you read those four papers one after the other, you really felt it was nailed down that this was the cause of AIDS. And that information caused us to redirect our efforts towards therapy. Sam sat us down and said, "Look, there is a small possibility that the idea is wrong, but let us put our marbles on this one. Let us really think of what we could do." Sam was quite taken with the idea that you could treat this disease and that this would be our focus.

We discussed this a lot. We thought that this was a virus that infects CD4 cells. It was probably killing CD4 cells directly after infecting them. It seemed fairly straightforward. So this suggested that ongoing viral replication was continuing to be an issue in patients with AIDS and continuing to cause the destruction of the CD4 cells.

We knew that the immune system had some ability to reconstitute itself,

and that by blocking this process, there was a good chance that the immune system would come back at least partially. So there was at least value in blocking viral replication with an anti-HIV approach.

We went through this formal thought process before launching into a new area of research. The situation in AIDS was different from that in HTLV-1 leukemia lymphoma, because in leukemia, it appeared that once cells were infected, an antiviral drug would not be able to block the tumor process. But here was a very different situation in that the virus was continuing to go from cell to cell. So then we started to think about how we could block this process. The literature on other retroviruses, animal retroviruses, gave us a place to start. We did not know whether it would work or not, but we thought that it was certainly a logical thing to do.

Hannaway: Was Dr. [Hiroaki] Mitsuya also working with you and Dr. Broder?

Yarchoan: Certainly. He had actually come to work with Sam before Sam had moved up to the thirteenth floor of the Clinical Center, in about 1982, as I recall. Again, I may be off. It seemed to me he came around August of 1982. So he had moved up with Sam to the thirteenth floor, and then I went up there.

Hannaway: Can you describe how you went about this? You came to this decision, this is what we want to do. What sort of procedures did you establish?

Harden: Walk us through it.

Yarchoan: There is one point I would actually want to interject. It does not fit in here, but...

Hannaway: That is fine.

Yarchoan: ...it is sort of in the same area. One thing I very distinctly remember was, when those first *Science* papers came out, [Dr.] Gene Shearer had been trying to look at some immunologic models of this new immunodeficiency disease. I think Gene is really to be admired for being a very basic research immunologist who with two feet jumped into this very murky area of a new human immunodeficiency disease. In retrospect, I think it is quite amazing that he was willing to stand on the edge of the cliff and jump. But he had been studying a cohort of gay men from the D.C. area who were relatively monogamous. When Bob Gallo was testing his initial HIV assay, he wanted some sera from gay men, and so he used some sera from Gene Shearer's group of gays. I cannot remember the exact number, but about 60 or 70 percent of them were HIV-positive at the time. I remember after reading the *Science* galleys doing a rough mental calculation of the number of gays in the country and the percentage who were likely to be HIV-infected, and estimating that there were half a

million to a million people infected with this lethal virus who did not know it. There was a weird feeling of having this cataclysmic information that the world was not aware of. I could not go out there and give a news conference saying that a lot of people are going to die and that it is a real crisis. But it was a very weird moment for me, feeling that I was privy to this information that had not perked through people's consciousness yet. Then there were endless debates about how many of them would get sick and how many of those would die. Unfortunately, the more pessimistic views turned out to be correct. But it impressed me at the time how cataclysmic a disease we were dealing with.

Hannaway: This was in 1984, when you were reading the four papers together?

Yarchoan: Yes. What Sam first did—I think Sam deserves a lot of credit for pulling things together and moving forward—is to hold a small meeting. He used to have an office on the sixth floor, in the 6B corridor, and there was a little conference room there. Sam pulled some people together. We have tried to reconstruct who was there, but it has been hard. [Dr.] Peter Fischinger was one of the people that he called in, and I just do not remember who the other people were. [Dr.] Dani Bolognesi, I think, was one of them, although I am not a 100 percent sure. The meeting was to brainstorm about various and sundry strategies to stop this retrovirus.

What I remember from that meeting was that Peter Fischinger—he confirmed this when I contacted him later, trying to jog my memory as to who was there—had talked about treating patients with thymidine or some related compound, because there was evidence to suggest that that approach might do something. There had been work in the laboratory of [Dr.] Prem Sarin, who had been in Bob Gallo's shop, that some rifampin analogs—rifampin is an anti-tuberculosis drug—had activity against other retroviruses. We thought that we would try to get a hold of some of these rifampin analogs, if any existed, and see if that strategy might work.

Meanwhile, Sam thought it was very important to get a clinical trial going. We had no idea how to even test if a drug was working in AIDS. What do you use to follow these patients? If they got completely better, you would know it was working, but the disease was relatively silent. People could be infected with HIV, as we now know, for a number of years without even being aware of it. Would the CD4 count go up? Would that be something to follow? It would be nice to follow the viral load, but there were not any assays for that. The best you could do was to culture HIV, and that was not quantitative. So we were struggling to try to figure how to even go about doing a clinical trial to test an antiretroviral drug.

During this time, Mitch [Dr. Hiroki Mitsuya] focused on the laboratory approach. Sam had Mitch try to develop an assay to detect whether a drug was working in the test tube. As I recall, initially Mitch went over and

worked with [Dr. Mikulas] Mika Popovic and learned some techniques in his laboratory. Then he brought the virus back and started working in the laboratory in Building 10. He first tried to look at p24 production, or production of RT, the reverse transcriptase. A problem was that it was very hard to tell whether you had an antiviral drug or just a drug toxic to the cells.

Mitch had been doing some work with T-cell clones, and since HIV killed T cells—Sam and Mitch and I all batted these ideas around—it seemed that if you could block the killing of the cell with a drug, that would be a very nice test, because you could show that it was both an antiviral drug and that it was not toxic to the T cells. Thus this drug could let the immune system at least continue to live, and perhaps even grow. So that was a very nice model. Mitch had these tetanus-specific T cells, as I recall, and he tested them. But these T cells are very difficult to grow. You almost have to talk to them, and they are just...

Hannaway: Encourage them?

Yarchoan: Really hard to work with. Then Sam and Mitch got the idea of infecting one of these cells with HTLV-1, and they developed this T-cell clone that was actually very sensitive.

*****BREAK IN INTERVIEW*****

Harden: We have been talking about the differences in why people go into medicine. I had asked you about people who are interested in both clinical and basic research. We were talking about Dr. Gallo as someone who does not want to do clinical research, but you were pointing out that he thinks like a clinician.

Yarchoan: We have interacted with him on a number of occasions. During that period in June of 1984, we attended his annual laboratory meeting, which, at that time consisted of about 30 people meeting in a room in one of his contract laboratories. It was truly a laboratory meeting with a few international collaborators, rather than the big, international meeting it is right now. That was the most incredible meeting I have attended in my life. We heard all of this unpublished information about HIV and retroviruses, and it just completely opened up that field for me.

But it always impressed me there and in other places that Bob—in spite of the fact that he leads a basic science laboratory—does what I would call translational work, and he can think of clinical things and draw laboratory associations from them. He is very good at that, and he keeps his clinical thinking and clinical connection in a way that is, for me, quite remarkable.

Harden: Now, when we stopped the tape a minute ago, before we started this side discussion, you were walking us through...

Hannaway: We were talking about how Dr. Mitsuya had developed a clone.

Yarchoan: Right. He had developed this clone. Meanwhile, I was trying to think of what else we could do to move towards a clinical trial. As I mentioned, I had been collaborating with Brian Murphy before on the influenza project, and I used to eat lunch with him and some of his colleagues. Sometimes [Dr.] Jay Hoofnagle, who is another virologist, would join them. And that particular day, Jay Hoofnagle came in. I remember saying, "We had this meeting about HIV, and we thought about using some rifampin analogs. Do you guys think that this would have a chance of doing anything?" The answer I got was, "Yes, it could work. Might as well try it." And Jay Hoofnagle said, "As long as you are trying that, why don't you try this drug suramin. It is an extremely potent anti-retroviral agent." I said, "Sounds good. Thanks for the tip."

So I went up to the library, and I remember trying to look up suramin. I thought it was spelled something like "cerimen," and I could not find it. I finally called Jay back and said, "Jay, how do you spell the name of this drug, and do you have a reference on it?" I cannot remember if he spelled it for me or gave me the reference. I tracked down this article by [Dr.] Eric DeClerq in which he showed that suramin was an inhibitor of the reverse transcriptase of murine retroviruses. I brought it to Sam's attention, and he said, "Let's get a hold of this and test it." I do not know where he got a hold of it, but somehow he did. Mitch and Mika tested it in the laboratory, and it turned out to be active against HIV. So we started writing a protocol.

This was a drug that had been given to patients before. At the beginning, we were most interested in testing drugs that had been used in humans before. The reason was that doing so would cut out what we thought was two years of animal toxicity testing, GMP [good manufacturing practices] production, and all the rest of it, and we could get a trial going soon rather than two years down the line.

So suramin was great in that respect. It was a drug that had been used in people before, although it was not used in this country, and it worked in the assays that Mitch was setting up. Sam and I worked together on writing the protocol. One thing I remember is that we did get a lot of support in terms of things moving quickly, and it certainly helped that Sam was the Associate Clinical Director and knew how the system worked. My recollection is we started writing the protocol in June, and I think it was August 6 of that year that we treated the first patient. So it took us about a month and a half from concept to treating the first patient.

Harden: What is involved in writing a protocol? I presume it is saying just what you intend to do and how many patients and so on, but there is bound to be more. I know that you have to go through an institutional review board.

Yarchoan: Yes, and the process has actually become more complicated since that time. At that time, you had to write down a pretty detailed blueprint of the experiment, defining what you were going to do, although you could give yourself a range of doses and leave some things undefined. Ideally, it should be written, so that, if after writing it you got hit by a truck, someone coming along could take that protocol and follow it. It had to go through the Institutional Review Board of the Cancer Institute. Since suramin was an investigational drug in this country, we had to get access to the drug. Someone had to file an IND, an Investigational New Drug application, with the Food and Drug Administration, and they had to approve the experimental use of the drug and to approve the protocol if it was the first IND application. That was basically what had to go on during that period of time.

Harden: While you are working with this first Phase 1 part of the trial, are you in close contact with somebody at the FDA [Food and Drug Administration], or is it more that you get the approval, you do it, and then it goes back.

Yarchoan: As time evolved, we actually started working reasonably closely with the FDA, calling them up periodically and even meeting with them. But I was not personally involved with the FDA at that time. My impression was that Sam spoke to people at CTEP [Cancer Therapy Evaluation Program]. For the NCI, CTEP are the people that generally hold and file the INDs. There is a regulatory part of the CTEP that has expertise and experience in pulling together INDs and filing them with the FDA. They really acted on this one very, very quickly, and they got the company that made this drug to let us cross-file with them so we could use all the background information that they had.

Hannaway: The animal trials and things that they had done previously.

Yarchoan: This drug was used in Africa as a treatment for onchocerciasis. The company then filed the drug with the FDA, and the FDA gave us very rapid turnaround on it, so that people really did get a sense of urgency and moved things along.

Hannaway: How did you recruit patients for the trial of suramin?

Yarchoan: They found us. We wrote the protocol and...just to backstep a little bit, one of the real issues was, again, we did not know how we were going to monitor the patients. At the time, there was someone in Bob Gallo's laboratory who was trying to develop an assay to measure one of the proteins of HIV, p24, but that assay really was not yet working. We wrote

the protocol to use this assay, but it turned out that it was not developed enough when we began the protocol. But we gave ourselves leeway to do other things.

One of the things that we did, actually, was collect samples, freeze them down, and then look at a variety of assays to try to see whether the drug was working or not. We also figured that if it was really working, the immune system would have to get better. I remember tracking down [Dr. Ronald] Ron Gress—he had done some work in transplantation—and with him trying to figure out how long we would have to give a drug to get improvement in the immune system. He noted that if you get an animal depleted of CD4 cells, you start to get them back in about four months. So we decided that if a patient can go for ideally four months, or maybe two months, and you do not see some improvement in the immune system, probably you are not there. Again, there was just no template for what would happen.

Hannaway: It was empirical.

Yarchoan: It was a hypothesis. The irony is that suramin had been tested—and this was a story that I took as a little bit of a warning—suramin had been tested for onchocerciasis down in Africa. It was tested under very primitive bush conditions where the researchers would go, on bicycles, from village to village, and they would give the drug on Monday to village A, on Tuesday to village B, and then they probably rested on Sunday; then the next Monday they would go to village A again. They would give it over a six-week course. That is what we did: we gave it once a week based in part on this African schedule. As an aside, I believe suramin was actually first synthesized by [Dr.] Paul Ehrlich.

Hannaway: My goodness.

Yarchoan: But the researchers in Africa initially concluded that the drug did not work, because initially they did not see anyone with onchocerciasis, or river blindness, get better. They went back the next year to visit the same towns, and they found that they had cured the blindness in a number of the patients. What had happened was that when the blindness got better, the patients just stopped showing up at the clinics because they could now go back out in the fields. So it was actually a warning to us that you have to make sure that you don't miss beneficial changes. It was amazing to me that you could miss curing blindness in someone, but I understood that it could happen.

Hannaway: If the patient disappeared and did not come back, you did not know.

Yarchoan: But when the paper describing the *in vitro* activity of suramin got accepted in *Science*, at that time NPR [National Public Radio] picked it up. I

remember I was down in Sam's office, and Sam said, "There is some radio show, like National Physicians' Radio or something like that, and they want to talk to us. Could you speak to them?" I said, "Sure." I got on the phone and there were typewriters clicking in the office, and the interviewer said, "Could you go and find a quieter room, please. We're trying to record this." I said, "Okay." So I went and got permission to go in Sam's inner office, and I closed the door and gave the interview. At the end, I said, "By the way, can you tell me what this is? Sam said it was National Physicians' Radio." The interviewer said, "No, it is National Public Radio." So this interview about the drug then appeared over NPR, and that was actually a very effective recruiting mechanism for patients.

But we wanted to make sure that the patients entered into the study had virus that was replicating, so the protocol required that they had to have virus that could be cultured. This was only done in a few laboratories, so as a practical matter we wound up getting referrals from other academic physician-researchers who were beginning to be able to handle this virus.

Harden: Moving from the in vitro studies to the actual trial, how long did it take before you realized that the drug was going to be too toxic?

Yarchoan: The main issue was not that it was too toxic. It just did not work at levels that could be tolerated—or we could not tell that it was working. If that drug had clearly worked, I think we would have done more to try to get around the toxicity.

Hannaway: So it was not inhibiting reverse transcriptase.

Yarchoan: It actually would be very interesting to go back and figure out what went on with those patients. What we found was that the first assay that we thought we could use never got developed. Then we thought we would look at lymph nodes, because a paper had come out suggesting there was more virus in lymph nodes than in peripheral blood. For this first patient, we took two lymph node biopsies before we treated him, and we had [Dr.] George Shaw in Bob Gallo's laboratory look at them for HIV by Southern blot. He could see a fair amount of virus in one lymph node and not that much virus in another lymph node. So, it became apparent to us that there was a certain amount of variation even before treatment and this was going to be very hard to use. Also, the lymph node biopsies were invasive, and the patient was becoming resistant to having more biopsies.

Then we tried collaborating with Mika Popovic in culturing the virus, but the system really was not quantitative enough to do it. So we were looking at CD4 counts and basically freezing down specimens for later studies. Then [Dr.] Mary Harper in Bob Gallo's laboratory developed a method for *in situ* hybridization, so we used that in a number of patients, but the

number of HIV-infected cells that they could detect was about one in 100,000, or one in a million, and it was too low to see differences.

Then we found, collaborating with [Dr. Philip] Phil Markham, that some patients appeared to become culture-negative, or that it took longer and longer to culture the virus after they received suramin. This suggested that there was a decreasing viral load. And we wrote this up in the publication from the trial in the *Lancet*. So this actually suggested that the drug might be doing something. But we never saw the CD4 counts go up. On the one hand we were a little bit optimistic because we had the virologic data, but in our hearts we did not feel it was working. The patients did not feel any better. That could have been in part because of toxicity. But we did not see any immunologic reconstitution. We thought that it was worth looking at further, but we did not feel we were seeing what we wanted to see with this drug, and the thing to do was to try other drugs.

In fact, suramin then went on to be studied in cancers. One of the patients in our trial developed adrenal insufficiency. Other researchers found that suramin induced consistent adrenal insufficiency at high doses, and they thought that it might be useful for adrenal tumors. Snuffy Myers, [Dr.] Charles Myers—everyone calls him Snuffy—and [Dr. Seymour] Sy Stein, who is now, I think, at Columbia, started looking at this in people with adrenal carcinoma and then switched over to another hormonally sensitive tumor, prostate cancer. But they have been doing a number of trials with this, so it is not too toxic to give to people. It just did not clearly work against HIV.

Harden: I was about to ask you. That is why I was looking for the paper.

Hannaway: Yes. This is the *Lancet* paper.

Harden: I was going to ask you if you were collaborating also with [Dr. Anthony] Tony Fauci's group, and obviously you were because you all published together.

Yarchoan: We treated some patients, Tony's group treated some patients, and then [Dr. Robert] Bob Redfield over in Walter Reed treated some patients with suramin, so it was really a joint effort of the three groups.

Harden: Was there a fair amount of collaboration across institutes in these efforts?

Yarchoan: Yes. There was some. Tony Fauci and [Dr. Clifford] Cliff [Lane] were focusing, as I recall at the time, on their IL-2 [interleukin-2] effort, which is now coming to fruition. They had a program of bringing in patients and testing them with IL-2, so we thought of linking up with them and doing this first study.

Harden: Is there anything else we ought to say about suramin before we move on to AZT?

Yarchoan: The one thing I will say is, just to give us sort of a chronological history, that Sam had organized a conference in December of 1984 on retroviruses that was published in a supplement of *Cancer Research*. At that time, we had the sense that maybe there was some virologic effect but that this drug was not going to be very useful for people unless we dramatically figured out different pharmacokinetics. I remember we were all a little bit down about it at that time and looking for other things to do.

Harden: I have often gone back to the diagram that Howard Temin made. I think it was in 1986. It was soon after the HIV virus was defined, and it showed the viral life cycle with the idea of the points at which it might be interrupted. Was this mechanism in your head when you started working on the AZT class of drugs and were looking for a drug, too, beyond suramin? Were you thinking theoretically at that point?

Yarchoan: The story of how AZT was settled on is somewhat complicated. From our perspective, Sam felt that drug discovery was a complex process; that there were a number of pharmaceutical firms out there that did it; and if he could link up with such a firm, it would help things along. We all had a sense of the urgency about the disease and wanted to move as fast as possible. By linking up, we could tie in with a group that had expertise in some of the important steps in drug development, and they could organize the large trials and quickly bring it to market. Sam sometimes said that federal government is not in the business of selling drugs. My recollection, from what he told me, was that, in the late summer and fall, he went around trying to talk to anyone he could get interested in developing drugs. What he found when he spoke to a number of pharmaceutical firms was that they were not interested at that time. In effect, they said, "Look, it is an epidemic, but there are only 50,000 people with the disease, and we can't justify a big program to our stockholders for 50,000 people."

Harden: Okay.

Yarchoan: We were focused on reverse transcriptase at that time. We had done some library research trying to look up reverse transcriptase inhibitors that had been studied in animal retroviruses, because this was a clearly unique viral enzyme, and it was an obvious target. The rifampin analogs that we had thought about earlier were reverse transcriptase inhibitors, and we had settled on suramin as a reverse transcriptase inhibitor.

There was literature indicating that some nucleoside analogs were reverse transcriptase inhibitors and/or some of them had antiviral activity. So there was an interest in nucleosides. How Sam had the contact down at

Burroughs Wellcome, I do not know, maybe through Dani Bolognesi. What happened there has been subject to varying interpretations, but my understanding is, Sam went down there to find a firm that he could collaborate with, possibly because they also had some nucleoside expertise. He gave a talk at Burroughs and then met with David Barry, and they settled on a collaboration. My understanding is that Burroughs had been testing some drugs themselves and had murine retrovirus expertise but essentially no HIV expertise. We had the HIV expertise, and it looked like a nice match. So they agreed on a collaboration where Burroughs would send some compounds up for us to test. Sam took it very seriously and rededicated a lot of the laboratory effort to testing those drugs during that period of time.

Hannaway: This was in 1984 or 1985?

Yarchoan: No, we are talking about from October 1984 to March of 1985.

Harden: But clearly before the Technology Transfer Act of 1986.

Yarchoan: Yes.

Harden: Would the whole thing have been handled differently if that act had been in place, or not? Did the act itself dictate certain relationships?

Yarchoan: I never read the act from beginning to end. But my impression is that, as a result of the act, the whole process of collaborating with industry became much more formalized and required formal agreements before things could move forward. Before that time, a lot of stuff was done just on a handshake or signed boilerplate documents drawn up by a company.

Harden: That is the impression other people have given us. Because of the subsequent legal problems, I am, I suppose, in one sense just asking, would it have been less complicated if there had been a formal mechanism before the fact, before that handshake? It is an interpretive question. Could you comment?

Yarchoan: Your question is whether the lack of a formal process, and whether the Technology Transfer Act and the processes put in place in that may have affected the collaboration and avoided some of the complications and arguments that have happened since then. I would say, in a sense, yes, but one has to ask whether the collaboration would have occurred if all the agreements had to be brokered before we started doing it. Certainly negotiating any agreements take time, and I think it is quite possible that the collaboration would not have taken place at all, or it would have been substantially delayed, if all this had to have been done ahead of time. Certainly, if the whole process was in transition and people were skittish about what the final outcome would be, that would have posed a major

problem. So it would have solved one problem, but it could have introduced a much bigger one.

Hannaway: You received these compounds that you were testing in this endeavor to find a treatment for AIDS with alphabetical labels?

Yarchoan: Right.

Hannaway: So AZT, in effect, had the label of compound AS.

Yarchoan: No, it was just S.

Hannaway: Just S. But had there been the whole alphabet to test before that?

Yarchoan: We had not gotten all of the alphabet. It was really Mitch who was doing the laboratory testing. We divided our efforts, and I was initially focusing more on the clinical aspect. So, for a period of time, it was really Sam and Mitch who were involved in this collaboration with Burroughs Wellcome. Then I got brought in when it started to move towards a clinical trial.

Hannaway: So it was Dr. Broder and Dr. Mitsuya who were doing the in vitro testing.

Yarchoan: Right. Although we all worked together and bounced ideas back and forth. I would go to the library and think of some compounds and bring it to their attention, but they were doing the hands-on laboratory testing.

I do not think we tested all the drugs between A and S. I think we tested a number of them. I know B was one that they had tested. But my recollection was that Burroughs had a set of compounds and only sent some of them up, but these were coded. But I am not 100 percent sure.

Hannaway: But what other drug companies or sources was the laboratory getting compounds from?

Yarchoan: We were getting them from a variety of different sources. I remember going to Cliff Lane's laboratory and getting some acyclovir, I think, that he had in the refrigerator to test. We were trying to pull in things from a variety of different sources. Some compounds we ordered from chemical catalogs. I think there was collaboration with one or two other companies that happened later.

Hannaway: With Abbott?

Yarchoan: I would have to go look in the old documents. I just do not remember which company they were getting compounds from.

Harden: When you got to the Phase 1 trials in July 1985, I believe, what happened?

Would you walk us through the process?

Yarchoan: The trial included 19 patients. We treated 11 and Duke treated 8. My best recollection is that the draft protocol was originally written by people from Burroughs with a fair amount of consultation from Sam. We had sent down a copy of our suramin protocol, and then Sam had communicated to them things that we would have done differently based on what we had learned from that protocol. So it incorporated their expertise in terms of doing Phase 1 testing and such, and what we had been learning from the suramin study. We then made some changes to the study. The Burroughs researchers were also interested in having something done down there, I think, because they knew people at Duke and they could go across town and see the patients. So it was agreed that the protocol would be done at Duke and at the NCI, and we would take the lead on it.

We got the protocol through the IRB. Then my recollection is that the first patient—I may be off a day—came in on July 3 and was treated July 5, or something like that, up on 13 East. And the first treatment was an intravenous infusion. The first patient to receive AZT was from Boston. He had full-blown AIDS, he had had *Pneumocystis carinii* pneumonia, and he had about, 40 or so CD4 cells per cubic millimeter.

Hannaway: That is not many!

Yarchoan: The patient received an infusion that was for the initial testing for pharmacokinetics, and Sam and I sat around and watched as he got a syringe full of AZT. I remember that night he developed a fever, and we came in and tried to figure out what the cause was—was this drug toxicity or was it the disease. We could not figure out what was going on. The temperature was not high enough to stop the treatment, and it looked like it was consistent with some sort of minor opportunistic infection or a cold, and so we continued on. The fever then went away.

He perked along, receiving the drug three times a day intravenously. It was initially supposed to be a two-week protocol. At the end of the two weeks, we found that his CD4 count had gone up, and we did not know what to make of this. We knew that CD4 counts bounced around, but this was a bounce in the right direction. We thought we had enough to push the company and the FDA to extend the treatment, so we got an amendment to extend it for another two weeks. The CD4 count was up around 200 by then. It was also getting really tiresome to give this drug three times a day intravenously, and there was reasonable evidence from the animal studies that it could be given by mouth. So we got permission to amend the protocol to change to give it by mouth. The patient received another four weeks of treatment by mouth. His CD4 count did not get much higher. It bounced around and actually was dropping back down by the end of the eight weeks. I guess, in retrospect, we were also learning

about resistance in that first patient, just the way the first patient with AIDS that we saw was like the whole epidemic rolled into one patient.

But he really felt a lot better. We also were doing skin tests, and we found out after a few weeks that his skin test—which is a way of measuring the T-cell responsiveness—had changed. He was anergic at the beginning of therapy, which means he did not respond to any of the four test antigens. At the end of a few weeks of AZT, he had a very robust skin test to tuberculosis. This was a PPD [purified protein derivative] test. So, again, in the sense that these initial patients were really textbooks—there was the tie-in with tuberculosis and HIV that we now appreciate in this patient. But we were very impressed that not only were the number of CD4 cells going up, but they were working.

Then we started getting concerned that this was an artifact that occurred just because we were immunizing him by giving him repeated shots. Normally you do not apply PPDs every few weeks. We found some articles related to this. The literature was pretty murky, but the sense we got is that if someone were truly anergic, they would not have a positive skin test to an antigen if you retested them a few weeks later. That made us feel fairly confident that this was something real. So we were excited about this patient, and we wrote to the FDA and Burroughs Wellcome.

Meanwhile, the second patient that we had treated at this dose had severe Kaposi's sarcoma, and this Kaposi's progressed while he was on AZT and he had a minor CD4 count increase. There was another patient that was treated down at Duke. He started at about 200 CD4 cells, and his count went up a little bit. And there was a fourth patient that we treated that started with five CD4 cells and went up to 10, then dropped back down to five again. So, in retrospect, they all moved in the right direction. But it was just this first patient that really looked like something.

Then we went to the second dose, in which I think we doubled the dose. And six out of six patients at that dose had an increase in their CD4 cells. At a certain point, we did the statistics. And around October, we realized that we were having statistically significant increases in the CD4 cells. It was just over the level of being statistically significant. We were, at that point, very, very excited that we really had something. The one reliable test that we had at that point was the CD4 count. We did not have any truly accurate viral load studies. We had a culture technique, but it was hard to know what it was telling us, and the results were coming in all over the board. But it was the immunologic changes that impressed us—they were relatively small, but they were always in the right direction.

Harden:

You are presenting a picture of seeing through a glass darkly and just trying hard to find a way.

Yarchoan: Yes. We have used the analogy of seeing a ship in the fog. You see these patterns and you are never sure whether there is really a ship coming or just eddies in the fog.

Hannaway: That is a good analogy, and probably a good way to think about it.

Yarchoan: We were excited but did not want to be too excited. Both for ourselves, and also because we felt then, and have always felt, that to try to give false hopes to patients is a highly unethical thing to do.

Hannaway: Had you recruited these patients by a talk on NPR or by other means?

Yarchoan: No. I think, again, these were recruited largely from calling up other academic clinicians, like [Dr. Jerome] Jerry Groopman, who, I think, sent down the first patient from Boston. Walter Reed was a source of some patients. Basically, there was this small community of people who were doing AIDS research, and you could call some of these people that had clinics and say, "Please send me a few patients."

Harden: One of the other points that we have seen in all these interviews is that there is no question that the response to AIDS at this point was grassroots. This was not anything being directed by some higher authority. But you knew the people who were interested.

Yarchoan: That is very true. Just one of the things was that it was not clear what sort of safety precautions you should take. I was worried about working with HIV in the laboratory. And we were trying to figure out what precautions were needed. What were the rules? There were no written rules. I remember calling [Dr. Bernard] Bernie Poietz, who had discovered HTLV-1 working with Gallo. He had been housemate in medical school, and was now up in Syracuse. I called Bernie and said, "What are you guys doing for it?" He sent me some guidelines that he put together, and we set up some procedures in our laboratory that fit the guidelines that they were using. But there were not any formal biosafety procedures for working with HIV at the time.

Harden: Do you remember, when we were talking about the first patient in 1981, and I said it was probably too soon for the panic. But, during the time of your clinical trials with suramin and AZT, I believe that [Dr.] David Henderson had set up some epidemiological rules in the Clinical Center. Did you find the staff or the nursing staff or the housekeeping staff or any of the other staff to be very nervous about dealing with these patients?

Yarchoan: Not too much. There was a certain amount of nervousness. There had been, by the time we did that trial, a reasonable amount of work that had been done with HIV in the clinical setting. Ed Gelman had been doing some trials with Kaposi's sarcoma within the [National] Cancer Institute,

so that there were AIDS patients coming in the institute. NIAID had been treating some patients. There were levels of anxiety that ran the spectrum, but, I think, in retrospect, the staff really behaved very professionally at that time when dealing with the patients. But I think everyone had some level of concerns about it

It was potentially a scary situation. We were dealing with a virus that either was 100 percent lethal or something less than that, that seemed to lead to a very miserable death, and that you could spread to close family members or at least spouses. There were reports of needlesticks in some health-care workers leading to HIV infection, but it was still not clear whether that was how they were getting infected. Also, there were so few laboratories that were working with concentrated virus that the risks in the laboratories were really an unknown factor, because you just did not have a large denominator. There were a number of people who were quite concerned about it. But people were generally quite professional in the clinical setting.

Harden: Let me just ask one other question as long as we are on this topic. We have talked to some people who experienced pretty negative responses among friends, even co-workers, because they were working with HIV. They encountered people who would not shake their hands. They told of visitors who would get up and leave the dinner table when they learned that their hosts did research on AIDS. Did you or your family have any negative consequences in that way?

Yarchoan: No...but then, I did not talk too much around our child's nursery school about being an AIDS researcher.

Harden: But your kids were very little too. They were not at that, say, junior high age where...

Yarchoan: Right. We actually did not advertise that fact in the school setting. With people whom we know as scientists, it was generally a good thing to be working on AIDS. We just did not want our kids to be affected by people who might have weird impressions about it.

I think some of the other investigators who were not dealing with AIDS tended to view AIDS as something dangerous. A few investigators would tease me sometimes about not wanting to come into our laboratory or borrow our equipment. But I personally was not exposed to a lot of that.

Harden: One more question along these lines. One of the great criticisms of the NIH is that everybody did not just stop and turn their entire efforts to AIDS, and that seems a very naïve statement to anybody who works here. But, from the point of view of the activist community, it appeared that a lot of people were very callous, they were only career-oriented and they

did not care about the public health. But you were one of the people who did work on AIDS. Would you comment in general on whether you think people who did work on AIDS were more altruistic than the others? Or do you have any thoughts about all of this?

Yarchoan:

We really reprogrammed our laboratory to work on HIV when the virus was discovered. My impression is that, until the virus was isolated, it was relatively hard for most scientists to get a good handle on how to attack AIDS. You could document how the immune system was going down, and you could show a number of epiphenomena. But people did not have a handle on the pathological root of the disease. If someone was working on cardiac metabolism or lipid metabolism, there would be no reason for them to switch over and do AIDS. They would not necessarily add much to it. And heart disease is also a public health problem.

I think a good number of people who were working in fields where their expertise could be turned to AIDS did it, and often they did it without getting extra money for it or because someone told them to do it. They did it because of the combination of reasons you do science—because you can help people, because opportunities exist to contribute something, and for a number of other reasons.

I think the irony is that I have heard the NIH also being critiqued for too many people working on AIDS in those days. So it seems that whatever we do, we get some criticism. But I do believe that if there are interesting scientific puzzles, a number of people will work on them if they have the tools to work on them; and that discovering the virus made the disease much more amenable to scientific work. In fact, if you look at the papers on HIV, there is first a smattering of papers of all sorts of quality, and as soon as the virus was discovered, you saw an explosion of papers because people could get a handle on how to study it. I am sure that if you graphed the number of scientific papers, there would be a steep break upward in the curve at about that time, or probably a year or so afterwards, as people geared up.

Harden:

Now, I have wandered around in the questions. Do you want to go back to the Phase 2 AZT trials?

Hannaway:

Yes. How did you get from the Phase 1 to the Phase 2 trials? You have some promising increases in CD4 counts?

Yarchoan:

We really did not do the Phase 2 trial. Just to clarify what happened: we did the Phase 1 trial, and we did a number of extensions of it, and small pilot studies. Actually, when the protocol was first written, we had to take people off the drug after a short period of time. Then, when it became evident that this drug was doing something, we badgered the FDA and got permission just to continue people on the drug. We escalated up in doses,

and, at a certain point, we felt we had doses that were fairly reliably increasing the CD4 counts of people. We had one patient who really made an impression. A nurse from New York had gotten AIDS through a blood transfusion and had a horrible fungal infection of her fingernail. When we gave her AZT, the infection cleared up, and you could start to see where the normal nail was starting to grow. That was very dramatic for us. She also had severe oral canker sores that cleared up. But to see this normal nail growing out at the start of this drug, that really convinced us that we were doing something.

Hannaway: Was this 1985?

Yarchoan: Yes, November-December of 1985. At that time, both we and the people at Burroughs to whom we were reporting the data were convinced that this drug was doing something. It was worth moving forward as quickly as possible. They felt that unless they showed that they could really improve the clinical lot of patients, that people would be arguing endlessly about whether this drug was worth giving to patients or not. I think that is correct, because even after the results of the Phase 2 trial were released, some scientists challenged us heatedly, saying that the immunologic changes induced by AZT were not enough to make any clinical difference. Some scientists and others still believe that this and related drugs don't work in HIV infection.

For the Phase 2 trial, the placebo-controlled trial, we had a series of meetings discussing doses and trial design. And the dose that was picked was reasonably high. My understanding was that the people at Burroughs thought that it was better to be a little toxic but to have the drug work than not to have the drug work. They felt they really only had one shot to show that it was working, and so they designed this trial. They had a series of investigators, some of whom they had worked with, who they recruited to do the trial. This trial was then launched in January-February of that year.

Hannaway: This was in 12 centers.

Yarchoan: In 1986, in 12 centers. By September of that year, they had a data and safety monitoring report that looked at the trial data, and at that time they had 19 deaths on the placebo arm and one death on the AZT arm. It was highly statistically significant. It was felt to be unethical to continue the trial, and the trial was stopped. Everyone on the trial was offered AZT, and then, over the next few months, they collected the data and reported it to the FDA. I think it was approved in March of the following year.

Hannaway: Were you surprised by this outcome of the Phase 2 trials?

Yarchoan: No.

Hannaway: Was this a greater success than you had hoped?

Yarchoan: No. I was glad it was as clean as it was, but we were not surprised. The thing that we were struggling with at the time was how long AZT was going to work. We were continuing to follow these patients on AZT. What we were seeing was that the CD4 count was going up and then it was coming down. For me it was something like *Flowers for Algernon*. My best guess was that we were buying people 20 weeks with AZT.

Hannaway: You did not see this as the solution because you already knew long-term studies showed the CD4 count coming down.

Yarchoan: Right. So it was very distressing for us.

Hannaway: And this was really going on in parallel with this outcome of a Phase 2 trial.

Yarchoan: Right. So we were very pleased that it was working, but we were starting to see the limitations of it.

Harden: If AZT was interrupting the reverse transcriptase phase of viral replication, why did it stop working?

Yarchoan: Part of it is that the drug is toxic to lymphocytes, particularly at higher doses. But most of it is resistance. What happens is that HIV has reverse transcriptase. It is a very sloppy enzyme and it makes a lot of mistakes, and it does not correct these mistakes. By contrast, the human genetic replicative machinery is very accurate, and it has many mechanisms to correct mistakes. If you think of it, we have an enormous genome, and we just cannot tolerate that many mistakes.

The genome of the virus is about 10,000 base pairs long. It basically works on a brute-force mechanism. It produces all sorts of variants, and many of them are not infectious. That is just fine, as long as some of them are infectious. In fact, the ability to mutate turns out to be an advantage for the virus because mutations are selected in response to antibodies that are produced. It is one of its tools. So if you expose it to AZT, there are several mutations that can confer resistance to it. Most of these mutations exist before you give people the drug, just because the virus is so sloppy. Those particular variants now have a selective advantage, and over the course of six months, they can grow out. There are some drugs that can induce highly resistant virus in four weeks in patients.

Harden: So you were aware that the increase in CD4 counts was not going to last, that it was not going to buy more than about 20 weeks.

Yarchoan: But we did not know what the mechanism was. That did not come to light

for a few years. But we knew that, for whatever reason, it was not working all that well for a long period of time.

Harden: At that point, were you thinking, then, about alternate drugs of the same type, or of seeing what you could do to combine AZT with other things? What were you thinking about?

Yarchoan: Actually, just taking you back a little—again, I may be off by a month—AZT's activity was discovered in the laboratory around December, January, February of that year. But we initially did not know its structure, because it was sent under code. Also, during that time, Sam had been going around talking to everyone about what should we try, and he was interested in looking at some other nucleoside analogs. He had come upon a paper by Fermanski in which it had been shown that dideoxythymidine had some activity. He pushed Mitch, saying, "Why don't you test this?" He would come back the next day and ask, "What are the results with this?" When Mitch looked at related compounds, including dideoxycytidine, dideoxydenicine, and dideoxyinosine, these all worked. Some of these were actually quite highly active.

Harden: What we would call ddI and ddA and ddC.

Yarchoan: And ddG was also one that worked but never got put into patients. These were compounds that, basically, we just ordered from chemical pharmaceutical houses, so they were completely devoid of any drug company support.

So while we were collaborating with Burroughs, Sam presented these results to the NCI and encouraged the parts of the NCI that were involved in drug development to help develop these drugs. Those NCI researchers made a decision to do so, and ddC was the next one chosen, because it seemed to be more straightforward than ddA or ddI. So while this work with AZT was going on, there was animal toxicity work being done within the institute on ddC.

Hannaway: These other drugs just did not have the track record that AZT had with the animal trials and other research already having been conducted.

Yarchoan: Yes. Burroughs had previously been looking at AZT because it had some antibacterial activity, so animal testing had already been done with it. These new ones were really starting from scratch. There was not a drug company involved, so the NCI did it, and the people did a very good job of moving that along quickly and finding out enough about it to get it into clinical trial. And that trial started maybe—the dates are a little bit more...

Hannaway: In 1986?

Yarchoan: Maybe the beginning of 1987, something like that, the end of 1986, the beginning of 1987. So we were moving on to the next drug. There was initially not so much the idea of combining drugs. We just hoped that the next one was going to be better.

There was then some interest in combining AZT with acyclovir, which is an anti-herpes drug and also another Burroughs drug. That drug had some very weak anti-HIV activity, and there was some evidence that combining it with AZT boosted the activity of AZT. We did a small trial of combining AZT and acyclovir. Probably, in retrospect, those effects were relatively minor, and that combination has never really become an established therapy.

But then we tested ddC in the clinic. It was very different from AZT in that, although the drug was eventually licensed to Hoffman-La Roche, it was really an NCI drug.

Hannaway: You found that it had different toxic effects and different positive effects?

Yarchoan: Yes. ddC is still somewhat of a puzzle. It had a fair amount of toxicity but was, in patients at least, extremely active against HIV. In fact, it was active at lower doses than what we would have anticipated. But the toxicity prevented us from going much higher on the doses, and it did not induce as many immunologic benefits as AZT except in doses that over a period of weeks wound up being toxic.

But by that time, Abbott had developed an assay for p24, and we started collaborating with them on looking at our samples with this assay. Dr. Jean-Pierre Allain was the person we collaborated with there. He has since, unfortunately, become embroiled in a controversy in France over the hemophilia issue there.

Hannaway: What did the assay with Abbott show?

Yarchoan: This was an assay looking at one of the viral proteins, the p24 *gag* protein. It is basically an assay for measuring it in the serum. This was, ironically, a better version of the assay that someone in Bob Gallo's laboratory had been trying to develop and we had planned to use in the initial suramin trial. It took about two years for the assay to be developed in a way that was usable. The trial showed that ddC could drop the p24 level quite convincingly.

Harden: I was interested in the paper that you did on AZT's effect on the neurological manifestations of AIDS. That whole area is of considerable interest. Do you want to comment on that?

Yarchoan: Yes. That was actually quite satisfying for me. What happened was we had a patient referred down from Memorial Sloan Kettering, who had AIDS, who had had Kaposi's sarcoma, and who had had some documented neurologic dysfunction with AIDS dementia complex. And he came onto our trial. The trial involved two weeks of inpatient therapy, and then the patients received more drug as outpatients. The man was quite confused when he was an inpatient here, and was even having some delusional and paranoid ideas. He thought one of the nurses was trying to kill him by not giving him his AZT. We were quite impressed that, after he was on AZT for a bit, his thinking seemed to clear up, and he functioned a lot better. He had been on interferon before that for his Kaposi's sarcoma, and interferon can sometimes cause some CNS [central nervous system] effects. As I recall, when he went back to Memorial, they had tested him and actually found some improvement in his psychometric tests. So, we were quite taken with this, but still thought it could be from stopping the interferon.

We had amended the protocol to allow us to treat some additional patients with AZT to gain some more experience with it. So, during this period of time, we recruited some other patients with neurologic disease. We knew that there was a lot of virus in the brain—this was actually shown by [Dr.] George Shaw in the end of 1984. We had this idea that once a patient became demented it was supposed to be irreversible, but based on this first patient we thought we might be able to reverse this. We recruited, I think, six or seven additional patients with neurologic manifestations. A few people with neuropathy appeared to derive some improvement, but it was relatively minor. We had one patient with a hemiparesis because of spinal cord involvement, and he did not improve much at all. But the patients with dementia generally improved, in some cases quite dramatically, and usually within eight weeks or so. We wrote up the initial four cases in *The Lancet* and then presented the information at a meeting. The neurologic community was quite surprised by this, and we were challenged aggressively at some meetings. The arguments were made that we were not neurologists, that dementia should not be treatable, the data were too good to be true, and that these were anecdotal cases. But it has subsequently been shown that, in fact, it does work and that there is a reversible component to AIDS dementia complex. AZT is actually one of the drugs that gets into the brain the best.

Harden: This is an argument for not cutting off AZT therapy completely.

Yarchoan: It is an argument against stopping it in such patients.

Hannaway: Would you tell us about how thinking on using combination therapies for AIDS evolved? There was a growing recognition in the articles that you, sometimes in collaboration with others, published in the late 1980s and early 1990s that HIV provides a number of opportunities or target areas.

Yarchoan:

Yes. It became, as I mentioned, evident fairly early on that AZT as a single drug had but limited activity, and the other drugs that were being developed also appeared to have limitations in themselves as single drugs. We thought, for a variety of reasons, it would be worthwhile to combine them. The simplest reason was that they often had two different toxicities. In cancer therapy, if you combine drugs that have two different end-organ toxicities, you can often get more anti-tumor activity by combining them than with either one of them individually just because neither of the end organs cries uncle. We did this early on with AZT and ddC.

There were a number of other reasons to do it. There was some laboratory evidence that the drugs had at least additivity and perhaps even synergy. There was an idea that if resistance was a problem, it might be harder to develop resistance to two drugs simultaneously. In fact, with tuberculosis therapy, that is one of the reasons you give two or more drugs. We found that ddC had a very different toxicity profile than AZT. At the same time, we thought it would take some time to get a trial approved to administer both at the same time but that we could move quickly if we proposed alternating them. We were actually able to do that right within the Phase 1 study of ddC. This was a time that we had very good personal interactions with the FDA. We were able to get the FDA's permission to do something that was really pushing the envelope a little. [Dr] Ellen Cooper was the person we were dealing with at the FDA. She was actually, I thought, very proactive during that period.

Then, after ddI was developed, we started to wonder whether it would be better to use the two drugs simultaneously or alternate them, and we did a trial in which we formally compared the two options. We found that people did much better combining the two drugs simultaneously at half dose rather than alternating the two at full dose. Over a period of time, people got the same dose of both drugs, but the way that the drugs were given made a big difference. Part of that is resistance. Also, part of it is because the two drugs hit two different cell populations, and this came out of some work that we had done in macrophages. Also, Mitch found the same effect in lymphocytes. In both cells, the thymidine-based drugs such as AZT work better in replicating cells because they are better metabolized to the active form. At the same time, ddI works somewhat better in resting cells. If we combined the two of them together, we were hitting both cell populations.. And we found some patients that, after over a year on simultaneous AZT and ddI, still had CD4 counts that were higher than when they started. So we had gone from 20 weeks of benefit to well over a year.

The question of whether it was better to combine two different targets rather than single targets came up again when the protease inhibitors were developed. They had very profound suppression of the virus, but resistance

would often develop within about 16 to 18 weeks. But if they were combined with the nucleosides, you were really able to suppress the virus. Actually, now you could suppress it to the point where there was so little viral replication that resistance was slowed substantially. This is a finding that was presented in a meeting about a year and a half, two years ago. So this is now the paradigm for how to treat the disease, to suppress the virus to the point where resistance development is slowed.

Again, even though the nucleosides were not ideal drugs, they kept patients going for a while. But, also, they provided the framework so that when the protease inhibitors were developed, the combination of the two gave very effective therapy.

Hannaway: Do you feel optimistic that this process of management with several drugs will have long-term success?

Yarchoan: That is a good question, and it is one that I have agonized about. I sometimes wonder, are we talking about tuberculosis in the 1950s when really there was a dramatic change and you could suddenly cure most patients, or are we talking about cancer in the 1960s, where you had one disease, childhood leukemia, that you could cure and many people thought that with combination therapy, we would be able to lick many other cancers. I think if we can develop other active drugs that target perhaps one or two more sites, and combine them with the drugs we have, we really might be able to start to move in the direction that a majority of people can live with this disease for a substantial number of years.

In terms of eradicating the virus, I am a little less optimistic, although I think that if you combine good anti-retroviral therapy with either the natural immunity or boosted immunity, that you may be able to live with this virus and keep it suppressed much the way we do with a variety of viruses. All of us are chronically infected with a number of viruses right now.

Hannaway: People often refer to herpesvirus as something that most of the population lives with.

Yarchoan: Yes, chicken pox virus, for example.

Hannaway: Yes.

Yarchoan: The other possibility is that we are going to get stuck on some of these new targets and that in three years we are going to start to get a wave of breakthrough as resistance develops to the available drugs in many patients. I am pretty optimistic that, as we identify new targets and get new drugs, we can continue to improve things. I have sometimes commented that we do not need to cure a disease, but if we can keep

patients alive for 60 or more years, that is probably good enough for most people.

Harden: What I am hearing, too, is that you are coming back around to combining drug therapy with immunological reconstitution. Do you want to expand any on immunological reconstitution?

Yarchoan: Again, we have done some work in that. A number of years ago, when we became aware that this was a disease caused by a virus that was killing T cells, we felt that that the attempts to reconstitute the immune system would often be limited by the virus's substantial efforts in killing whatever cells you wanted to reconstitute. Now that we are able to get the virus under control, it opens the door for efforts both specifically and non-specifically to reconstitute the immune system. Again, people can argue over beers whether this is going to have an effect or not. I think Cliff Lane's group is very nicely showing that IL-2 therapy, combined with anti-retroviral therapy, can make substantial improvements in CD4 counts. They are doing a trial now to look at the clinical benefits of this. It is not an either/or situation, but a situation of working on both and then putting them together.

Harden: Let us talk about how AIDS changed your overall career. Obviously, when you started, AIDS was not recognized, and since you got into AIDS, you have continued with it. You have been a senior investigator in the Clinical Oncology Program and Chief of the Retroviral Diseases Section in the Medicine Branch and now HIV and AIDS Malignancy Branch Chief. How have your actual activities changed, in terms of research and administration? Do you intend to stay with AIDS? Somebody in the last interview that we did shook me up. Somebody in another interview said that he was already thinking about what to do after AIDS.

Yarchoan: Let me just say it has given me great satisfaction—I was just thinking about that as Sam Broder and I are writing a chapter together, and we have been e-mailing each other back and forth. It has given me the opportunity to do what I really dreamed about doing when I was in college, to actually make a difference. When I get away from all the little daily imbroglios that go on here, it is very satisfying to feel you have actually made a difference somehow, even if in a small way. At the same time, I wish I did not have this opportunity in that this disease never appeared.

It is sort of funny in retrospect. I was training for a career that did not exist, and suddenly the career plopped down in my face. It was not clear to me what I was going to do after I finished my work in the Metabolism Branch, and probably if AIDS had not come in, I would have gone into more classic immunologic research. I was actually looking at a variety of different options at the time that I was finishing there.

Suddenly, an epidemic immunodeficiency disease came along, and I was lucky enough to be in a situation where I could expand my knowledge and learn more virology and more about drug development. I fell into a team led by someone I have great admiration for—Sam Broder. And Mitch was also a great teammate in our research. So AIDS has given me an opportunity to make more of a difference than I probably would have been able to do in other areas. Again, I wish the opportunity was not there, but I am glad I was able to do something about it.

Harden: How do you think AIDS has changed the NIH overall, the balance among the institutes?

Yarchoan: I am not sure I can really address that.

Harden: You have seen changes within your own institute?

Yarchoan: I think that, within the Cancer Institute, there has been an evolution. At first, people redirected whatever funds they could get their hands on to do AIDS research. Then the Institute was given AIDS money that went both to people working specifically on AIDS and also to people doing basic science that was related to AIDS. Then, when concern arose that AIDS money should go only to research directly linked to AIDS, NCI reprogrammed some work to focus either directly on AIDS or to not use AIDS money. These are changes that evolved over the last 14 years. But I really cannot address the larger issue of how much it has changed NIH or even NCI overall. There are a number of very dedicated people within the Institute and on campus who are interested in the disease.

Harden: You do not have a strong sense yourself, then, that AIDS has just taken over. As we said, there have been critics on both sides.

Yarchoan: No. I think there was probably a period of time when people would get AIDS money and use it for a research project that was somewhat related to AIDS. But the fact of the matter is that, because of the nature of AIDS, it meshes with so many areas of critical importance in so many fields of medical research that—I do not know quite how to word this—it has probably boosted medical science in general, even though it has posed an additional problem of focus. A lot of immunology has evolved during the study of AIDS. The study of retroviruses and retroviral vectors, T-cell immunity, apoptosis, and oncogenesis are other areas that have advanced. If you look at the study of retroviruses, you can see how it relates to the core of other fields, and people can go fairly quickly from retrovirology to a number of these other fields because they are so closely related. So, I know there are endless debates about whether some of the AIDS money was used on non-AIDS research and whether there was too much AIDS research, but a lot of cross-fertilization has come out of it, and that has to be good.

Hannaway: I think many people see that. The knowledge of immunology has been enhanced by this research in so many ways. The other thing that I think that some people see, in the larger picture of medicine as a whole, is that people thought that the primary focus of disease research would be on chronic diseases at the end of the twentieth century. Yet here you have an infectious disease, and this changed the perception across the board of what diseases to work on and what the concentration in research was going to be. It does not mean that the chronic diseases have gone away, but you also have renewed interest in infectious diseases.

Yarchoan: We also helped make AIDS a chronic disease.

Hannaway: Yes, that is true.

Harden: But also, in one sense, there has been a sideways shift, because both infectious and chronic diseases are now studied via molecular techniques, so there is not much division anymore in the way you approach understanding it all.

Yarchoan: I think that Drs. [Harold] Varmus and [Richard] Klausner support the notion that there are a number of critical medical problems, and in addition to attacking them directly, we should focus on basic science with an eye to those problems. As you get to the more basic levels, the amount of cross-fertilization that you get increases substantially. I feel the distinctions between the fields are not really so important, unless you are talking about truly applied research, and even out of that you can learn a lot of basic information if it is done well.

Harden: Is there anything else that would like to say?

Yarchoan: Just that ddI was yet another drug that was developed here, and that was also very satisfying because it induced greater immunologic changes than ddC and it was a drug that we really saw through from the very beginning, from the laboratory concept, through its preclinical development, through the Phase 1 testing. The NIH holds the patent on this drug. Then we worked with Bristol Myers, to whom it was licensed. Again, it was one of the drugs used in combination therapy that I talked about. It was very, very satisfying that ddI is probably, of the single nucleosides, the most active and, for reasons that still are not clear, works for the longest period of time. It is also, I believe, the cheapest on a patient-year basis, and thus it is more affordable for patients in third world countries.

I am also grateful that NIH gave me the opportunity to do research on AIDS. NIH deserves the credit for putting the tools in my hands and the collaborators within reach to work together on it. And finally, this was the effort of a number of very dedicated people.

Harden:

Thank you very much for the interview.

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