

***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.



























































