This is an interview with Dr. H. Clifford Lane of the National Institutes of Allergy and Infectious Diseases (NIAID), at the Clinical Center, Building 10, of the National Institutes of Health (NIH), in Bethesda, Maryland. The interviewers are Dennis Rodrigues, Program Analyst, and Dr. Victoria Harden, Director of the NIH Historical Office. The interview was held on March 12, 1990.

Rodrigues: I'd like to begin by asking about your professional training and your background before you came to NIH. How did that lead you to become involved with patients with PCP [*Pneumocyctis carinii* pneumonia] and Kaposi's sarcoma?

Lane: I did my training in internal medicine at the University of Michigan. Afterwards, I came to NIH in 1979 to do a clinical associateship—a fellowship training in infectious diseases and immunology. My initial research was studying the normal adult human immune response.

Harden: Let me back you up for a minute. Who offered you the fellowship?

Lane: I came here to the Laboratory of Clinical Investigations as part of the NIH Fellowship Training Program. So Mike [Dr. Michael] Frank would have been the person who made the offer. That program allows you to do clinical training and also spend time in the laboratory. I spent time in the Clinical Physiology Section of the Laboratory of Clinical Investigation. That was Tony [Dr. Anthony] Fauci's section of that laboratory. He was a section head at that time. So, that was how I came here.

My initial work was studying antigen-specific human B-cell responses. I was studying how normal volunteers respond to immunization, and through that, trying to understand how the adult immune system worked. You may or may not be aware that a lot of the work in immunology involves pediatrics, or developing immune systems. There isn't as much work, or at least in the past hadn't been as much work, studying the adult human immune system. Immunology research often focused on either involved pediatrics, because of the immunodeficiency diseases of kids, or on the immune systems of small animals. In any event, I was doing this sort of work then.

Harden: This was in 1979, when things were peaking after the early explosion in immunological knowledge, was it not?

Lane: Hybridomas were just being made. It was before the molecular biology innovations had really become established, so it [immunology] was still predominantly a cellular science. It was just before, I would say, things really took off in immunology.

Harden: What did you hope to do at that time? Where did you see your career going at that point?

Lane: I was interested in studying the way the immune system recognized specific antigens and decided to make antibody to A rather than to B, C, D, E, and F. I was interested in how that process was regulated, with an eye on trying to better understand autoimmune diseases. In fact, I began to collect a cohort of patients with a disease called Sjogren's syndrome, which is a disease of oligoclonal B-cell activation. Basically, I was studying specific responsiveness and hyper-responsiveness of the immune system.

Around 1982 or 1983, when I'd just been extended to stay on beyond the usual time, which is three years, there were a couple of different patients on our ward. Steve [Dr. Stephen] Straus brought one in. I don't know when [Dr.] Henry [Masur] came here exactly, but Henry had brought in a couple of patients as well. The patient Steve brought in just had immunodeficiency. I don't know if that patient had AIDS or not. But it was just an unusual immunodeficiency disease. Steve studies herpesvirus infections, and the patient had severe herpesvirus infections. To this day, I don't know if anyone knows if that patient was HIV-[human immunodeficiency virus]positive. In any event, shortly thereafter, when AIDS was something that people were aware of, Steve brought in a couple of patients with AIDS. Henry and Tony [Dr. Anthony Fauci] were starting to bring in some patients with AIDS, and I was in the laboratory, helping one of our technicians, who was also doing some basic research with me, some immunologic profiling of these patients as they were coming in. She was looking at a variety of immunologic functions in these patients. I wasn't really involved in that directly other than by giving her a little bit of advice. I had other projects that I was much more interested in.

Then two things happened to me at about the same time. I was looking at some of her data with her. At this time, we knew there was a T-cell defect and that there was a numerical decrease in the helper cells—that had been published. But what struck me from the information she was generating—no one had really looked at this—was the amazing polyclonal B-cell activation. The B-cells of these patients were just incredibly turned on, more so than in lupus patients. This was something that I had been studying in normal volunteers. I had been looking at some autoimmune diseases, but this B-cell hyper-reactivity was something that superseded any of it; so I got very interested. I then started studying the mechanisms of the polyclonal B-cell activation in patients with HIV infection. That got me going on the laboratory side of things.

Harden: Did that then lead you into the study of how the B cells were also affected?

Lane: Yes. Actually, we had a paper published in *The New England Journal of Medicine* around 1984, which was sort of the outgrowth of that work. Working on it took about two years; we did a lot of things to put everything together. But an interesting thing happened to me at about the same time that I started becoming identified as someone in the laboratory with an interest in the immune systems of these patients. I started taking a little bit more active role in looking at patients with Lynn Edgar—looking over Lynn's shoulder—and we started working on it a little bit more.

Then one day I remember I was down in the intensive care unit in Building 10, talking to [Dr.] Henry Masur. Henry said that he had just seen a patient in the clinic with AIDS, and the patient had an identical twin brother. Would I be interested in doing any immunologic studies on that patient? The thing that jumped to my mind was what a great opportunity to do some *in vivo* immunologic studies. We could do bone marrow transplantation between this guy and his twin brother without a need to ablate the patient.

There had been some attempts at bone marrow transplantation, but when you condition the recipients with cytotoxic chemotherapy and radiation, they die. This had been the experience up to this point with everyone using ablative therapy. So I was interested. This was around 1982 or 1983, I don't remember exactly. I said, "Well, yes. Why don't we bring this person in and talk to his brother and see what we can do."

So I talked to the patient and his brother and they were interested in pursuing something like this. I can remember vividly that we admitted the patient in July; probably 1983, I'm not sure. And the first thing we did was get together a group of people—Tony [Dr. Anthony Fauci], myself, [Dr.] Henry [Masur], [Dr.] Dan Longo from the [National] Cancer Institute, and someone from the [NIH] Blood Bank, [Dr.] Harvey Klein, because we decided eventually on a program where we would do adoptive transfer of lymphocytes. We would take lymphocytes from the healthy twin, give them to the patient with AIDS, and then, after doing that study, see what happened. Then we would do a bone marrow transplantation. So we brought the patient in in July; we gave him the first few doses of lymphocytes; followed what happened; and then did the bone marrow transplantation that fall, I think in September. We watched with great excitement, because we saw the T4 count come up in the patient after we infused the lymphocytes; then it went right back down. Then, after we did the bone marrow transplant, the T4 count came up and it stayed up for a

while. We were getting extremely excited. This was before HIV, before we knew what we were really dealing with. We were monitoring skin tests. The skin test response was getting bigger, and the T4 count was going up. So we were ecstatic. But then the T4 count started going down. The patient developed Kaposi's sarcoma, after which he developed cytomegalovirus [CMV] retinitis. The interesting thing was that up to this point, I had not been involved clinically. But right now I run the [NIAID] intramural clinical program, and this is how it happened. With this patient, I spent hours every day in his room explaining what we had done that day, what the lymphocytes were doing. Because I gave him the skin test myself, I wanted to be sure it was given the same way. I would give him the skin test, read the skin test, talk about something new, whatever. I would just spend hours and hours. Then, it was horrible—he started to develop CMV retinitis. That is a progressive, destructive disease of the retina where you go blind.

We tried high-dose acyclovir first, but that didn't do anything. That got me thinking, "Well, what else can we do?" What could we do? We had some work we had done in the laboratory. We had looked at some of the defects in cytotoxic cell function. You could boost cytotoxicity with interleukin 2. But interleukin 2 wasn't ready to go into clinical trials yet. We had tried hard. Humans had not received interleukin 2 at that point in time. So there was another T-cell derived lymphokine, gamma interferon. Gamma interferon had been, in clinical trials, a natural product not a recombinant product. A doctor in the Cancer Institute named Steve [Dr. Stephen] Sherwin, who went on shortly thereafter and became a vice president at Genentech, helped me in this. Steve helped me get some gamma interferon to treat this one patient. From there we developed a gamma interferon study in a larger number of patients. But the problem was that gamma interferon did nothing. In fact, if anything, it hurt these patients. In that particular clinical trial, that agent was not helpful. This is now six months or so later, and the patient's CMV retinitis is getting worse, and he is now starting to go blind. We had worked very hard to get the interleukin 2 contract in place.

We went through procurement. You know what a nightmare that is, and it cost us, I forget exactly, about $250,000 to get interleukin 2, just enough to do a reasonable clinical trial, not on just the one patient but on several patients. We did finally get all the approvals. This is about the same time that Steve [Dr. Steven] Rosenberg was starting to use interleukin 2 in some of the cancer patients. It was the exact same thing, because we were talking to Steve at that time about the best route to take, all the different products, and the pros and cons. So this same patient who had gotten the bone marrow was the first to get gamma interferon, and then the first to get

interleukin 2, in any clinical trials. He went blind from CMV retinitis with interleukin 2. We had a little bit of excitement because it has some immunomodulatory effects. But by itself, it doesn't do much either. That patient eventually died here, but in the interim, he became the impetus for looking at immunomodulators—lymphokines, cytokines—in patients with HIV infection. That work continues up through today. So, we went into interleukin 2 trials. Now we're just getting into 1984 with the discovery of the virus. From there the emphasis clearly shifted to looking at agents that could block replication of HIV. So, that's really the early story, or at least how I got involved in the things that I was doing.

Harden: Your reason for being drawn into this was very clinical. It was due to these patients that you were involved in trying to find something to stop the disease process as opposed to research on any possible causative agent. Do you remember the various kinds of theories that were around?

Lane: Oh, sure. My interest was in what was going on with their B cells, so I had a research interest that was separate from looking for a cause. Most people at that time suspected that this was a retrovirus because of what was happening to T4 cells. We knew about HTLV-I [human T-cell leukemia virus I], and we were providing samples to anyone who had ways to try and find an etiologic agent. Samples were going over to the Laboratory of Tumor Cell Biology in Fort Detrick [Maryland]. In fact, they had some isolates at Fort Detrick shortly after [Dr. Robert] Gallo's paper in *Science* came out. So that actually was an independent confirmation of a retroviral-like agent from samples from these patients. We were helping to support that type of work, but we were not doing that type of work ourselves. What we were doing was trying to characterize immune defects.

So while all the clinical work was going on over here, we were looking at the B cells and describing their activation. Since it was a T-cell disease, for the most part, we were trying to focus on the nature of the immune defect. We were then able to home in very precisely, in a descriptive way, and say that the defect was an antigen- recognition, antigen-induced activation. This fit in nicely with what I had been looking at earlier, which was the role of KLH [Keyhole-limpet hemocyanin] and a specific antigen with the adult's human immune response. If we could immunize the patients with KLH, they would make no antibodies, and therefore they would have no T-cell responses.

It was mind-boggling looking at how immunodeficient these patients were, because I'd been seeing normal volunteers for three years, and I knew what someone should do when exposed to this very potent immunogen. We

would immunize the AIDS patients, and they would have no reaction. It was very fascinating because it was the first time that people were looking at that. You just don't expect it. Now, it's "Oh sure, of course." But when it was happening, you were saying, "Wait a minute, I immunized this guy with five milliliters of KLH; he should have 18,000 units of antibodies." But there was nothing. Their T-cells don't respond. At that time, we didn't have flow cytometry the way we do now. We were doing laborious physical techniques, like separating the helper cells from the suppressor cells. We were studying them separately because people thought there was too much suppression with the imbalance in the helper-suppressor ratio. We worked on that and looked at these cells. Clearly that wasn't the case. You could tell. The suppressor cells were there, in fact, they should have functioned normally, but they couldn't without normal inductive signals. It was the lack of that inductive signal from the helper cell that was the defect. So, that was work that we did. That was another *New England Journal of Medicine* paper that came out. I think it came out in 1986.

Rodrigues: Are you saying that work helped to define the understanding of the component of the immune system that made those responses possible? If someone told you at that point that HIV was knocking out that particular cell, would you have known that that was the reason that there was this complete lack of immune response, or was the role of that particular cell not known yet?

Lane: I would say that the level to which that cell population was affected was not understood at that time. We knew the numbers were down, but we didn't know that there was not only a decrease in numbers, but really a selective and very precise functional abnormality in the cells of these patients. Now, there is a ton of literature proposing hundreds of hypotheses describing thousands of immunologic quirks of these patients. You take the T helper-inducer cell and you eliminate it, and it's sort of like taking a symphony orchestra and shooting the conductor and not telling them the score to play, and then saying, "O.K., play." So some people are playing Beethoven and some people are playing Schoenberg; the thing is all discombobulated, and that's what happens in AIDS patients. The helper-inducer cell can't recognize specific antigen, as a result of which it can't call different elements of the immune system into play the way it should.

Harden: Is there some reason it can't recognize it, other than because it's been destroyed?

Lane: That's still unclear. It appeared that the memory subset of CD4 T cells is selectively destroyed by HIV. That's the way it appears right now. So it

not only hits the T helper cell; it hits just that part of the helper cell you need to respond to recall antigens at the T-cell level. Everyone is probably exposed to *Candida* and *Pneumocystis* early in life and has memory cells to them. You have to believe that they are not well-described, because with these suppressed T cells, why do you get such profound problems with those [infectious] agents—not just in AIDS patients but in other patient groups as well.

Rodrigues: I think it's interesting the way you describe the different types of collaborations that are going on here—you mention folks in Critical Care Medicine; you mention folks in the National Cancer Institute. Some of the people that look at NIH from the outside don't appreciate the diversity; they tend to compartmentalize people in groups. Could you say a little bit about…

Lane: Sure. The early days of AIDS were great in that regard. The early days were really very nice because everyone was excited and everyone wanted to figure out what was going on. Everyone had their own different little area of expertise. [Dr.] Henry Masur had taken care of AIDS patients in New York and he was here. Over at the FDA, a guy named [Dr.] Alain Rook, working with Jerry [Dr. Gerald] Quinnan, had expertise in cytomegalovirus and the immune response to cytomegalovirus. They were interested in studying the AIDS patients as well. You had people like myself who were immunology-oriented. There were people from the Cancer Institute—Ed [Dr. Edward] Gelmann, who had been in Bob Gallo's lab working on HTLV-1, had left Bob and was over here [in the Clinical Center], with an interest in the retrovirally induced diseases. He was working on AIDS before we knew it was a retrovirus. And there were people like [Dr.] Dan Longo, who were a little bit more peripheral at that point in time. Dan was interested in lymphomas and chemotherapeutic regimens, trying to make some contributions. So, there were a lot of people with different backgrounds coming in who were thrown together—not just from NIH, but from the FDA as well. [Dr.] Abe Macher, who was down in Anatomic Pathology at that time, had a strong interest in what was going on. Abe is one of the people who was bringing cadavers in to try to understand the disease. He would bring cadavers, from all round the country, to try to see what kinds of problems the patients had died of. He was doing his fellowship in pathology at that time. He had already done a fellowship in infectious diseases. There was a lot of interaction like that. That was a good time, I think.

Rodrigues: Sounds as if there was an informal network of people that gradually came together.

Lane: Exactly, exactly.

Harden: Was there any connection with people at the CDC [Centers for Disease Control and Prevention] on AIDS—or were they basically doing epidemiology, and therefore, not seeing clinical patients?

Lane: Well, while they weren't seeing patients, they certainly were doing their own research. But until we had a virus, it was a lot of shots in the dark. I would see them at meetings. The meetings were so different; the meetings were small. The meetings were small and they were fairly intimate, where there were good exchanges of information. There you would interact with the CDC people. I can't remember talking with anyone from CDC up here myself. But then we weren't doing things that really were pertinent to them. When we had the virus, the guys from the CDC were up here all the time, talking to Bob [Dr. Robert] Gallo about samples of some coded sera and what he could tell from those sera. I remember seeing them in the cafeteria and talking to them about what was going on. They were very excited.

So, it was, as you say, sort of an informal network of people who began to interact. Those of us who were taking care of patients started to have weekly meetings where we got together, and we started to use some electronic databases to keep track of what was going on. Then it started to expand. The guys in the NCI [National Cancer Institute] were initially looking at lymphoblastoid interferon to treat KS, Kaposi's sarcoma, and I was doing the immunologic monitoring on those patients. It worked out well, because it was the sort of thing where one person couldn't have set it up because it requires too many things, but we had people who knew enough about the different pieces. We needed oncology, we needed infectious diseases, we needed immunology—and we had all of that here. We just fit the pieces in, and I think made a lot of progress pretty quickly.

Harden: I think one of the things that we are very interested in is trying to get a picture of just how this process worked, because I think many people and journalists don't have a sense of how it works. They have a sense that perhaps the way the government deals with things and should deal with things is by appointing a committee that will then direct things. This is not what we are hearing.

Lane: Oh, not at all.

Harden: It begins at the grassroots. Everybody finding people when they needed them.

Lane: We did that because we wanted to do it. No one said to me: "Listen, you have to work on AIDS now." No one said that. The people were here because they wanted to [work on HIV/AIDS]. That's your best incentive to get people doing something that they like and they enjoy. As I say, it was just the right mix needed to get a productive effort going. There was a lot of collegiality; Henry [Dr. Henry Masur] and I still work very closely together. We built the NIAID intramural clinical program. It's my program and his program that stemmed from all of that. NCI had to develop their own intramural clinical program as that process evolved. But some of those things still exist from the past.

Harden: Did you have any trouble getting support from Ken [Dr. Kenneth] Sell and [Dr.] John Gallin over this period?

Lane: It was great. I can remember, when you say the word "bone marrow transplantation," you think of a lot of money. Here, it was no money at all, because no one was charging anything. We got the beds and everything else. It was sort of a fixed cost for us, the way we work. When it came to the interleukin 2, I can remember calling this person or calling that person. Finally after getting this astronomical figure, I remember talking to Tony [Dr. Anthony Fauci]. I said, "Well, let's go talk to Ken Sell." Ken was here at NIH. He was good; he made a great contribution that I don't know will ever get recognized, because it wasn't a publication or anything like that. But he saw the importance of AIDS. He put the resources into it. We went down to his office and explained to him why we wanted to use this [interleukin 2]. He said, " Two-hundred-and-fifty-thousand dollars—well, sounds like it should be done. We'll do it." I don't know if you went over to Dick [Dr. Richard] Krause and Chuck [Charles] Leasure, who was the executive officer at that time. I don't know where the money came from; it wasn't from a Congressional appropriation. Somewhere there was the money and we were able to get it. It wasn't a problem. Do you know Ken? Have you talked to him?

Harden: Yes.

Lane: So he got the lab going over there; he brought the people over to culture LAV [lymphadenopathy-associated virus]; he put the resources in to get the thing. He really played a major role in getting the Institute galvanized. It was my perception that he was instrumental in getting this MACS [Multicenter AIDS Cohort Studies] work going. He said that we needed to look at these people. This was before HIV. This is not my approach to science—"Hey, I don't know what it is, but let's get 6,000 gay men and collect every secretion from their body and freeze it, and some day it will be useful." But that's important to do. You need someone at that high a

level to get it done. He was very instrumental and very supportive. I give him a lot of credit. It's a tough position. Everybody wants something from the scientific director. He clearly made this priority, and I was impressed by that.

Rodrigues: Do you remember any particular meetings at that time that were important in helping you make intellectual progress on these problems? We've heard people mention a number of meetings. There was one meeting in New York, I believe in 1982, that people have talked about as a very important meeting.

Lane: I think I know what meeting it was. The New York Academy of Sciences? I think these are the proceedings from that meeting. I didn't find that meeting to be particularly enlightening, to be honest. I found that meeting to be anecdotal. But it was the first time, I think, that a large group was brought together to discuss the problem. I was at that meeting, but I just didn't get that much out of it. I generally knew what was being said, because it wasn't a very scientific meeting. What I'm saying is that there was a lot of description. This is what Kaposi's sarcoma looks like. This is what *Pneumocystis carinii* pneumonia is. But then what? I guess that was all that could have been said. I wouldn't say that was a key point in my academic development.

Now, a meeting that was important, and people will probably mention, is the Cold Spring Harbor meeting shortly thereafter. That was a group that [Dr.] Bijan Safai put together. I don't have the proceedings from that. I don't know whether there were proceedings from that. That was the first time people talked about a retrovirus. Some people from [Dr. Luc] Montagnier's group presented some data, saying that this might be something. [Dr. Robert] Gallo was there presenting the stuff they had at that time on HTLV-I and serologic cross-reactivity. We presented the polyclonal B-cell activation for the first time there. There were a lot of things, as you start to think more. We were talking about acid-labile interferon being elevated—a lot of things that weren't generally known were coming out in discussion. It was a fairly informal setting. We met, had presentations, discussion, ate meals with these same people. We were there for about two-and-one-half days. I remember driving in from New York. It was snowing very heavily. I was in the cab with Marty [Dr. Martin] Hirsch who is a virologist from Massachusetts. I just can't think who the other person was. There were three of us in the cab. It was snowing so hard that the cab driver had to pull over, so he took us all out to a bar. We were sitting there discussing AIDS, well, trying to, because we didn't know anything about AIDS then. We had seen a few patients at most. But I remember those times so vividly.

Harden: That brings another question in my mind. How fast was research moving here at NIH as compared to the other places?

Lane: Well, this is awful to say, I guess, but I think that we were light years ahead. I think we were moving extremely quickly.

Harden: Is that because they needed to apply for grants to get money and so couldn't get moving, whereas you could?

Lane: I think so. I don't know. I don't think that the people weren't qualified. I think they were qualified. That's the strength of NIH. It's a horrible thing for a taxpayer, but if tomorrow I wanted to do something different, I would do something different. When I got reviewed by the Board of Scientific Counselors, they might recommended that I get the boot. But nonetheless, I have that sort of independence, that freedom where I feel I can do that; I can do something new. You can move quickly into something new, as long as you have the support, like we did from Ken [Dr. Kenneth] Sell. That helped us moved very quickly. We really did. The funny thing is that we moved quickly, but it's not as if we got space all of a sudden, or we got people all of a sudden. Those were very tight constraints. FTEs [full-time equivalents] were like gold; they still are, but not for AIDS. We've had it pretty easy going for the last several years, and we've been able to build because of that. We've gotten money, space and FTEs in the last few years. But in the early days, we didn't have any of that. We just had our own initiative to move into new areas, and that was supported. That was good. NIH moved extremely quickly, and despite all bad things that people write about what went on here, I think we moved very, very quickly. I think we made a contribution because of that, which I don't think any other place could have made. We had patients here, we were seeing the patients; we were trying to find [etiological] agents, trying to understand the immune system, and a lot of good work got done. But, you know I'm totally slanted.

Rodrigues: Given the criticism that was coming from different quarters, how did that affect you and some of your other associates? Was it troubling to hear people on the outside saying things such as: NIH didn't know what it was doing; the effort was completely disorganized; or there was no leadership?

Lane: It was a matter of looking at where those comments were coming from. That never bothered me, I have to say, because I never felt that way. I never felt that was going on, and I didn't feel if an objective person came in and looked at it, that they would feel that way either. Yes, there was a need for so much, but one place could only do so much. One disease has

so much priority in the public health of the nation. When I looked at it and tried to put it into perspective, I thought we were doing a good job from that point of view. The people who were very critical were often from the lobbying groups, the gay community. I can understand them wanting more, more, more. They were saying what I would have said were I in their place. You have to be on one side or the other if you want to make change. They wanted to make change, and I understood what they were saying. It didn't make me feel persecuted. We were seeing a lot of gay patients. I knew very little about the gay community; I became very good friends with the local gay community over time because of what we were doing. I found them very supportive of what we were doing. The criticism to me wasn't directed at NIH or the scientific community. It was directed at the government, the Congress. That was how I felt it. I didn't feel it personally as someone at NIH.

Harden: This is what I feel. I think sometimes the blame is displaced onto the wrong agency of the government. I've been attacked on occasion because I was representing NIH. The political process sometimes is what people were unhappy with, the leadership at the top. Not to mention frustration because their friends are dying. People observed this same phenomenon with the Three Mile Island incident; the CDC apparently couldn't even get in and do studies because the people wouldn't talk to them because they were the government and these people were so unhappy with government.

Rodrigues: Leading up to some of the work that you're doing now—given the availability of therapeutics—probably with AZT [3'-Azido-2',3'-dideoxythymidine] and ddI [2',3'-dideoxyinosine], if you repeated the same bone marrow transplant experiment how do you think it would turn out?

Lane: Well, we've done that. I can answer that precisely; it would not have turned out differently. We still don't get rid of the virus. The virus is still there. You can get transient improvement in immune reconstitution, although with time it still falls off. You're probably aware of the one experience at [John] Hopkins [University] where they claim eradication of HIV. I don't know; only time will tell if that's accurate or not. I tend to be skeptical of it; because I don't think you can eliminate every infected cell—just some cells. The monocyte/macrophage reservoir is going to be resistant to those types of ablative therapies. The risk to that patient was great. That patient died shortly after the conditioning regimen, 44 days, or whatever it was. In any event, we have repeated that work; and in fact, that work goes on.

I'll tell you what we're going to do next. We looked at AZT plus bone marrow transplantation plus lymphocytes in syngeneic twins. Actually, we

have a paper in review on that right now. We did sixteen [such transplants], because we thought we had some good results with bone marrow transplantation alone, and we knew that there were good results with AZT alone, so we put the two together and thought we might be able to get something more substantial. We really couldn't. What we're going to be doing next is looking at a combination treatment regimen of AZT plus interferon plus [soluble] CD4 to try and block the virus. What we're going to do now is see how it all fits together. That's one of the nice things about it. We're also doing a Phase I vaccine trial with gp160, a full-length envelope protein. We now have good dose-ranging data on that toxicity, so we know how to immunize someone to gp160. We don't know if that protects them from HIV, but we know how to immunize someone to gp160. We're going to immunize the [bone marrow] donors to gp160, so the immune system we transplant, the lymphocytes we transfer, will be primed to gp160. We'll have an immune system that we're transplanting that's already primed to at least some of the antigens of HIV. So, those are some of the things that we're doing differently. But that is where that work is at present. Plus, there is one other thing we're thinking of doing again with Mike [Dr. Michael] Blaese and [Dr.] Steven Rosenberg in the Cancer Institute. They have techniques for growing enormous numbers of cells, these TIL cells—tumor infiltrating lymphocytes. We've talked about getting some gp160 cell lines or clones from our immunized donors who have the identical twins. We will grow these clones, or those cell lines, and then infuse those into the HIV-infected people. The foundations for many of the things we are doing now were back in those days when we didn't know what we were dealing with. We were looking at it as an immunologic disease and trying to come up with strategies.

Harden: This then moves into my next, two-part question. I was reading Bill [Dr. William] Paul's presidential address to the Society of Immunologists, and one of the things he was saying was that, at that time, immunology lacked a quantitative approach. It was pretty qualitative but not quantitative. What kind of impact has AIDS made on improving immunological knowledge, in general, and quantitative knowledge, in particular?

Lane: That's a very good question. I think it will, but it hasn't yet. I'll take one thing that AIDS has done for immunology. It has justified all the FACS [fluoroscent-activated cell sorters] that were ever made, and all the monoclonal antibodies that were produced. The T4 [CD4 cell] count of value is an example where the clinical immunologist can really play a major role in helping management of the patient. When the count goes below 200, that patient is at risk for *Pneumocystis carinii* pneumonia. If that count is above 300, that patient probably isn't going to get *Pneumocystis carinii* pneumonia. So that is a very quantitative assessment

of immunologic function based on the number of circulating CD4 cells. I don't think that is what Bill is referring to in his presidential address, but at least it is a quantitative assessment. What I think we will learn from the study of patients with AIDS and HIV infection is the precise role of the CD4 cell and its subsets in regulation. The way we'll do that is as we find out, as the memory clones are selectively infected. But others are infected as well. If we take the elements that are infected away, and then try and replace in some more precise fashion different elements of a specific immune response and try to rebuild what was destroyed, I think we can. It will help if we get some quantitative information about which cytokines are important. So basically we have an experiment of nature where there is a selective injury at least early on, and I think the more selective the injury is, the easier it is to find it. We will be able to do that with time. We haven't done that yet; we've described it, but we haven't really understood it. So I think we're still at that point.

Rodrigues: Another question I have has to do with the CD4 receptor. What normally hooks on to the CD4 receptor?

Lane: A class II MHC [major histocompatibility complex] molecule; it's felt to facilitate or stabilize cell-cell interaction. So, if you have a cell that's presenting antigen to a T lymphocyte—let's take a monocyte or macrophage—that cell will engulf, let's say, a foreign protein. It will digest it into fragments, and some of those fragments will bind inside the cell to the class II MHC molecule. Then antigen and class II MHC will be presented on the surface of the monocyte or macrophage. CD4 cells recognize antigen in association with class II MHC. The T-cell receptor will bind to the MHC-antigen expressed complex, and then the CD4 receptor will bind to class II to stabilize that cell interaction. Now CD8 plays a similar role for the CD8 cell in class I MHC, so in the induction of a CD8 response, we generally have a protein made within the cell, like a virally infected cell making viral proteins. Those viral proteins will associate with class I MHC and be expressed in the surface of the cell; the CD8 antigen receptor will recognize antigen in the context of class I MHC, and then CD8 will bind to MHC class I to stabilize that cell-cell interaction. It doesn't appear to be in the place of CD4-class II MHC complex; it doesn't appear to be an essential binding to get cell activation. Blocking that interaction is what happens in AIDS—the cell is infected and destroyed. You can block that interaction with soluble CD4, for example, and you still get antigen presentation and antigen activation. Well, does that answer the question?

Rodrigues: Yes it did. Is there much variation if you look at a CD4 receptor? Is there variation in the molecular structure of that protein?

Lane: There is. In fact, there's a very common variant of CD4 receptor seen in the black population, and I can remember an interesting experience with this. This has been recognized for about four or five years. We were studying a patient with HIV infection—he was a black patient with KS and with no CD4 cells, and I, of course, said, "Well, this patient, immunologically, looks very bad. I think he is at high risk for infection." Four years later, the patient is doing well. What it turned out to be, I don't know, maybe it was the case with this patient. In the interim we learned about the Leu-3A antibody. Leu-3A is the CD4-HIV gp120 binding epitope. That epitope, one of the classic and first antibodies used, was made by Ortho. Leu-3A antibody used in CD4 cell tests recognizes an epitope on the CD4 receptor that a certain percentage, maybe 5 or 10 percent, of the black population don't express. So there is some heterogeneity there. I don't know anyone who has had heterogeneity in the HIV binding site, which is in the fourth domain. I've never heard of a naturally occurring mutation in CD4 receptor that prevented the binding of HIV, but that certainly could be possible. To answer your question, yes, there is some heterogeneity within that molecule.

Rodrigues: Have you had any interaction with or involvement in the international arena? This seems to be one components of this whole story, that hasn't been covered as well as we think.

Lane: Well, you're going to get a story now. I guess that's what you're after. This was either in 1983 or 1984. Dick [Dr. Richard] Krause could probably tell you exactly. The decision was made from the NIAID director's office— Dr. Krause's office at that time—that it would be important for NIAID to send a group of people to Haiti, because we had this disease. It was before HIV—it must have been 1982. It must have been 1983, I guess. I don't know. In any event, he wanted to send one person with clinical experience, another person who knew immunology, and a third person who knew epidemiology to accompany him to Haiti. I got a call and was asked if I would be interested in accompanying the director on the trip. I was just out of my fellowship at that time, totally awe-inspired, but to be honest, I really had no desire to go to a country that might be the seat of AIDS. I enjoyed studying in my own controlled laboratory, and I didn't want to go to some hotel where I wouldn't know how the water would be. So, I said, "No thanks. I'd really rather not go." And they said, "Well, we'd really like you to go." I said, "Really? I'd rather not go." I heard this second-hand, but I believe it's true, knowing him. When he got the second refusal, he said to someone—Ken [Dr. Kenneth] Sell, probably—"Is Dr. Lane a member of the Commissioned Corps of the Public Health Service?" Dr. Sell said, "Well, yes, he is." He

[Dr. Krause] said, "Well, then, I'm ordering him to go." So, I thought, "Oh, what the heck. I'll go on and I might as well make the best of it." So, I packed up my suitcase with water and candy bars and headed out with them. We went down to Port-au-Prince, and it was a very enjoyable visit. I had to come back and give a lecture. In fact, I ended up there a day by myself. We met with the ambassador and the minister. It was one of these official type visits that I don't really find a lot of fun. We got into the hospital a bit and actually saw a patient—a woman with very severe genital herpes. So, when I came back after giving the lecture, we brought some intravenous acyclovir down. I then saw when they were ready to put the IV [intravenous line] in, they had this jar of straight needles. I mean, not butterflies—just straight needles that they reused. It was just so enlightening to me—my having only seen medical care in the United States—to see the bedpan, buckets, and flies. This was a University Hospital—an open-air hospital. They had private clinics that were quite a bit better. Seeing them, and talking with people down there, made an interesting story for me.

In any event I thought we really hadn't gotten into it. We had met all the officials and been to the hospital. We hadn't really met the people. It's somewhat of a ritualistic society. There still is quite a bit of the African culture there. They have the Hoogan, which is the witch doctor that many people trust. Many people go only to the traditional doctors *in extremis*, and then there's not much that can be done. In any event, I was there by myself for the last day, and I was talking with an immunologist down there, [Dr.] Robert Elie. A cab driver was driving me back. This is an awful story but it's sort of funny. Driving me back, the cab driver looked over at me and he said, "Would you like to meet some nice Dominican women?" The Dominicans are fairer-skinned than the Haitians. I thought, "Oh, God, what have I gotten myself into?" It then hit me, "This might be my chance to meet some people." So, I said to him, "No, but would you know where I might meet some men?" I took the chance. He was shocked. I explained to him why I was there and why I made that request. He'd actually seen something about this on TV. We'd been on TV when we arrived. So, he took me to one of the Hoogans, witch doctors. So we were sitting down, talking over rum and coke. He'd seen these people with fever and said he could take care of them; he used a special extract from the aloe plant. So I said to him, "Are there gay men here? You hear that there are. But we haven't seen any. Could I meet some gay men in this area, just to talk to them and their friends?" So, he [the Hoogan] talked to the cab driver in Creole, and the cab driver took off and drove me around. I was really getting a little bit scared because we were in a part of the city that is pitch black. They shut the electricity off in parts of the city at night. It was pitch dark and I didn't know where we were. He stopped the cab.

We got out of the cab and knocked on this door. It had a little slit. Somebody came up and opened the slit, and they spoke Creole back and forth. I have no idea what they said; finally the door opened. The guy on the other side had a gun tucked into his pants, and I thought, "Oh, my God, they are having me assassinated, or something. What have I done now?" But everyone was pleasant; no one looked sinister. They all looked pleasant. We walked in; went through another door and there was this neon sign saying, "Ricky's Tropical Bar." So, I was in a resort where there were only two people, who both worked there. There were no tourists. I was trying to get information, like "Have you seen any new diseases?" etc., etc. We had no luck; no luck at all. So, we left there and he [the cab driver] tried to look for another place; he couldn't find it. So the cab driver stopped and picked up a male prostitute to help us find another place. That was a little uncomfortable. He put his hand on my shoulder and said, "Well, I'll come see you tomorrow." And, I said, no, I was leaving the next day. In any event, he took us to another place that was closed. Just closed. We were knocking on the door. A man on the roof, with a rifle, yells down in Creole back and forth. Then the cab driver said, "They're closed until Saturday. Only opened on Saturday." So, all I could glean was the gay tourist trade had gone down, but I really got no information about whether or not there was a new disease. There clearly was one, but the question was, whether it in gay men, or in the general population. That was a question that remained unanswered at that point, which later on was answered to be found more in the general population. It seemed more like the African picture than the picture in the United States. But that was my one experience over there. When you said international that's what you meant? You didn't mean international conferences, right?

Rodrigues: Right.

Lane: The other thing that I did, subsequent to identification of the virus, was go to Khartoum a couple of times. I had a friend in the state department who was stationed in Khartoum. That's in the Sudan where the White and Blue Nile come together to form the Nile. I had mentioned to the associate director for international affairs that if they ever needed someone to go to Khartoum, I would be willing to go because I had a friend there. So when they were setting up some collaborative agreements on a variety of infectious diseases, they asked me, since they needed somebody to go over and see what capabilities they had. I went over there and met with some of the people in the Sudan and helped them establish their AIDS advisory group. They are a fairly progressive country. I wouldn't have thought that from what I read about it in the newspaper. When it came to health matters, they were actually quite progressive. It was an English colony, so it was easy to communicate. Most of the people spoke English, actually

spoke fluent English. The second time I went over, we had sent some equipment over to help them set up an HIV testing lab. I actually did a TV interview live. Until they told me, I didn't know it was a live TV interview. In there, I mentioned how the disease was spread. At that time, it was still a very strict Muslim society, so they weren't real open about some of those things in public. But privately, they were a fairly progressive society. That was enjoyable. I still have contact with the people over there. More recently, I've been to Russia and Poland on a collaborative agreement between the United States and the USSR [Union of Soviet Socialist Republics]. That was sort of interesting, but no where near as exciting as my other two trips had been. It was much more predictable.

Harden: One of the major problems that you're pointing out seems to be the general level of hygiene in the hospitals was a major factor in the transmission of AIDS.

Lane: A guy in Poland brought it all home to me when I was saying, "Well, you know, what are you going to do about this [AIDS] and condoms and AZT...," and he says, "Listen. People can't eat. You have got to put it into perspective." I was there in October, so this was during their transition. He was an academic surgeon and was going to be joining the Ministry of Health in the new government. Clearly, the problems of health care worldwide are great, and AIDS is going have a major impact on them. You have to be ready for it; but the pressing needs of today sometimes make it hard to look at tomorrow.

Rodrigues: Well, I think that finishes my questions.

Harden: I was going to ask about where you are and where you see research in the future. Is there's anything else you want to bring up?

Lane: I can tell you where I'm going—that's sort of pleasant aside. As you said, there has been an evolution in immunology over the last few years. Taking cells and describing what they did has gone quite a different way with the identification of the virus. What I'm currently doing is taking different genes of HIV, transfecting them into T-cell lines with known function, and then studying how those functions are altered by infection or transfection with the different HIV genes. Clinically, we've grown from Henry [Dr. Henry Masur] and myself seeing patients in clinic to a much larger scale. I don't know how many people we have, actually. We currently see about 400 patients a month in the outpatient clinic, which for NIH is a lot of patients. We're moving from the 11th floor—half of the ACRF [Ambulatory Care Research Facility] Clinic on the 11th floor, to

the entire ACRF clinic on the 8th floor. We have a good integrated team with primary care being delivered by registered nurses, with the physicians to back them up. We're actually trying to model the best way to do clinical research. A side contribution we can make from the resources we've gotten for AIDS is to try and help people in other settings as well by looking at as many things in experiments as we can. So we look to therapeutics now with combinations blocking different stages of viral life cycle, and also look at antivirals plus immunologic reconstitution. That's where things are.

Rodrigues: That prompts one other question for me. How did you go from the informal network of collaboration to the formal group that you have now? Was that a process of people finally saying, "Look, this has gotten too big for us to handle this in an informal way. We need a more solid administrative structure to handle this activity?"

Lane: It just happened over time. It's happened gradually. There was no decision to do things differently. The first thing that happened was we approached the Clinical Center Nursing Department to give us two nurses dedicated solely to AIDS, for whom we would develop a new role. That role now has the name of case manager and is taken from other similar roles where the nurse provides the primary liaison between the health care team and the patient. We did a study with a drug called HP-23, using that model. That was the first time we tested something over there with that particular model. The model worked well, and then it went from two nurses to four nurses. Having got the four nurses, we said we really needed to have a head nurse to help supervise and six to eight other nurses. Then we needed one to run the studies; we needed study coordinators; nurses at a higher level; seven study coordinators, and then Henry and I needed more doctors. We couldn't spend all of our time taking care of patients and still get other things done. So we hired an additional four doctors to help do a rotation; so, it just grew. It wasn't anything that happened as an event. It just expanded gradually, just as I was finishing my fellowship. Now I have more people that I'm responsible for, and my ability to just go over and talk to somebody has just diminished some. That I don't like very much and so I try and recapture it. But I have a hard time doing so because there's always some administrative detail that has to be taken care of.

Rodrigues: Is that's why when we were talking about the earlier days, you referred to them as "great days"?

Lane: Yes. I have fond memories of the time when the work was so much and administrative stuff was so little. Now it's a little bit different. We're still

trying. I enjoy seeing people who are coming in now being able to do that. I think it's very important to maintain a multidisciplinary approach. So we have now people from NIMH [National Institute of Mental Health] come in and help us with neuropsychology; people from NIDR [National Institute of Dental Research] look at oral manifestations of HIV. There's an interest and a discipline to not just do it, but to do it the right way—identify who's going to have the leadership role and make sure that people funnel in through that person and try to maintain that same sort of esprit d'corps in clinical areas.

Harden: We thank you very much.

Lane: Sure, it was fun for me too.

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