This is the second oral history interview with Dr. Robert Gallo of the National Cancer Institute about the history of AIDS at the National Institutes of Health. The date is 4 November 1994. The interviewers are Dr. Victoria A. Harden, Director, NIH Historical Office, and Dennis Rodrigues, program analyst, NIH Historical Office.

Gallo: Before we go any further I thought it might be useful to offer greetings to my unauthorized negative biographer, Mr. Crewdson. I know he will be interested in this program, as he has been interested in so many other things. I just wanted to say that I appreciate the unique honor of being the sole [person] followed now for eight years in a row. This is even more years than the bobbysoxers followed Frank Sinatra. I think I am paralleling Elvis Presley in having attracted the interest of an individual for this many years, so I wanted to thank him for this honor.

Harden: Dr. Gallo, when we ended the first interview, we had set the stage for the discussion of AIDS. We had talked about when [Dr. James] Jim Curran [of the Centers for Disease Control] came to the NIH [National Institutes of Health] and was prodding you to go into AIDS research. Much of your early work has been detailed in many different places--in your book and in a variety of other publications--so what we would like to do in this interview is to have a few points amplified, not to attempt to recount all the facts.

One of the key questions that has come up over and over again is how, when a new disease appears, can it be demonstrated

that a particular agent is the cause of it? Chronologically, the French isolated their virus, LAV, in 1983, but they did not demonstrate conclusively that there was a causal link [between their virus and AIDS]. You waited until May 1994, and then published four papers in Science to do this. In fact, you wrote to [Dr.] Jean-Claude Chermann noting that you wanted to wait to publish in order to obtain a certain number of papers to establish the etiology. Why did it take four papers to establish it and what particular points were you trying to make with those papers?

Gallo: That is a good question. First, it did not take four papers; that was just the number that Science accepted. It is a large number obviously. We wanted to get the maximum [amount of] data published in as rapid a period of time in the most visible journal that we could. In fact, we sent a fifth paper with more antibody testing [data] in it, at almost exactly the same time, to the Lancet. It was a paper by [Dr. Bijan] Safai, a clinical collaborator, myself, and my colleagues, in which there was 100 percent accuracy in blind testing of patients with AIDS for antibodies, the tell-tale sign of the infection. Let me just say that there is nothing magical about having four, five, or six papers. There was a lot more data from many other collaborators, including the CDC, that we did not include in those five papers, but that we had in hand and were ready to write up in subsequent papers.

The question you asked is interesting. John Cohen of

Science asked me the same thing following his long interviews with and questioning of Peter Duesberg. That [article] will come out in Science within a week or two. So I have had a chance to think about that question again. John said to me, "Obviously things pointed to the cause steadily thereafter, but how did you know that soon?" The answer is something like this. Somebody like Duesberg focuses on the .01 percent uncertainty, or the 0.1 percent [un]certainty, but most scientific answers that you obtain related to a human disease--and very often in many aspects of science--are never 100 percent certain. If, let us say, you were 99--I think I was maybe 99.9--percent sure [that the virus was the cause of AIDS], you would have to act. The alternatives were not good. I felt as confident as I had ever felt about anything at the time, and the reasons were as follows:

First of all, this was a new kind of virus. That was already established in the paper from the Pasteur Institute in 1983. We could certainly confirm, and extend [our knowledge], by greater characterization of the virus, that this kind of virus was new. It certainly was not HTLV-I. It was not HTLV-II, and, if it was related to them, it was distantly related.

Second, we demonstrated that it [the virus] targeted the CD4+ T cell, and we learned from clinical people that this [AIDS] apparently was a disease chiefly of CD4+ cells. This fitted.

Third, it fitted with our hypothesis that a variant of a certain kind of retrovirus might produce immune deficiency. This was based on the feline leukemia virus model in early work from Glasgow by the Jarretts [Drs. William and Oswald], and work by [Dr. Myron] Essex and others in Boston that modification of feline leukemia virus could produce an immune deficiency. We were thinking that this was a retrovirus that might either be distantly related, or more closely related, to the HTLVs, and there was precedent for modifications of such viruses being able to cause immune deficiency. Along those lines, we knew by 1984, from the epidemiologists, that the disease was transmitted by blood, by sex, and from mother to child. We knew that retroviruses were, in general, often transmitted that way in animals, and certainly we knew that [occurred] for HTLVs.

Fourth, we obtained a very large number of short-term isolates of the virus--let us call them detections--or what I sometimes would call a true isolate, where we could transmit the virus, as well, or keep it going for a while, in association with AIDS. The French group's paper was on a patient with lymph gland enlargement. That patient did not have AIDS. He did not develop AIDS until many years later.

What we were trying to do was establish the linkage [of the virus] to AIDS itself. So, after the first paper, the second paper,

which I co-authored, was [on] establishing frequent isolation, or short-term culture, of the virus in a great number of people with AIDS or [who had] the symptoms before AIDS, [which] at that time [was] called ARC (AIDS Related Complex). We published on 48 such detections or isolates, and that gave us a lot of confidence that we were finding it in many people with AIDS. Not 100 percent [of the people], but that is easy to explain with the technology at the time. Yet, in healthy donors we could not isolate the virus, and a tremendous number of attempts [to do so] were made in a variety of blood cells from a variety of normal donors. I cannot remember if we included [donors with] other diseases, but the association with AIDS was dramatic.

Fifth, or whatever number I am up to, we developed a blood test--I will not go through the technology that led to that, perhaps we have discussed that already--but we established a very sensitive and specific blood test in which we brought the Western blot [test] into clinical medicine for the first time. We based it on an ELISA and a Western blot and we based it on the ability to mass produce the virus in continuous culture. We knew, although obviously, in retrospect, the public health people were not aware of this, that antibodies meant active replicating virus. In many other viral diseases if antibodies are present, you may simply have been exposed [to a virus], but in animal retrovirology and HTLV, we knew

that the presence of antibody for any length of time definitely meant infection with a retrovirus. By the time you mount an immune response, you have integrated the viral gene, so you are infected, and when you keep antibodies at a moderately high level, you are replicating virus. So we knew that [the presence of] antibodies was equivalent to meaning that there was active replicating virus. I repeat that some of the public health people did not know this. I remember one of the first difficulties I got into in debating [the cause of AIDS] was when an epidemiologist on the West Coast said, "We do not have any idea what is the meaning of the antibodies." I responded, "You may not, but we do." It was important and it meant active infection.

What then did that antibody test tell us? It told us that 90 percent--at the time 88.9, 89 percent--then in the Safai study, we already had the data of 100 percent from blind studies that if you had AIDS, you had antibody, and you were infected with this virus, whereas if you looked at the healthy heterosexual population antibody was very rare. I think in the total sera we had--remember we only published part of the data in Science because of authorship problems--people forget the reality that so many people want and deserve first authorship and we had to divide the papers--but all together we were holding in our hands, I suspect, somewhere upward of 1,000 to 2,000 tests of healthy

heterosexuals in which antibody was rare. I think it was only once or twice that we found antibody. I do not want to make this an official [record] of the exact number [of test results that] we had, but it was large.

Now, in the midst of this [research] we looked at what were known as the four "H's" at the time--people who were having a high incidence of AIDS--homosexuals, hemophiliacs, heroin addicts, and Haitians. In collaboration with a wide variety of groups, we had shown and we had the data in front of us--part of which was published in the Science papers, part of which was published later--that all these groups had a very significant percentage of people positive for this new virus, in contrast to people not in the risk groups at the time, where it was rare. This was perfectly compatible.

Sixth, we had data we did not publish, from collaboration with the CDC. I cannot remember exactly when we got this data, but it was early. The data was that blood transfused from persons who had AIDS--I think the numbers were small, but it was like six out of six--were all positive. People without AIDS who received blood were negative. But what was more interesting, the people who received blood who were positive--who had AIDS--had one or more donors who were positive and who had AIDS, whereas if you looked at the blood donors in general it was unusual to find a

positive. This was rather dramatic.

Finally, we had data that in a number of countries, where we looked at some sera that were older, before AIDS was present, and [with] the antibody negativity but in the same risk groups and the same people with the disease AIDS, we had positive serology. We were preparing papers on this for publication either at that time or soon thereafter. I cannot give you a precise chronology, but I remember [Dr.] Jörg Shüpbach, who was a key postdoctoral fellow with me from Zurich, Switzerland, had a great deal to do with the introduction of the Western blot into clinical medicine while here. He had obtained serum from Switzerland and there were many people developing AIDS in Switzerland. That paper was subsequently published in the New England Journal of Medicine. We were looking at a number of countries and collaborating with many people and things consistently fitted.

I could not conceive of any other data that we would need in order to say that this [the virus] was the cause [of AIDS]. What other data was there? To try putting it into an animal and seeing if the animal got AIDS? Something that many people do not appreciate is that viruses are often species-specific. [In fact,] they usually are. Sometimes you get the right result. Take gibbon ape leukemia virus. You can put it in a young gibbon and it produces leukemia, and so everything seems to fit fine; but if you are a

human, you cannot put the virus in a human so you go into another species. If gibbon ape leukemia virus is put into another monkey, it does not infect at all or, if it does, it does not produce leukemia. On the contrary, Herpes saimiri in its native species produces nothing. But if you put it into some other monkey--I cannot remember the type--you can produce a lymphoma. Doing that kind of experiment [putting a virus into another species] is not necessarily meaningful and many people do not understand that about viruses. I did not see what else could be done [about showing the AIDS virus was the cause of the disease]. What else was there to do to establish etiology until you saw more people dying? We felt that the blood test was, in fact, an emergency, and to say that this was the etiology [of AIDS] was the right thing, and that was it was urgent to do so.

Harden: From a philosophical point of view then, you were saying that if a person did not have the AIDS virus, he or she did not have AIDS?

Gallo: That is correct.

Harden: That was your bottom line?

Gallo: Absolutely.

Harden: You did not believe that you had to demonstrate that this virus would cause AIDS in some other species. You could not use humans obviously.

Gallo: Exactly. My position has been unchanged from the beginning to now. I

think it has been misinterpreted here and there in news articles, but my position has not altered.

Harden: This brings me to the next question, which has to do with the critics of AIDS, beginning with Dr. Peter Duesberg, and recently there has been Robert Root Bernstein who has written a book called Rethinking AIDS. Also [Dr.] Luc Montagnier has suggested that there might be cofactors in the development of AIDS. Here we may be moving from etiology to pathogenesis. Then there are all the quacks and all sorts of...

Gallo: I am glad you said it.

Harden: I did say it, but what I am trying to get at is that there are a range of people, from the fringe to the mainstream, who are questioning the virus as the cause of AIDS.

Now, I believe it was in 1988, that you, Dr. [William] Blattner and Dr. [Howard] Temin published a position paper in Science in which this was all hashed out. It seemed to be a straightforward matter, but the debate is still going on six years later.

Gallo: Yes.

Harden: What is happening, and what impact do you think that all this controversy has on AIDS prevention?

Gallo: There are two questions. What is happening and what is its impact? I believe that what is happening is nothing unique, except that we live in a time of media--cameras, instant action, and wide transmission of

information--so many more people have a chance to get involved, but it is no different than [it has been] in all of human history in medicine or in related fields. The media, currently, and particularly with regard to AIDS, can make an instant expert out of anybody--[out of] somebody who has not paid their dues, somebody who just talks, somebody who does not work on a problem or does not have any expertise on the problem. So, as soon as you say something about AIDS, if you have any kind of a degree, or even if you have no degree, often you are treated as the equal of somebody who has been thinking about it, or of all the scientists involved collectively. All you have to do is say something astonishing related to AIDS and you know that you can get attention.

In the first place, part of what is happening is the modern media. I do not mean to blame it. I just think that is the way it is. There are many more opportunities for many more people to be out in the public. That is obvious.

But, if you look back in history at almost every epidemic, every plague, every serious disease--and even now with cancer--there were [always] people saying all kinds of things. It just did not get as much play in the media. There are many people who think that cancer is a curse from the devil, or a curse from God, or that cancer is caused by eating almost anything you want to name. Any theory goes, doesn't it? If you wanted to play every time somebody had a theory about the cause of cancer and make a cult out of it,

you would have dozens of them in cancer.

But if you look beyond the "Black Death," the Pasteurella pestis plague, you can find parallels where people were blaming... In my book I have a chapter, as you know, on the cause of diseases with special emphasis on HIV and AIDS. But, in another chapter, "A Single Disease With A Single Cause," is the title, I believe--somebody was showing it to me yesterday--I have a long quote of Alessandro Manzoni's statement in his classic book The Betrothed, which is a 19th-century Italian book about a young man and his wanderings around Lake Como. It is something like The Canterbury Tales in a way. In any case, Manzoni has a wonderful statement about how first the notion of the disease, of the epidemic, of the plague, did not exist and then, after a while, of course, it did, but [it was] not as serious as one thought. Well, of course, it does exist, and it is as serious, and [then comes] "You caused it," or "Somebody else caused it," or "It is not what you think," or "It is due to foreigners," or "It is due to this or that." These things happen all the time, and, with AIDS, the media have given tremendous opportunities for this to grow.

Now, it is also seductive. It is a theory that is seductive. But if I came along and told you that I have a blood test and [it showed that] you were HIV infected, the first reaction of some people was, "My God, this is like, in World War II, when Jewish people got the

stamp." They were worried. People infected were worried that this was a stamp on them. But then they realized, certainly in a short period of time, that this was the way the epidemic could be monitored, the way the disease could be treated and followed, the way that we could save people's lives by testing blood. But if somebody else--instead of bringing you this bad news and the test--said you have a disease which may be fatal and a bad virus, maybe you know that you have infected somebody else, so you have a certain feeling of responsibility. But if somebody else comes along and says, "That is not the cause; there is no cause, everything is the cause, lifestyle is the cause," you feel much better. Young people especially are prone to this because a percentage of young people are rebellious and they are often rebelling against their father figures, or the establishment. I think if you put all this together it is not difficult to understand [the criticism].

The impact? I think the impact is serious. I think, for a while, from my vantage point and from the vantage points of many people who are involved, the idea was so incredibly ridiculous that it strained one. You do not want to talk about it and you do not want to respond to it because it does not do any good to respond to it. As you pointed out, they [Drs. Blattner and Temin] responded in Science. I wrote a chapter. I tried to deal with every argument. It

does not seem to have done any good. The arguments change in time and are modified. With some people I think it is due to confusion or a lack of adequate information. In fact, I have evidence of that, that I think is incontrovertible. I talked to a professor who followed this idea [that HIV is not the cause of AIDS], who was from Berkeley. It was not Duesberg, but a more elderly scientist. His argument was that he knew plenty of people who were promiscuous and they did not have AIDS, therefore HIV could not be the cause of it. He said that this was a reaction against freedom of sex. I asked him if he understood the difference between exposure and infection, and, quite frankly, I do not think he did. It was quite remarkable, but this is true.

I think the idea [that HIV is not the cause] will last as long as we do not have a cure for AIDS--or, let me put it this way--as long as we do not have an extremely effective therapy it will last. All kinds of theories and passions will last, all kinds of misrepresentations, distortions, historical and otherwise, will last. When the right therapy comes all these things will settle down. But there is no experiment that would effectively counter such arguments. If tomorrow we developed a successful vaccine, would you say, "That settles it?" I doubt it. Somebody would argue, "[It is] non-specific stimulation of the immune system." You will never win the argument because, in fact, science is never--almost never--

100 percent [certain]. Either you spend your life focusing on the .0001 possibility, or you get on with the problem and attempt to save life. But I think the impact [of not believing HIV is the cause of AIDS] is serious, particularly on young people, particularly in some of the big cities in the United States and in parts of Germany today.

Harden: Let me go back, just briefly, to the Science articles and ask, when you were working in this period of great discovery between 1982 and 1985, when information was developing rapidly, how did your thinking evolve about the nature of this virus? I know initially you thought that it might be HTLV-I, or if not, something close to it.

Gallo: No question about that. In 1982, when we first began thinking about the virus--we means myself in discussions with [Dr. Myron] Max Essex--we thought that the best idea was [that it was] a T lymphotropic retrovirus. That was correct. That is what has turned out to be right. But we were basing this on [our knowledge of] HTLV-I and HTLV-II, in other words on the HTLV family. Our reason was, as I have indicated to you before, that feline leukemia virus with a minor modification of its envelope could cause immune deficiency. That had been demonstrated.

Exactly at the time that Essex was reminding me of that, in our laboratory--and also Dr. [Anthony S.] Fauci's laboratory at the time, I remember, was working with HTLV-I, partly in collaboration with us and partly independently--we saw that with HTLV-I and HTLV-II there could be immune impairment of T cell function.

When it was not immortalized in the T cells, it could modify T cell function. You think about that a little more and you realize that it targets T cells. You start thinking about how HTLV-I is endemic in Africa and Haiti and there is reason to suspect a Haitian connection, and a Haitian to African connection [in AIDS], and a heck of a lot of monkeys are infected with related viruses and you have just discovered HTLV-II. We have HTLV-I and HTLV-II, and we are in the midst of discovering modifications of HTLV-I, something we called HTLV-IB, HTLV-IC, so we thought the best idea [for the cause of AIDS] was a new virus, not HTLV-I, but an HTLV-I based virus. In fact, I wrote a memo to Dr. [Vincent] DeVita sticking my neck a million miles out and predicting there would be a variant in what we call the 3' region of the genetic information for the virus, namely where the envelope is, and where some of the regulatory genes for HTLV-I known as tax and rex are located, the X region. We were predicting that the region that makes the core proteins and the reverse transcriptase would be kept common, be more HTLV-I related, but the 3' end of the molecule would be different.

I will not go into all the thinking that led to that, but that was, in any case, how we started out. That was in 1982 and early 1983. It lasted to about the middle of 1983.

How did the thinking evolve? I should say that there was

reason to be stimulated further in that direction by some data that was not, in the end, correct, and I will summarize that as we go along. But one important piece of data was that Montagnier, in early 1983, said he had a new retrovirus, but that [his] retrovirus, in a certain test reaction, had a one-way cross-reaction with HTLV-I, [or] at least [with] HTLV-I infected cells, If I remember the experiment correctly, the serum from their patient reacted with that. That turned out to be an inaccuracy, but it gave further credence to the notion that there might be an HTLV-I relatedness.

You have to know the context of the field. The idea of a retrovirus was not accepted, as far as I know, by anybody. I remember [Dr.] Paul Black wrote a letter to the Editor of the New England Journal of Medicine pooh-poohing the idea that a retrovirus could cause anything other than a cancer, not being aware--he was a DNA virologist--of some of the things retroviruses could do. The climate was not ripe for a virus [as the cause]. But our thinking intensified. Montagnier did not have linkage to AIDS, but, nonetheless, here was a new retrovirus and it was early 1983.

Now, by then, we had already seen evidence of a new retrovirus too, but could not put the pieces together.

Essex used HTLV-I infected cells in people with AIDS who were something like 35 percent positive on the assay system he used. Montagnier, using what turned out to be the right virus, was

only 18-20 percent positive. We did not know both results were wrong. We suspected that they might be, but we did not know that. In any case, this gave us further reason to believe that, if this new retrovirus was involved in AIDS, it was HTLV-I related. Finally, and ironically, in Montagnier's paper, where there was not much characterization of the virus, there were three things that further spelled an HTLV relatedness in my mind:

One, he called the virus Type C. HTLVs are Type C. We now know that HIV is not; it is a Lentiretrovirus, not a Type C.

Two, the size of the central core proteins that he described was 25,000 Daltons. Now, I knew that among retroviruses HTLV-I and II had small core proteins, 24,000 Daltons and something, but all the other retroviruses we knew about were bigger--28,000, 30,000 and 32,000, something like that--so that fitted.

Finally, Montagnier's assay for reverse transcriptase that he referred to was his optimum. He referred to the assay they used and, in discussions, that was his optimum, and that reference was to our 1980 paper on HTLV-I. It seemed to me to be self-evident that it [the new virus] would be very close to HTLV-I.

Now I come back to what we were starting to see. We got tremendously misled--let us say we lost half a year--again by something quite ironic. The truth is better than some of the nonsense. There is a book that just came out called The Dancing

Matrix, and the author's name is Robin Marantz Henig. Anyway, in reading that, [I found that] she starts the book with Mr. Chardon. Mr. Chardon, a young Frenchman, goes to Haiti, gets in an accident, has blood transfused, and gets AIDS.

If I remember correctly--I have to go back to my [own] book--but I think it was in the summer of 1982 or in late 1982 that I was having discussions with [Dr.] Jacques Leibowitch. Jacques Leibowitch was a clinical immunologist in Paris in the Hôpital Raymond-Poincaré and Jacques Leibowitch was interested in things that I had just written in August 1982, and elsewhere, proposing that a retrovirus was the cause of AIDS. He became excited and interested in this and encouraged me to work more on AIDS than I was doing. He was another provocateur. Instead of working with one or two fingers [on the phone], Jacques came over with one of these containers of liquid nitrogen filled with samples from AIDS patients. The most interesting one was this one from Mr. Chardon. "CC" we called him, but since his name is in the book [The Dancing Matrix], I guess it is all right to say his name. This became some of the material that we focused on hard because Jacques was such a pusher and so dynamic and [said that] we had to get more involved in it, and so on.

Parenthetically, the story of how the French got involved in looking for a retrovirus is that Jacques returned to France--I just

met the man, Paul Prunier, who is the Head, I think, of Pasteur Diagnostics--and he told Prunier about our work. Prunier told the people at the Pasteur Institute to follow our ideas. That is how they got started. It is not a secret. Dr. Montagnier has already published that [information] in several of his research papers and elsewhere. So, that started the two laboratories, their laboratory and our laboratory, going on this, and [there was also] Max Essex. I think the three [laboratories] were the only ones [working on this] at that period of time. In fact, I am quite sure we were alone.

Coming back to the story of Chardon and the irony in what happened to us, Chardon's cells grew. Previously, in looking for HIV, or looking for the AIDS virus, or looking for a retrovirus, what did we see? Prior to Chardon we had a few short-term cultures. Sometimes there would be an HTLV-I reactivity, but most of the time there would not be. We would have a little bit of reverse transcriptase and we could not interpret the data. Were these really isolates? It depends on how you define isolates. As short term cultures? I do not want to say how we would define this. But we had these as early as late 1982. When we were in the patent discussions, the lawyers looked back in time, [and asked] "When, in retrospect, did you first detect this?" In retrospect, it was in the late part of 1982. We do not want to claim priority for that. That has been misrepresented by my [unauthorized] biographer many

times. We do not claim that. That [response] was [in] answering lawyers' questions. In retrospect, that is what our books showed. We had no clear interpretation of those data. I will be the first to say that. The first publication is what counts with regard to "firstness."

In any case, we had these detections and we did not exactly have good production of anything. But Chardon's cells immortalized and they grew forever. What were we getting? We were getting exciting results, exactly fitting the theory, namely the virus coming out... Chardon's cells were growing forever in the laboratory and they were producing a reasonably good quantity of virus. The exciting thing was that the virus was able to kill target T cells. It was producing a cytopathic effect. That was extremely exciting. So we figured we had the virus, but we had not linked it to AIDS yet. In keeping with the theory, when we tested those cells for whether they had any gag proteins related to HTLV-I, the answer was yes, they were expressing p19 and p24, core proteins of HTLV-I, and they fit the theory perfectly. In fact, it was at that point that I became more certain of the hypothesis.

Now, what was the reality and how did our thinking change? We continued looking at other patients. We got something from Chardon a few more times. But from the bulk of AIDS patients we did not. I brought [Dr. Phillip] Phil Markham, our contractor and

close colleague from ABL [Advanced Bioscience Laboratories] into the problem and also another person in my laboratory, [Dr. Mikulas] Mika Popovic, in addition to the people already involved. Their goal was to try to see if we could establish linkage. They were not to worry about producing the virus for a long time; just to see if they could detect this new virus in patients with AIDS. By the summer or maybe the fall of 1983, they were starting to get a significant number of detections of this virus in short-term culture and, most of the time, no HTLV-I relatedness at all. Yet we had a few other immortalized [cell] lines coming along that also had this cytopathic retrovirus and that did have the HTLV-I relatedness. The light did not dawn yet, and I will tell you what was happening in a second.

By September of 1983, we were preparing for the Cold Spring Harbor [laboratory] meeting. What happened at that meeting? One, [we learned that] Montagnier's data had progressed some. He now had about five cases in which he had some, at least short-term, detection or isolation of this kind of virus. I did not present our isolates. We did not say anything yet. [Dr.] Marjorie Guroff presented our serology data, our antibody testing data, using HTLV-I and HTLV-II as probes. She said, "I cannot understand this. It is just 35 percent, and we are getting, with all kinds of assays and even with loosening the conditions, only eight to ten percent." I looked at Popovic's records, at Markham's

records, and at Salahuddin's records, and [they were] getting isolates of the virus less than 10 percent, somewhere around 5-10 percent, [that were] HTLV-I related. Yet a number of times they were finding something that we could not get a handle on, that did not grow well, but had no HTLV-I relatedness that we picked up.

It finally dawned on us that those [instances] where we had the HTLV-I relatedness were doubly infected. Chardon received blood transfusions in Haiti, an endemic area for HTLV-I. He was doubly infected.

Why did we not think of it earlier? It depends on how you look at it. Whether we knew too much, or too little. In a sense maybe we knew too little, but we knew, in a sense, too much. If you have an HTLV-I related retrovirus as the cause of AIDS, or an HTLV-II retrovirus as the cause of AIDS, or something coming along that fits closely with that family, generally speaking there will be interference--if you are infected with one, you will not be [infected] with another--so I was not expecting two viruses. It was a whole new category of retrovirus. It was a Lentiretrovirus infecting the very same cell. So we realized by September 1983 that we were seeing double infections in those that we had been trying to characterize the best. This probably cost us a solid six, or maybe eight, months in time of confusion, and that is what you can bang your head on the wall over. I try to think of what the lessons are in

this, but I do not know. Certainly, coming back from the Cold Spring Harbor meeting, we knew exactly what to do. We needed to mass produce, in one way, by getting just the cytopathic retrovirus. Popovic already had that as a goal but, at the same time, was accepting anything that was HTLV-I related, [from] the double infections, and that would cause confusion. We could not use as a blood test to try to prove the--to get a lot of antibody data linked to AIDS because you would have the mixture of the viruses, so it would be a very difficult interpretation.

We were still not convinced of the etiology, by any means. We were convinced that this was the right path, the best path. You have to recall the time. This was the time when an Adenovirus strain had been claimed by [Dr.] Marshall Horowitz, from Albert Einstein [Medical School], as a good candidate for the cause of AIDS. This was the time when [according to] an odd theory, EBV (Epstein-Barr virus) variants were thought to be the cause of AIDS by people from NYU [New York University], because there was so much B cell proliferation. I do not think, in retrospect, that that idea was very good. It was also a time when some people were proposing chemicals. It was a time when people were proposing poppers. It was a time when [Dr.] Gene Shearer had proposed semen as the cause of AIDS, and I came to the meeting at Cold Spring Harbor and asked, "What about women who had been

exposed for a few years before AIDS ever appeared?" But the immunologists were big on that theory. So this [the retrovirus theory] was still not a forefront theory. But, by that period, September 1983, we had enough short-term detections of the other thing to make this a very high priority--that is not the word; it was always a priority--but now it was becoming a probability instead of a good idea. But we still did not have the data in hand until the production came.

When the mass production came we knew. On 23 December 1983, there was a Christmas party here. That Christmas party was kind of a routine event at the time. But that day "Sarang," our collaborator, [Dr.] M. G. Sarngadharan, came to see me and told me that there was an advance that was being [with]held from me because they were afraid I would talk too much about it and get too excited. That step forward was, "That Mika [Popovic] knew how to culture the cytopathic retroviruses." That was a plus. Indeed, it was a plus. Popovic had, by then, been able to put into cell lines several [HIV viruses]--not just the virus from France--which at the beginning was difficult to grow, but the virus that France sent us the last time was a contaminant which Mika was able to grow for the first time, but he lost one culture. The second culture he had--I did not check that data--but when I knew we had so many other isolates, I told him, "Focus on our isolates.

Put that aside." By February, let us say of 1984, we had enough data to conclude that this [retrovirus] was the cause of AIDS, for the most part. We had a lot of detections, short-term isolates. Popovic had ten viruses in cell lines by then, HIVs. These were the first ten. Nobody [else] had any. Of those ten, in retrospect, by the time we submitted the papers there were ten, two were contaminated with French virus, but eight were not, and the 48 detections and isolates that I described were all documented in the most intensive evaluation probably anybody had ever been through. We felt this data established the cause of AIDS. But the production of virus in quantity was necessary to get enough pure virus, or relatively clean virus, free of cell debris, so there would not be cross-reactions. Large-scale testing could be done rapidly. In my mind, this serologically defined this kind of virus as the etiologic agent, when [it was] combined with a large number of detections.

Then the other studies I told you about earlier were quickly carried out beginning in the spring of 1984.

Rodrigues: Our next question probably will not elicit a story as fascinating as that, but we were curious about the evolution of the nomenclature of HIV.

Gallo: That is a very good question.

Rodrigues: I am sure very few people outside of virology understand how viruses are named. We would be particularly interested to hear about the story of how this was negotiated.

Gallo: Sure. The question is about the nomenclature of human retroviruses; how it eventually got sorted out and how HIV became the name. I will tell you what I know and there are probably pieces of this that even I do not know. But let us go back to the first human retrovirus. What would you have called it? It was a Type C virus in association with a leukemia. If you looked to the animal systems you had many viruses named after people, such as Rous sarcoma virus, Raucher leukemia virus, Gross leukemia virus, Kirsten sarcoma virus, Moloney leukemia virus, Moloney sarcoma virus, Thelan cat leukemia virus, Harvey strain, Friend's strain, Rich strain. It was endless. So they were named after people. That began to change as the field moved above felines. In chickens, mice, and cats, viruses were often named after people, but with the name of the species, feline leukemia virus, the strain with a man's or a woman's name.

By the time we got into primates, cows, and other animals, it was just named bovine leukemia virus and the strain might be given a number or [the name of] a city or whatever you want. We tended simply to follow the pattern. Our virus was in humans. It was a leukemia virus, and it targeted T cells, and we were worried about just [giving it] a name, given [that it was] a leukemia virus. It was so specific for one form of leukemia that we figured we had better put "T cell" in, so it became "Human T cell Leukemia Virus." That was the name.

When we discovered another type of human retrovirus that

was related to HTLV-I, we simply called it HTLV-II, and, right from the beginning, the plans were to name them sequentially. If there was another T-tropic human retrovirus, it would be HTLV-III. It was not dependent on whether or not it caused leukemia. That is also a point that has been distorted. It has been said that we changed the name to lymphotropic and that you could never call the AIDS virus HTLV-III because it was not causing leukemia. But please keep in mind that feline leukemia virus can cause aplastic anemia, it can cause immune deficiency, it can cause many things, depending on the strain, but it was still called feline leukemia virus. We were following a precedent. Some strains of the mouse leukemia virus can cause spastic paralysis and it is still called mouse leukemia virus. HTLV-I could cause a spastic, paralytic, neurological disease, but it was still called human T cell leukemia virus, and no one complained. This became politics in my view, scientific politics.

We changed the name to "lymphotropic," but it was not me who thought of that; that was a suggestion, if I remember correctly, by Dr. [Luc] Montagnier, who did not want to use the terminology of "leukemia virus" because it might cause confusion. So we called it "lymphotropic." That was agreed upon.

In September of 1983, from the twenty-first to the twenty-second, we were at the Cold Spring Harbor meeting on tumor virology. I think that meeting centered around human retroviruses.

[While] at that meeting we had a subgroup meeting of people from England, Scotland, the United States, and Japan. We made a signed agreement, which sits in my drawer to this day, in which human retroviruses would be named in the order of they were discovered, simply by the number, and if it was T cell tropic--not if it caused leukemia--it would be HTLV-III, HTLV-IV, HTLV-V. That was the pattern that was set. So I more than resent the notion--it is a false notion--that the discoverer of a virus can name it and therefore the other person has no [chance to give it a] name. We feel that we independently made isolates, including in 1983, and that there was an agreement and a precedent for the name of these viruses in the order of their discovery if they were T tropic, as HTLV-I, HTLV-II, and HTLV-III.

However, certainly it was Dr. Montagnier and his colleagues' prerogative not to follow this, and they did not. They called the virus "lymphadenopathy virus." I do not think lymphadenopathy virus was a very good name because it said the virus was associated with lymph gland enlargement, and that was not the key thing with this virus. Secondly, there was not much of a precedent for that in animal retrovirology; [it was] a very unusual name.

When this was going back and forth we agreed to give the virus a double name, [with] the hyphen, LAV-HTLV-III, or HTLV-III-LAV, which we knew would never last forever. Subsequently, a

Nomenclature Committee was generated, and the current NIH Director [Dr. Harold Varmus] took a role in that. That was his entry into [developing] some interest in AIDS, so far as I know. I was asked to be a contributor to that [committee], and so was Dr. Montagnier. In 1985 Montagnier wrote me a letter, in March of 1985--a very interesting month actually, but I will not go into that--in which he [said that he] wanted to keep the name "lymphadenopathy virus," because he felt that he had conclusive evidence that it caused mostly benign disease. He was wrong, of course, but he wanted to keep the name. We wanted to keep the name HTLV-III. So things were not working [out]. Suggestions were coming in.

In retrospect, I wonder if Howard Temin's idea would not have been the best. From the start he wanted me to make a break with the past and he said, forget HTLV-I, forget HTLV-II; let us just call them human retroviruses. No one can say anything. One, two, three, four. That way you cannot be accused of naming it [HTLV-III] because HTLV-I and HTLV-II were your babies from the past. That probably would have been the wise, quick thing to do to end this debate.

But I did not go in that direction and Temin's idea did not win out. The name AIDS virus almost won out. I feared the name AIDS virus because what if, 5, or 10, or 20 percent of the people

who got the AIDS virus as was then determined did not get AIDS? I preferred a more technical name like HTLV-III, or maybe human retrovirus III, but the name immunodeficiency virus won out in the voting. I cannot remember the exact date of that, but it was probably some time in late 1985 or in 1986. I hope that answers the question adequately.

Rodrigues: Our next question has to do with the level and intensity of the rhetoric that has appeared in the press. In the beginning you mentioned that this sort of coverage had been going on for over eight years. Has it taken a toll on your ability to function as a scientist?

Gallo: Yes. The press rhetoric, in some quarters, particularly since 1987--there were press problems as early as 1984. The first time in my life I had press problems was at the beginning of AIDS research. It started in 1984, but then it got better. But from 1987 on, particularly with one reporter, it has been eight years relentlessly, sort of regularly, often front page. Yes, it took a heavy toll, emotionally, and time-wise, responding to the never-ending Freedom of Information requests, and also just responding to rumors.

On the other hand, I think we can be proud, and no one can take this away from us, of the fact that, in the decade of the 1980s, this [laboratory] was the most referred to laboratory in the world in science. Second, in the period from 1989 to 1992, which was in the midst of the worst of this business, we were still the most

productive laboratory in publishing in the peer reviewed journals in which scientists publish.

But--I do not mean this to sound in any way as [though I am] just being diplomatic, or trying to be nice; it is the truth--if I did not have very good, young postdoctoral fellows this never would have happened; if NIH were not the right place to work this never would have happened. I was saved in this period by the dedication, intelligence, and the abilities of wonderful postdoctoral fellows from all over the world.

Rodrigues: I think some of what you just said ties in with our next question, and that has to do with the problems of working as a federal scientist, being under the Freedom of Information "microscope," as it were. In your book you also talk about a number of the bureaucratic problems at NIH that seem to be increasing and that hamper your ability to function. In addition, we have read that you have undoubtedly received attractive offers outside of NIH but you have elected to stay here.

Gallo: You are right. I wrote about the increase in bureaucratic responsibilities at NIH, the increased administrative load. Yes, I have elected to stay here, and yes, I have had attractive offers, sometimes monumentally attractive offers. I am sorry that I forget the first part [of your statement], but you said something important and I must have repressed it for some reason.

Rodrigues: Was it about the Freedom of Information Act?

Gallo: Yes. I was repressing it. You also asked me about the Freedom of

Information Act. Obviously, having gone through the experience I have gone through, I think the Freedom of Information Act is for the birds and the bird-brains. This is a self-destructive process. I know it was the creation of an act of good will by an intelligent Senator, [Edward] Kennedy, but it can be, and has been, abused and will continue to be abused by some people. Like many things in a democracy, it is a wonderful idea, and maybe in the end it will do far more good than harm, but it also has a horrendous down-side. One can understand why we are the only country I know of in the world with anything like this. If we keep doing things like this, we might just as well close shop because if somebody wants to abuse Freedom of Information they can, and they have abused it. Yes, there has been more bureaucracy. There has been a fear that if we do not take care of our own responsibilities... In part some of that was justified. I do not want to speak without any responsibility myself. If I have a problem in the laboratory, [it is that] if everything had been governed better day-to-day, those problems would not have occurred. I do not think I can blame anybody but myself for some of that. But, on the other hand, we came out of medical school and I had never even had a job. I went to medical school. In college, medical school, internship, residency, you do not have much free time. You are not roundly educated in life. You come to NIH, you work very hard, and you want to make your career in research. You are insecure so you work excessively and you try more and more. What experiences do you have

in life, in general? Very few. All of a sudden you find yourself a Branch Chief at age 31 or 32, and you are responsible for a whole program. We are not exactly money managers, we are not investigators; we do not have access to peoples' records, or bank accounts. We cannot be policemen and judges. We cannot be lawyers. The situation exists in the Cancer Institute now--I do not know about the rest of NIH--but Dr. [Samuel] Broder's policy is that we have no administrative help, so all responsibility rests on the Branch Chief's shoulders.

I think he is wrong. If he were here I would say it and I would argue with him. I think it is just the opposite of what should be done. We are often incompetent managers. We are scientific directors, but not many of us were born to be managers. I consider myself a lousy administrative manager, but that is what our jobs are now. I mean, I do not know if I am a lousy manager, but I am not great at it. I do not know what I am doing in such a position.

We used to have administrative help. We used to be able to have scientists who decided to become administrators, who were not going to make it in pure science, and they could help. We called them Associate Branch Chiefs. We have no such positions now. Everything is the responsibility of the Laboratory Chief. So, if something goes wrong, if somebody does something wrong, if a mistake is made, whether it be in the budget, or anything else, it all rests on the [shoulders of the] Laboratory Chief. You find yourself

increasingly unable to have the freedom not to be pressured and not to be thinking, but just free to have those rapid ideas come into your head.

Now, it is either age, stress, or lack of time, one of the three, but I do not have as many free [ranging] ideas as I used to have. I used to get ideas constantly. If anything, developing hypotheses, trying to test them and work them out, and seeing concepts were what I think I was best at. It is hard now for me to have free thoughts, to have that moment of relaxation, or peace, or whatever you want to call it. Of course this has taken a lot out of us. Anybody who says otherwise... You do not want to say that you are not productive, because you still want to be thought of as productive and to be able to sell yourself properly, so we are productive. But if somebody asked me, "What more could you have done if this had not happened?" I [would] have no idea. I only know that I spent a good 50-60 percent of my time for many years on administration. What about when I was free and was not having to spend my time on this stuff? Was my mind free, or was I thinking, "What does tomorrow bring?" I went through a period, and I may have said this to you before, but this is literally true, when I used to wear shoes that did not ever have strings on them because I did not want to take the time to tie my shoes. I could not wait to get to work. I notice that today I do not have strings [on my

shoes], but I was going to say that now I almost always have strings. I guess that I could not wait to get to talk to you.

Harden: Good. We are glad. I want to ask one more question along these same lines before we move back to science. This is more a rhetorical follow-up question. One of the things that has struck a number of people--with regard to all this controversy--is that the scientific community has not fallen into line and said, "A scientist is being challenged here." There has been a split. Someone suggested that this may be because of the highly competitive nature of biomedical research and that other disciplines are not so highly competitive. I know Freeman Dyson wrote a piece in The American Scholar about this saying that scientists should be sticking together. I wonder whether there is any validity to this? Do you think biomedical research is the most highly competitive scientific discipline? Is it too competitive?

Gallo: Let me answer your question of whether biomedical research is too competitive and whether that contributes to the scientists not being unified in responding to some of the, let us say, media addicts, or political pressures, or rhetoric, by saying that is a possible interpretation. But let me remind you that, whatever the interpretation is, it is a constant. It was true in [Dr.] David Baltimore's case. It was true in the President of Stanford's case, [Dr. Donald] Don Kennedy. It was certainly true in the [Dr. Bernard] Fisher case. It was true in mine. It has been true

historically. I do not know if the existing scientific community [at the time] rallied so well for Galileo. Show me a period where anybody was really rallying and how effective it was? Was it effective with [Robert] Oppenheimer?

Part of it, I think, is human nature. Part of it is who knows the truth? First of all, scientists on the outside could not know everything. Second, if a scientist is your friend and knows [what happened], he is identified as your friend, so he is dismissed quickly. He is not valuable. His word does not mean anything; he is your friend. So they get your enemy. Then they have a real honest opinion. That is the way that things go. Your enemies can talk but your friend cannot. If you get a third party, who is neither your friend nor a problem for you, generally they do not know and so what do they say? They cannot say too much. But if they try to get involved they lose time from their own research. Moreover, those who speak the truth become targeted, don't they? What happened to people who did? I had better not [discuss this]. I do not want to get to specifics. But, sometimes when a scientist comes forward, they can, in turn, have problems. If scientists unified and came forward, if there was an organized body and they spent, I would say, two to three days on this problem in the open air, like Pericles in the Forum, we would have this over in one or two days if there was a population watching the interactions. But

behind the scenes you cannot do anything. When it is not open you cannot do anything. People can say and do what they want. They can release reports, they can stimulate the news media, and there is no response you can make, particularly if you work for the government.

It is highly competitive in science. I cannot tell you that it is more than in business, or more than in politics, but it is more than in some fields, without doubt. But I also believe that in science there is--maybe--more self-interest, a little more paranoia, a little more narcissism, or else why do we go into it? You think you are good enough to solve problems of nature? Many scientists tend to keep things to themselves. If the other person does not get funded, maybe you will be funded. All these things are in play, but these are the worst elements of science or of scientists. This is not [true of] everybody and this is not [true of] most everybody. I think the chief reason is lack of time and information, though sometimes people must enjoy the comedy of it all if they are at a safe distance.

Harden: I want to ask you to reflect on one more topic. When you described in your book the development of the ELISA test for AIDS, you noted that you had never previously applied for a patent. We have heard this from many NIH scientists. Suddenly, in 1986, the Technology Transfer Act was enacted and NIH scientists had to be involved in patents. I would like for you to expand a little more on

the changes that have been wrought by the biotechnology revolution and the commercialization [it brought] because many people have also talked about the French-American controversy over the money that is involved [in the patent for the AIDS test]. So we were dealing with commercialization. Would you expand on those?

Gallo: Yes. The biotechnology revolution, as you have put it, and the commercialization in science obviously have had a dramatic impact. You used the patent problem, the United States-French royalty problem, as an example and you pointed out that it came--unfortunately, with us having no experience--precisely at the moment that we were finding the cause of AIDS and developing the blood test.

Truthfully, I did not even know you could patent [such things] when we were told about patenting. In my naiveté I tended to think of patents as, for example, when you make a light bulb, that should be patented. It is [for] an invention, it is not [for] big laboratory science, biomedical science. I never really knew or followed the development of patenting, even as late as 1983-84, I was not aware of it. I heard a few things about it, and the biotechnology industry was already on its way, of course, but we had never patented anything. To repeat, we had not patented interleukin-2. We did not patent HTLV-I. We did not patent HTLV-II. We did not patent the discovery of the myc translocation in Burkitt's lymphoma.

We did not patent multiple cell lines developed by this laboratory, some of which are commercially available.

We were told to patent the blood test, period. I just learned from Suzanne Hadley--I could not remember what was going on in that period of time, and she provided me with an answer, earlier this week--that I was not here. I was in Cremona, Italy, and my colleagues were pressed to move fast. Moving fast, she reflected, was probably [needed] because I was starting to talk, not about the data, but [by saying] that we had this thing wrapped [up], that it was definitely the cause of AIDS, and that we were developing a blood test. So the government had to move quickly.

I was told the reasons for that were because we had to protect against fraud, we had to get the big companies involved, and there needed to be some exclusiveness. I think those were legitimate and valid reasons. But, of course, patents breed money, money breeds many things--lawyers, problems, arguments, and governments--and the whole business that I saw before my eyes. It was just an incredible saga. I tried to follow what I was asked to follow by the government, and that is what I can say.

But, to answer your question in the way you put it, in a broader context and not limited to the blood test patent and the controversies that surrounded it, it is obvious that the biotechnology revolution has done, and will continue to do, great things for

medicine. That is the positive edge of the sword. The other edge is that it creates all these other things. It holds back information, it looks for money, it has to be fueled by money, and it leads to hyper-competition. It is not going to be stopped. The culture of science has already changed. It will change more and it will evolve like the chemistry industry and like physics, I suppose. Maybe it already has. But the good should outweigh the bad. As better rules are formulated, the bad [aspects] will be more controlled. But clearly it has catalyzed moving information forward in record time and bringing things to the clinic in record time, and it is not yet anywhere near reaching its stride. So it is a necessity. We are going through very difficult growing pains and we are going through it often without having a clear head.

Rodrigues: Our next question is something a little closer to home. We know that your annual laboratory meeting is now quite an event, attracting, as I understand it, researchers from around the world. I was wondering if you could tell us a little about the evolution of that meeting, how it got started and how it evolved into the form that it has now?

Gallo: Our annual laboratory meeting is a large event today, and it does have a history of multiple transitions. I cannot remember the exact day, or even the year, when it began. But, as our group was becoming a little larger than a small group, we felt that we needed to evaluate where we were, why we were, and what we were on an annual basis. We needed to

evaluate what we would be doing in the next six months or year, maybe even more intensively than it would be done on the outside of NIH because we had this assurance of funding, especially whether we should make a change in direction, and especially which person applying to the laboratory should we try to take. So it started as a retreat. At first, we held it right here on the campus. Then we thought, "Gee, it would be a nice idea to hold it where the phone does not ring and where nobody could interrupt us." We thought of holding it away from the laboratory. We started [meeting] in some of our collaborators' laboratories, or in a farm out near Frederick. We did not stay overnight. We would go back and forth to the farm. It started with only our laboratory [attending]. We would look broadly at everything we were interested in and [decide] where we would go. This was some time in the early and the mid-1970s.

Then we started to invite our collaborators, of whom there were a few. There became more collaborators, and then our collaborators' collaborators, and it grew. We started having the meeting at hotels out in Gaithersburg [Maryland] and elsewhere.

Then we took some years off, years that were more years of frustration, and we did not have the meeting for--I do not know--three or four years maybe. This was precipitated by a meeting in Blackwater State Park. We were told never to come back to that state park because people were up all night, [Dr. Marvin] Marv Reitz was playing his guitar and other people could not sleep.

People were making a lot of noise. It was like we were let out of our NIH cage. So we did not go back to Blackwater State Park. We took a few years off. It was appropriate to do so. Then we restarted in hotels or motels out in Gaithersburg. By then the Europeans were involved because we had those collaborators.

The numbers really increased with the discovery of HTLV-I and HTLV-II because the field of human retrovirology was now born. People were coming to learn about these viruses, more of them from Europe, in fact, than proportionally we would have expected. But it was still a moderate size meeting. There was our senior staff--say 20 [people]--and maybe we would have 40 from outside, so we would be 60, 70, 80.

Then all of a sudden came the disease called AIDS and the numbers increased to around 100 or so. After 1984, they were doubling every year until Dr. [Samuel] Broder put a cap on the numbers and the maximum is now 700. But, to be truthful for Dr. Broder, we had 800 people this year. He was among them, I think, but I thank him for not noticing. And so, the problems are now fire problems and being able to control it.

We lost something in the largeness of the meeting. We lost the intensity of discussion. We lost the flavor of a more personal relationship with people, real friendship. Now it has become a mini-congress, or maybe not even a mini one. It is a different beast

now.

But we have always have used this [meeting] to develop our interests; not just cover exactly what we are doing, but broaden out our interests. It is not just an AIDS meeting. It is perhaps 60 percent AIDS. But it also includes quite a bit of cancer and we often have outside lecturers, very good ones generally speaking, who are in a field that our laboratory wants to learn more about. As an example, this year we had [Dr.] Harry Ginsburg, a leader on adenovirus. We had [Dr.] Peter Hans Hochschneider from Munich, a leader in hepatitis virus, giving special lectures. We had [Dr.] George Klein, on Epstein-Barr virus, giving a special lecture. We had [Dr.] Beech from Cold Spring Harbor [on matters] related to the cell cycle. Just to give you an idea of the variety, [Dr.] Judah Volkman comes every year and talks about blood vessel biology. We have our troupers that come every year, like [Dr. Thomas] Tom Waldmann, Judah Volkman, [Dr.] Hilary Kaprowski, [Dr.] Michael Feldman from the Weitzman Institute, [Dr.] Izaac Witz from Tel Aviv, the [Gunnel and Peter] Biberfelds and [Dr. Hans] Wigzell from Stockholm, half a dozen people from France at least, and a few from Belgium. These people have come annually for a long, long time.

In other words, out of the 800 there is a solid core of 100 people that is always there. This is not 800 people; this is 800

scientists. It is not like a congress. You can say the International Congress [on AIDS] in Japan may have had 10,000 people, but they probably had 1,000 scientists. Our meeting is a good meeting, but it is now seven days long. That is a long time for people to be there.

Harden: Seven days?

Gallo: Yes. From 8 o'clock [in the morning] until 6:30 or 7:00 at night every day for seven days.

Rodrigues: Do proceedings come out of your laboratory meeting?

Gallo: We do not like proceedings. We do not like to demand manuscripts. What we have done in the last few years is to ask at least some of the people who have given special lectures to make short synopses of them and we have published the abstracts in the journal called AIDS Research and Human Retroviruses. This year it actually starts with a chapter by me--a few pages by me--which is on the same kind of question you asked me. It is called "Reflections" on the meeting and it gets at it from an historical perspective. It is not about the people from outside our laboratory who came, not the interesting tales, but simply about the question you asked, the formation of the meeting, how it happened and why. I tried to focus on people who were in this laboratory and left or who are in this laboratory now. I am not talking about outside people.

Harden: I think Dennis is going to follow up later about our interest in perhaps getting some of the pictures of the annual laboratory

meeting. Could we get copies?

Gallo: You can have all of them. My office can tell you about that, and there are extra ones. I know Latta Nerukah, who is Journal of NCI now, she used to take care of all of this. The last two years she did not, and [Dr. Genoveffa] Veffa Franchini next door did.

Harden: Good. We will follow up. I would like to come back to science for a moment and note that much of your AIDS research has already been detailed, again. Aside from what you have documented already in your book, is there any of that work that you would like to expand on, that more needs to be said about?

Gallo: Sure. I think Kaposi's sarcoma, for example.

Harden: I would like to come back to Kaposi's sarcoma as a separate issue because you have continued to work on that.

Gallo: If you want to know what I think are the major contributions of the laboratory--the contributions that I consider fascinating. Are you talking about AIDS? Is it just AIDS?

Harden: Just AIDS.

Gallo: The contributions of this laboratory, counting the... I am going to leave out key people and what they think is their great contribution, and I will speak as me, but really this is the lot.

First, I would say the idea that AIDS is due to a retrovirus. Even if the idea was imperfect, it was the idea that worked.

I would say, second, the evidence that HIV is the cause of

AIDS came first and chiefly from us.

Third, the blood test, with the mass production of the virus, came from our laboratory, that is, a blood test that worked and a blood test that was put into operation.

Fourth, the nature of the genes of HIV came from more than one laboratory. It came from [Dr. Simon] Wain-Hobson and his colleagues at the Pasteur Institute, but it also came from our laboratory, particularly [Dr.] Flossie Wong-Staal, [Dr. Marvin] Marv Reitz, and Dr. Lee Ratner here, in collaboration with [Dr. William] Haseltine and with others like [Dr. Takis] Papas. So, defining the genome of HIV came partly from my coworkers.

The discovery of the tat and rev genes came partly from here, rev probably completely and tat partly, principally by Dr. Wong-Staal, but other people in the laboratory contributed to that.

That is five. Let us not number them. The discovery of the variation of the virus, ironically--because some people like to use that demonstration to indicate where there was a contamination--but we are the ones who discovered it first and published first, second, and third on the variation of the virus.

We also discovered and published first the variation within an individual, in other words, the micro-variation, of the virus.

We were involved with others--[Dr. Dani] Bolognesi and Repligen--in the discovery of the V3

loop in the HIV envelope that you hear much about.

Popovic and [Dr.] Sue Gartner discovered the macrophage tropism of the virus. [Dr.] George Shaw, [Dr. Beatrice] Hahn, myself, and Flossie [Wong-Staal] discovered the brain infection with the virus. We documented the first heterosexual transmission with [Dr. Robert] Bob Redfield. We discovered for the first time the virus in plasma, viremia, with [Dr. Zaki] Salahuddin and colleagues.

We did the bulk of the epidemiology in collaboration with a bunch of other people in the early period to document the presence in different countries. I do not mean the epidemiology--that is wrong--the serology, the antibody testing, in a variety of countries, let us say.

We discovered herpes-6 as a possible cofactor in AIDS. By the way, Dr. Montagnier believes HIV is the cause of AIDS. He just is looking at some, I think, fairly obscure cofactors as possibilities. We are too. I think HHV-6 may promote disease progression, but I do not think there is any specific cofactor necessary. So, if you

mean cofactor as something essential, I do not think there is any. If you mean something to make the disease go faster or slower, that is true of all human disease, and I think we should work on documenting such factors in HIV. It is appropriate.

We developed the first animal models and culture systems for Kaposi's sarcoma and there is extensive data available today on the pathogenesis of Kaposi's sarcoma. There is also a stream of subset observations from that, some of which have led to therapy.

In collaboration with Hybridon in Massachusetts we developed the first antisense RNA. They produced it, but we were involved as, I think, reasonably equal collaborators, for this antisense RNA against HIV which is now in clinical trials.

A recent discovery, as you know, is of the hormone, the first anti-tumor effect, of chorionic gonadotropin working on Kaposi's sarcoma in our mouse model.

We developed the first evidence that Kaposi's sarcoma can be a true malignancy. It [the paper on this] is now off to Nature. Before it was known to be hyperplasia only--non-neoplastic. Do you want me to continue?

Harden: I want to come back and go into some of these in more detail. I think Dennis wants to go into a few other puzzles at this point and then we will come back to Kaposi's sarcoma and some other topics.

Rodrigues: In our reading, we come across certain questions that seem to recur over and over again. Probably one of the continuing questions that comes up is, if we know so much about the virus, why is it that we still do not understand...

Gallo: Dennis is giving me a "meatball." He knows I have answered that before. He knows how I answered it too. Okay. I understand the question. You do not have to go further. If we know so much about AIDS, why are we not able to cure it, or "How come we can't treat it, Doc? Why can't you do better?" I will sort of tell you why.

> I do think we know a lot about AIDS. I think it is much more than people have portrayed recently. I think there is a tremendous wealth of knowledge about the biology of this virus and also about the molecular biology, and even about how it works. But that does not mean that we know anywhere near enough yet. I would like to point out the obvious, that you could know everything about the virus and not be able to solve anything. You might say, "That doesn't seem right?" But I once gave as an example to Nature magazine that I could know all there is to know about the Himalayas, every hole, every cave, every rock, their history, their origin, their evolution, its future, but I would not be able to climb these mountains until somebody else developed a new technology for me, such as the helicopter. It does not mean that if we gain every bit of understanding of the pathogenesis [of AIDS] that we

are going to get to a cure. However, it is obvious that the more we understand, the greater the probability that we can climb the Himalaya mountains. It increases the probability of that occurring.

It is a tremendously difficult problem. If you think of any virus that persists, how many can you get rid of? Virtually none. If you have a persistent virus, by definition, you cannot get rid of it. We do not have therapy that gets rid of many viruses. But the AIDS virus is a nastier one and can kill. It is nastier than many other viruses, so we need to develop a whole new area [of research], and that is antiviral therapy. AIDS will be the juggernaut of that. The timing is right because we know much of the molecular biology of the replication cycle of many viruses. I think AIDS will take the lead and that there will be spin-offs to other areas of virology. That will happen as surely as we are sitting here. AIDS will also take one of the leads in vaccinology. It already has, even if we do not have a vaccine for AIDS. Virus variation is complicated. We do not know why, but you do not get a very good immune response that is long-lasting, the kind you would like to see. It is complicated because if some viruses integrate and there is not the immune response right away, which is what happens, will you be able to keep the virus suppressed? If you can maintain that immune response of the right kind, yes. Animal models are not very good. Which one predicts for the vaccine? We do not know.

Which one predicts for each other? They do not. Each animal model is giving us different data. Oftentimes we get protection in a monkey against SIV or HIV-2 and there is no immune correlate. What do we get out of that?

Rodrigues: One of the things I wanted to get back to was something you talked about at the very beginning about the species-specific nature of retroviruses. Of course, one of the questions that comes up is how is it that chimpanzees can produce the virus but not get sick?

Gallo: Right.

Rodrigues: Do we understand exactly what is happening with these viruses in terms of why they are so species-specific?

Gallo: Yes.

Rodrigues: From an evolutionary point of view you would think that viruses would do better if they were less fastidious about the particular type of species they infect, but yet they seem to be extremely fastidious about what animal they infect.

Gallo: It is an interesting question about the species-specificity of viruses and whether or not their evolution would be better if they could jump from species to species willy-nilly. This is an interesting point. But if a virus is highly fatal and it is jumping from species to species, it will run out of things to infect to keep itself going. If it does not have to, if it survives within a species, it need not evolve to be able to go to other species.

In the wild maybe things are a little more separate than they

are here as we domesticate things. As we domesticate things it seems maybe there has been more jumping of species by microbes from one animal to another animal type.

Viruses are not always highly species-specific. Take rabies. It can jump into many different animals. But you are right when you say that I have said that retroviruses are generally species-specific. It is unusual for a retrovirus to go from one species to another. But it has happened in evolution that a retrovirus will jump species. There are many cases where we can document that.

But at any given moment in time, if you have in hand all the retroviruses that we study in the laboratory, and you say to a mouse virus, "Can you become a leukemia virus of cats," that is, the mouse leukemia virus is to become a leukemia virus of cats, the answer is generally no. So there is quite a bit of species restriction.

Now, HIV can infect chimpanzees. That is true. You wonder why they do not get disease. First of all, HIV does not replicate as well in chimpanzees as it does in humans. That may be one of the critical reasons. But there are a host of things that people have found that correlate with the chimpanzee not getting disease, not just that the virus does not replicate as much: there seems to be a greater cytotoxic T-lymphocyte activity; the chimpanzee does not have herpes-6, that could, I think, be a

cofactor in progression--I do not want to use that as a major argument--but there are differences in the chimpanzee that could lead to an all day discussion of the five, six, or seven reasons why the chimpanzee might not get sick from HIV.

I do not know if this is answering your question, but I cannot give you a better explanation of why, in the evolution of a virus, it would not be better if it jumped species. It makes sense that it would, and some viruses do. But I repeat, if it was a virus that caused real problems and jumped species a lot, it might run out of things to infect. But the reason it is often species-specific resides in the receptors on cells. For example, HIV needs the CD4 molecule and the CD4 molecule, as the virus needs it, happens to be on our cells and on those of chimpanzees, but it is different enough that the virus does not penetrate efficiently.

That is not the whole answer. If you put CD4 in a mouse it still does not get infected and replicate well. Why is that? It seems that there are also other factors, maybe secondary receptors or maybe cytoplasmic factors, that are needed to complete the virus replication cycle, and most likely both.

Rodrigues: My next question has to do with the question of the ability of HIV to mutate. From what I have read, it seems that when you look at HIV relative to some other viruses it has a very high, or higher than average, rate of mutability.

Gallo: Yes, and no. You asked me if HIV has a lot of variation? Yes. You asked me if it has more mutability, or if its mutation rate is greater, than other viruses? Actually, it is not that much more impressive, or maybe not more impressive at all, than a number of other viruses, especially, according to the analysis by [Dr.] John Coffin at Tufts University, who is the best thinker on this that I know, but it is because of the number of its replication cycles. Remember, it is a persisting virus and it is replicating much more than we thought. Every time it goes through a replication cycle it has golden opportunities to change by recombination because it integrates, by mistakes through reverse transcriptase, and by more complex mechanisms that we will not get into now.

Rodrigues: Because of this issue of the mutation of HIV, some people have suggested that it could possibly mutate into a form that would be more or less pathogenic. I think you addressed that question in your book. But another related question that I have has to do with mutations of HIV, what are the implications of the mutation? Is it just its antigenic presentation, as you might see in influenza, or is it something more fundamental?

Gallo: Mutations in HIV, depending on where they are, even very subtle ones, even of a single nucleotide, can sometimes lead to dramatic biological differences in a variant of the virus. For example, in laboratory studies it can make a virus go more towards T cells or more towards the macrophage. It can make the virus be more or less cytopathic, in vitro. It can make the virus replicate faster. It can make the virus replicate more

slowly. Theoretically, this should make great differences, in vivo, and it almost certainly does.

> Very subtle mutations in the wrong place, or right place, depending on the outcome, can make dramatic biological differences in the virus. It is not so much antigenic variation, because there is very little antigenic variation. The variation is in the behavior of the virus.
>
> This gives rise to the notion that we might create an HIV that is easy to spread all over the place. At an international meeting, Dr. Montagnier was saying yes to that question while I was, at the exact same time, saying no. I believe that that is exceedingly unlikely because to harm the immune system the virus has to keep some of its guns exactly the way it has them. If it mutates to become casually transmissible, which retroviruses virtually never do, it would certainly lose its ability to target the CD4+ cells. The virus cannot have it both ways. You cannot make a giraffe, a lion, or a lion a giraffe. You may change the spots a bit on the lion's mane, or the lion's color, or something like that, and in the case of HIV you would see many different colored lions, lions with bigger, thinner paws, and faster and slower lions, but it is not going to make it become a giraffe. I do not think there is the danger that this is going to evolve into a pathogen that is casually transmissible, the nightmare of nightmares.

On the other hand, I have no doubt that HIVs now in the population have substantial variation in their ability to cause disease at certain rates. In other words, I feel confident that some of the reasons for long-term survivors--not the only reasons--and also for short-term survivors are the dosage of the virus and the very virus type that the people get infected with. It is self-evident. Look at HIV-II. It is less pathogenic. HIV-II is 50 to 60 percent different from HIV-I. Well, there are HIV-Is that are 10 to 20 percent different from each other. Is not that also likely to make the virus biologically different to some degree in its ability to cause disease and its rate of causing disease, in short, its virulence? I believe so.

(Whereupon, the interview concluded.)