This is an oral history interview with Dr. James J. Goedert of the National Cancer Institute on the history of the NIH response to AIDS. The interview was conducted on 10 March 1993 in Dr.Goedert's office in the Executive Plaza North Building in Rockville, Maryland. The interviewers are Dr. Victoria A. Harden, Director, and Dennis Rodrigues, Program Analyst, of the NIH Historical Office.

Harden: Dr. Goedert, I would like to start this interview by asking you to tell us about your background. Why did you decide to go into medicine? What was your undergraduate and medical school education? How did you come to the NIH?

Goedert: I was born and raised in Chicago. I think I started toying with the idea of going into medicine probably in high school, because I felt some desire to be of service to people in a practical way. Although I never considered myself a scientist, I had some aptitude for math and science, and so I thought that medicine was probably a reasonable path. That [belief] continued well into the middle of my college years at Yale, which is where I went as an undergraduate. I did not go whole-hog into premedical studies, but started early and went through a gradual transition. Again I found that I was not a scientist, per se, and was rather clumsy in the laboratory. I never really had an affection for laboratory science, but I did find that I still enjoyed science in a more general way. I also found that I was one of those peculiar people who actually had a liking for statistics. In addition, I liked psychology, so I was a psychology major as an undergraduate.

I was adequate in other fields, and enjoyed a diversified experience in college, ranging from literature to architecture and art, as well as taking the typical basic premedical sciences and the psychology major. I went to medical school at Loyola University in Chicago, the Stritch School of Medicine, which, at that time, was a three-year medical school. This meant that I started on July 1, right after I graduated from college in May, but I was able to dispose of the preclinical sciences in twelve months. Since I was not very keen on laboratory science, that was fine with me.

I enjoyed medical school very much, and when I got to the wards and the clinical rotations, I also found that I was particularly drawn to internal medicine. It was not the hands-on kind of approach that you get in surgery, but it was more diagnostic, cerebral, and deciphering. Beyond that, I felt a calling to take care of patients with cancer.

Harden: That is interesting. Many people become depressed taking care of patients who do not have a good prognosis.

Goedert: Yes. I did reasonably well in medical school and got some strong recommendations. I applied for a number of internships and matched at one of my first choices, Georgetown here in Washington, D.C. I had an extremely good clinical experience at Georgetown in all facets of internal medicine, ranging from emergency care and intensive care medicine to taking care of cancer patients. Again I felt a particular calling to the cancer patients, perhaps because it was obvious to me that simply listening to them and responding to their basic needs, especially for pain relief, was so much appreciated. After three years of internal medicine, I went into a Fellowship in Medical Oncology.

Georgetown had at that time, and still does have, a very strong program in medical oncology, but it was very much oriented, as I think most programs are, towards pharmacology and basic laboratory science. The one limitation on my own affection for oncology that I discerned was that I probably did not want to be completely consumed by taking care of cancer patients. I felt that it would be–or could be–quite depressing to do that 100 percent of the time. I thought that I would probably like to do some research, but not in pharmacology. I got the NIH [National Institutes of Health]–or maybe it was the NCI [National Cancer Institute]–manual and thumbed through it and I found the Environmental Epidemiology Branch with [Dr. Joseph] Joe Fraumeni and [Dr. Robert] Bob Hoover. It was still the growth era in cancer epidemiology at the NIH, and they took me on for a second fellowship year.

Harden: You did not have any particular epidemiology training until you entered this fellowship at the NIH?

Goedert: Absolutely none. No training whatsoever.

Harden: Except for your inclination towards statistics.

Goedert: Yes. But my knowledge was very basic. I only had one course in college and essentially a non-existent course in medical school.

Harden: I would like to ask you now what you think you might have done had AIDS not come up. We are at the point in your career when you saw one of the early AIDS patients in the Washington, D.C., area. This appears to have changed the course of your career.

Goedert: It changed the focus of my research, I think.

Harden: That is a good distinction. Please go ahead.

Goedert: I had already decided to do cancer epidemiology as my cancer research focus. It is not an area that most cancer centers have as a major research interest, so there is not much funding in the outside community. But, fortunately, there is the large Cancer Epidemiology Program at NIH. I came with the idea that I might be at NIH for two, or maybe three, years, and then eventually go to a university and try to eke out a position on grant support. I think, as is true for most fellows who come here, that I was unsure exactly what kind of cancer discoveries we could make. I was never intimidated by my lack of formal training, because I think the clinical training affords at least as much insight into cancer etiology as does some kind of formal training in statistics.

Harden: Is there any formal training?

Goedert: In epidemiology?

Harden: No. In cancer?

Goedert: Not cancer, per se, but epidemiology certainly.

Harden: I was thinking in terms of the CDC's EIS [Centers for Disease Control Epidemiological Investigative Service] Unit, that kind of epidemiological training. But for cancer epidemiology, which is, as you say, a fairly new program...

Goedert: The EIS program is more what we would call public health, which is practical experience in disease control, identifying the bug in the mayonnaise or something like that.

Harden: That is not what you were doing in this program, because it was in cancer epidemiology?

Goedert: Right. I think one of the things that continues from very early on in my time at NIH, and continues to be true of the most successful work that we do, is trying to approach the problem of cancer, AIDS, or any other disease, with as much breadth of knowledge as possible and with an open mind toward new possibilities. Without AIDS, I would be doing very much what I am doing now, but with more of a focus on cancer. I am actually getting back to the cancer field at the moment.

To give an example of the breadth of experience I had in the first few months that I was at NIH, there was an investigator here named [Dr. Elizabeth] Beth McKean who was a year ahead of me. She had also done part of her fellowship at Georgetown, so I knew her from there. Just in

casual conversation we discovered that we each had a patient with an uncommon kind of cancer of the kidney, who had a minor congenital anomaly, an extra nipple. Beth had some formal training in clinical genetics and recognized that there could be an embryologic connection between the breast and the kidney. Through our connections with the oncology community here and at local hospitals where I had received some of my internal medicine training, we were able to address the question of whether there was a connection between extra nipples and kidney cancer. There was. Subsequently, we did this same kind of investigation with testicular cancer.

What I would probably be doing without AIDS is similar to that, identifying novel associations with particular cancer types, either in the clinical area, or, with the explosion in what is conventionally called biochemical epidemiology, using laboratory assays to identify new connections with disease associations, probably biochemical markers of cancer, as has been going on elsewhere in our program.

Rodrigues: I notice that you had another early paper besides the paper on the phenomena of the extra nipple. I believe that it had to do with...

Goedert: Polyarteritis nodosa?

Rodrigues: Right. I was wondering if there was any connection between that research and your interest in Kaposi's sarcoma, since it seemed that there might be a relationship, because the tumors have a lot of unusual vascularization. Was there a connection?

Goedert: It is a reasonable question, and it is not a potential association that has occurred to me before. I think polyarteritis is an inflammation of larger arteries, larger vessels, than is true of the small capillaries that proliferate in the Kaposi's sarcoma tumor. So I do not think there is any particular connection there. The potential connection that we identified in that one patient–it was a single case report of a woman whom I took care of when I was at Georgetown, (ironically, she had previously been seen at NIH by [Dr. Anthony S.] Tony Fauci because of her polyarteritis)–was the link between two diseases, that is, polyarteritis and hairy cell leukemia. The latter is a disease we still do not understand very well, but there have been some suggestions that it might be linked to retroviruses, to HTLV-II in particular. It is one of the few cancers that show remarkable regression with immune modulator therapy, that is, with IL-2 [interleukin-2] therapy. It suggests that there may, in fact, be some infectious disease link between the polyarteritis and the hairy cell leukemia.

I keep my eye out for such new associations, but I have not seen anything recently.

Rodrigues: But from what you were saying about the focus of your career, about looking for unusual associations, I can see why this early case of Kaposi's sarcoma in a young individual would be something to which you would probably gravitate.

Goedert: Absolutely. I do not know if we have talked about it before, but there is a personal story behind that case. It concerns my sister-in-law, who was in law school. An acquaintance of hers called me up and said, "Your sister-in-law said I should call you because my brother has a funny illness and his doctors can't figure out what it is." She told me, "My brother is at NIH. Maybe he would know what it is."

So I talked with this woman on the phone. Then I talked with her brother on the phone. He had had a biopsy and his doctors could not figure out what he had. The brother's question was, "They are going to do a lymph node biopsy. Should I go ahead with it?"

I said, "Absolutely. With the symptoms you have, it sounds as though it could be Hodgkin's disease, or something which is serious but completely treatable."

Harden: Could you expand a little more on the case of the brother? What kinds of symptoms did he have? Where was he in the disease process?

Goedert: He had a skin lesion on his thigh, and he had a lesion in his palate. Both of these had been biopsied and his doctors could not figure out what was causing them. He had the enlarged lymph nodes, and the question at that moment was should he go ahead with a lymph node biopsy. He had also had, as I recall, some fevers, night sweats, and chronic sinus problems.

Harden: Did he live in Washington?

Goedert: No. At the time he lived elsewhere. The lymph node biopsy was done at a very well known university medical school. He called me back, maybe a week later, and told me, "They said it was Kaposi's sarcoma." I said, "They must be wrong. That is impossible." I had, in my whole career, seen one case in an elderly Jewish man whose general practitioner had said, "I think this is Kaposi's sarcoma." Nobody else ever agreed with him. That was the only case I had ever seen or of which I had heard. I was very familiar with the literature and knew that this cancer just did not occur in young people.

Harden: What year was this?

Goedert: This was February and March of 1981.

Harden: The first publication on AIDS was in June 1981. Is this just before that, rather than a year or more before?

Goedert: No. I do not think so. The first phone call, I think, was in February [1981] and then the second conversation was probably in March. I remember that the man and his whole family ended up coming to Washington to see me. They brought the slides. I took the slides over to the Armed Forces Institute of Pathology and the eminent pathologists at AFIP in the Sarcoma Section said, "No, this is not Kaposi's sarcoma, this is angiosarcoma."

We worked out a treatment for the man based on that, but it was not appreciably different than what would be done for a Kaposi's sarcoma patient anyway. Actually, when I say we worked out a treatment, this happened just before the annual American Society of Clinical Oncology meetings. I made a number of phone calls and scurried around, as an eager young fellow should do, and I asked all of the sarcoma experts at the time what they would do for this fellow. Nobody really knew for sure. They all had their own ideas, but there was no clear, certain therapeutic approach for him in terms of what should be done.

His sister, meanwhile, who had originally been the one to call me, had been asking around in New York, where she lived, about different possibilities for treatment. She had discovered that there were a number of other young men who were said to have Kaposi's sarcoma. She put me in touch with a physician at the VA [Veterans' Administration] hospital, I think in Brooklyn. I had a conversation with this physician, and he said, "Oh yes, we had–I think he said–six [patients]," or something like that. I said, "That is amazing." He said, "Yes, and they are all gay. Is your patient gay?" I said, "I don't know." Times have changed in terms of what we ask our patients. In the end my patient reluctantly acknowledged that he was gay. That was a time, especially for a young professional, when it was not something that was out in the open.

Anyway, the whole family ended up moving to Washington, and the young man was treated indirectly by me. At that point I was at the NIH full-time, so it was one of the junior fellows at Georgetown who was his primary physician. As was true for most AIDS patients at the time–as is true for a Kaposi's sarcoma patient–he had a prolonged but not especially

successful treatment experience at Georgetown. Shortly after, on the heels of his occurrence, another essentially openly gay black man appeared at Georgetown, who had Kaposi's sarcoma and a number of other illnesses. I became involved in his case also, since at that point the information was exploding in terms of the immunology and so on.

Harden: This is still mid-1981?

Goedert: July of 1981.

Harden: In July of 1981 you were beginning to hear more and the *MMWR* [*Morbidity and Mortality Weekly Report*] publications and other information were coming out?

Goedert: [Dr. James] Jim Curran [from the CDC] had come by. I do not know exactly how I first got in touch with Curran, but we had a couple of conversations and my initial patient was included in that first *MMWR* report.

Harden: Right.

Goedert: I contributed some information from NCI's SEER Program [Surveillance, Epidemiology and End Results] in terms of expected incidence rates and so on.

Harden: What was going through your mind at this point? The disease could not possibly be Kaposi's sarcoma, but it was. Were you and your colleagues thinking about a new disease, were you trying analogies with other things, or were you thinking of zebras or horses at this point?

Goedert: This was certainly a zebra. There was no question about that. The first thought, before I heard anything about the other cases, was that the patient probably had some inherited familial susceptibility. We knew at that time that there were cancer families. Joe Fraumeni and [Dr.] Frederick Li had been studying them. They are now well known in terms of the p53 gene. I strongly suspected that the patient was probably a member of one of these cancer families–what we then called a sarcoma family. I drew blood from the other family members–there were two sisters and the parents–with the intention of at least banking it away until the time when we would have something that we could hang our hats on. There were some other tests such as HLA typing and the like.

Once it became clear that this was an outbreak among homosexual men, it completely changed the character of the disease. [Dr. Robert] Bob Biggar

arrived in our group at NCI almost at the same time as I did, and Bob came to us with more of an infectious disease orientation. We talked about two essentially different theories as to what the disease might be. We had some, at least for me, eye-opening discoveries as to the gay lifestyle of the time.

Bob and I initially took two approaches to this. First, I took the approach of characterizing some of the immune abnormalities. We had, in early to mid-1981, bought into the new technology of flow cytometry by getting a cell sorter. [Dr.] Mark Green suggested that I try to recruit some gay men and see what their cells looked like. I went back to my sister-in-law and asked for her assistance. I knew she had some acquaintances that were gay. In fact, she put me on to a fellow who helped me set up a pilot study of fifteen gay men in Manhattan that we still have going twelve years later. Essentially, we characterized the CD4 and CD8 populations in the first two [AIDS] cases at Georgetown and then in these fifteen gay men in New York. We came up with the startling discovery that half of the asymptomatic New York men were immunologically abnormal and also that there was an apparent association with nitrite inhalant use.

Shortly thereafter, Bob Biggar, who has his own novel way of thinking, with the epidemic breaking out in Los Angeles, San Francisco and New York, hopped on a plane and went to Denmark. His idea was to try to leap ahead of the epidemic. In the end, the studies were complementary. Then we put our heads together in terms of a more complete study of the two theories. Bob, coming from an infectious disease orientation, thought that there was likely to be an infectious agent. I, with a more simplistic approach and having noted the original apparent association of nitrite inhalant use, said, "I think the cause might be these nitrite inhalants." Bob was right and I was wrong.

Harden: Much may have been made of being right and being wrong, but what we are trying to do is to see what led you to these assumptions.

Goedert: We had a unique disease and a gay lifestyle.

Harden: Are there other examples of environmental substances like the inhalants, which were causing immunological problems? Or were other factors leading to these conclusions and suggestions?

Goedert: There were certainly a number of occupational exposures that led to very uncommon malignancies. It had not been very long before that a pathologist in Ohio had discovered the link between angiosarcoma of the liver and vinyl chloride in the vinyl polymer industry. I think that my

orientation was on the toxicology, occupational associations. There was a rather lengthy literature about certain occupational exposures and bladder cancer. But when there is a case of a very unusual cancer, like angiosarcoma of the liver, and then I learned that a nitrite inhalant user had Kaposi's sarcoma, it seemed to me as though the nitrite inhalants were the most likely culprits.

Rodrigues: I imagine there was little information available about the effects of these inhalants with regards to long-time exposure or the way they were being used?

Goedert: Certainly not of long-term exposure. It was clear that they caused marked vasodilatation, and it was clear that the tumor was essentially a vascular tumor. Amyl nitrite had been used as a pharmacologic agent for heart disease patients for a long time prior to nitroglycerine. Essentially, nitroglycerine is a derivative of some of these substances. There was a discussion about whether you could look at elderly men, the classical Kaposi's patients, and see if there was any relationship between nitroglycerine use and pharmacologic prescription of amyl nitrite use. I do not think those studies have ever been done. There is, just now, a case-control study of elderly men in Greece, who have Kaposi's sarcoma, to get at some of these questions. Our opinion is that they probably will not find an association between nitrite-nitroglycerine use and Kaposi's sarcoma.

The other thing we had done for the first publication, since it looked like the amyl nitrite inhalant use was related to Kaposi's sarcoma, was we collaborated with people down the hall here [at NIH] in the National Toxicology Program to have them test for mutagenesis *in vitro*. They tested rather quickly four or five of these nitrite compounds, including amyl nitrite and isopropyl nitrite, which were the two commonly used ones, and a couple of others. They found what they still feel is sufficient mutagenic activity, suggesting that these substances could be carcinogenic in humans. I think it is by no means a far-out theory; it is just one that can only be disproved.

Harden: There was another theory by another group that had to do with antigenic overload of the immune system. Do you recall your reaction to that? There seemed to be three theories floating around for a period.

Goedert: I have had a lot of feelings about that theory over time, none of them strongly positive. It always seemed a little nebulous and rather diffuse in terms of the number of people that ought to be at risk if antigenic overload was the cause.

On the positive side, the one thing that seemed potentially to support that theory was the experience with non-Hodgkin's lymphomas. There is a fairly good animal model that shows that the combination of immune suppression and antigen stimulation led to malignant lymphoproliferation in rodents. I think there are some human experiences that are somewhat comparable in terms of congenital immune deficiencies and the idea that antigen stimulation, or antigen overload, if you will, can lead to non-Hodgkin's lymphomas.

It was obvious to me that the immune deficiency of the syndrome in general, the KS-PCP [Kaposi's sarcoma-*Pneumocystis carinii* pneumonia] syndrome, that we now call AIDS, was too restricted in terms of the kinds of populations that got it. It just seemed implausible. Especially, of course, once the transfusion cases appeared, which was not long after–about a year later. Once there were cases in hemophiliacs, and especially in transfusion recipients, I think that theory just completely lost all of its air.

Harden: There was a meeting, I think, at the end of June 1982 in New York where the hemophilia data and the transfusion data on babies were presented. It may have been Dr. Biggar, or Dr. Robert Levine, who went to the meeting.

Goedert: At Mt. Sinai?

Harden: I believe so. I do not know whether you were there. But after this meeting the disease looks like an infectious disease. It was not so much in question any more. The evidence seemed conclusive. Other people have said that they were not convinced at all at that point. In July 1982, you were appointed to the AIDS Working Group that Dr. James B. Wyngaarden set up across NIH. Maybe you can talk about how people's minds were changing about the nature of this disease, and why there was a need for an NIH AIDS Working Group at that time? Was this seen as a potentially explosive situation?

Goedert: Let me go back slightly. In June of 1982, I think it was, the CDC had a meeting at the Humphrey Building that I attended where they reported the first three cases [of AIDS] in hemophiliacs. It was a hot day in Washington. That was the day those of us who were there–at least those of us who did not have a particular political agenda–were thoroughly convinced that this [syndrome] had to be an infectious disease.

That day actually had a major influence on my subsequent career because I met [Dr.] Elaine Eyster and started the whole Hemophilia Project which

is one of the major research efforts our group has undertaken, and is modeled on the gay studies. We built on that rather quickly both to pursue the scope of the problem and to determine whether there were any particular associations. Right from the start, we looked at particular blood products and the like to see whether the links might be so strong that we could identify links between the first two AIDS cases in hemophiliacs which had appeared at her center, in Hershey, Pennsylvania. The meeting was in June or July 1982 downtown in Washington and, in the middle of September, I was at Hershey where I met and examined the first AIDS case [in a hemophiliac]. The second one occurred a week later. We tried to move quickly to see if there were links between them. Certainly, by September, there was no doubt in my mind that there was an infectious disease involved.

I think there was still some doubt about what the attack rate would be. In most infectious diseases, most of the infections turn out to be subclinical and do not cause serious disease. In this instance, the prevalence of immunologic abnormalities, both in the gay men and obviously in the hemophiliacs too, was widespread enough that I think there was concern.

The NIH Task Force you referred to, I assume you mean [Dr. Robert] Bob Gordon's?

Harden: Yes.

Goedert: What can I say? There were so few of us at NIH that had early on and quickly developed a strong interest in this disease that the Task Force was useful simply for informing people in other institutes, or elsewhere at NIH, what was happening. I can remember attending some of those meetings in Bob Gordon's office. People were astonished to learn about some of the conditions, the diseases, the prevalence of the problem, and just how potentially widespread, but also unusual, the whole thing was.

Harden: This is the initial list of who was on the committee. Most of these people were either seeing patients or involved in other kinds of studies, as you were. I do not know whether you were then going out and talking to other people. I do not know how much interest there was in this disease. We have asked many people whether they thought at this point that this would be an unusual phenomenon that had popped up and would then go away, or whether they thought it was something that was going to have an exponential growth and cause a great pandemic. What did you think?

Goedert: I do not think I want to claim to have any special vision at that point in terms of what the scope of the problem might be. I do recall Jim Curran

commenting to me, after the first 100 or 200 cases had been reported to the CDC, that he thought there would be 100,000 cases in a couple of years. I remember this statement as being incomprehensible when based on a few dozen, or maybe a hundred or so, cases up to that point. I think my focus at the time was not so much on how big a problem the disease could be, but on what it was and what we could do about it

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To be rather frank, I do not think that that group [the AIDS Working Group] ever accomplished anything that you could credit it with. I think that it helped to inform some of the people that were on that committee as to what was going on. Although some of them were taking care of patients, others were in more of an administrative position. That was useful in terms of ultimately mobilizing NIH and changing its rather sluggish research response.

The real urgency in my mind was one of trying to mobilize the premier virology laboratories into developing a strong interest in this disease. Contemporaneously, [Dr. William] Bill Blattner, who was a personal friend of [Dr. Robert] Bob Gallo's, had been working on HTLV-1 and HTLV-1 epidemiology. It was clear to me that we needed to have a number of highly experienced virology laboratories essentially diverting from what they had been doing, which is hard to do, and putting more effort and research into this disease. We looked to the CDC to be doing whatever they could–I did not have any familiarity with their laboratory capabilities–and to Gallo and to [Dr. Myron] Max Essex.

Eventually other institutes, obviously NIAID and others, got around to getting some people involved in this problem, but it was a secondary interest for a rather long time. Some of the other institutes, appropriately or inappropriately, still consider it a secondary problem. But I do not think that made or broke the successful discovery of the virus. The real need was to get the laboratories involved. That committee and the like served a useful function in terms of just letting people know what was going on. I suppose, because of the long process that is required in terms of putting out RFPs [Requests for Proposals] and getting in grants, that it was probably useful in ultimately getting some funding for the likes of the Transfusion Safety Study and the MAC [Multicenter AIDS Cohort] Study, but I do not think that it had a major impact one way or the other.

Harden: Dr. Gordon was the point person to answer congressional inquiries, and I see the first wave of the activist groups, in the fall of 1982, writing letters saying, “What is this disease? Why is NIH not doing more?” Your study was one of the few investigations going on at this point, and so there is a question from a Congressman, “How much money are you spending on

Dr. Goedert's study? We need to do more of this kind of research." You were following the gay men, and you had started looking at hemophiliacs. What did you do between 1982 and 1984 when the announcement was made by Gallo's laboratory and the Pasteur Institute that there was a virus causing the disease. What did you think needed to be done? How were you proceeding?

Goedert: Up to 1984?

Harden: Yes.

Goedert: Up to 1984, there were three general types of focus in collecting and analyzing the data from the gay men and the hemophilia studies. One was simply to try and convince people that we were dealing with an infectious disease. At that time all we had was the surrogate marker, which was the T4 count, the CD4 count. It was a very indirect, nebulous measure. As I get back into cancer, I have started to realize how much easier infectious disease epidemiology is than dealing with something that is not exactly the etiologic agent, but just a surrogate marker. Developing convincing evidence that there was, in fact, an infectious cause of this immune deficiency was one focus.

The second was trying to get some handle on the likely outcome for the people that had the problem. What was the scope of the problem in the communities that had been affected, in gay men and hemophiliacs in particular? What course were they taking immunologically and clinically, since we were clearly having AIDS cases developing? What was the link between CD4 counts and the development of AIDS, and the search for better surrogate markers? The latter, in our case, ended up focusing more on interferon, which had been funded with a small grant from the Heart, Lung, and Blood Institute in search of surrogate markers for AIDS. We ended up finding the interferon association and reporting it as a potential marker of AIDS shortly before the Gallo announcement.

The Gallo discovery, of course, changed everything. For epidemiologists it changed everything because they then had a test that they could use and were able to characterize much better what was going on. We were in the advantageous position not only of having Gallo in our institute, but he was also a friend of Bill Blattner's. We had started early enough that we had a relatively large, for that time, collection of blood samples that could be tested by him. That provided very convincing proof that there was infection, that it was transmitted through anal receptive intercourse, that the number of sexual partners was a factor in transmission, and that it was also transmitted by Factor VIII concentrate. In addition, there was a clear

link to the diseases that were occurring–frank AIDS, thrombocytopenia, herpes zoster, and some of these other conditions. We were able to get an estimate of the prognosis of the people who came up positive in the Gallo test by applying some basic epidemiologic and statistical models. These showed that the trend was going in the wrong direction and that the population in which the disease had appeared first, namely New York gay men, was probably a harbinger of what was likely to occur in other populations.

Harden: You have not mentioned Haitians. A colleague who is an immigration historian said that when he heard about the Haitians being infected he knew something was wrong. A disease does not target one geographic group, unless there is a biological component. Did you have any particular views on this? I know some of the people in your section were collaborating with people in the Caribbean.

Goedert: In the Caribbean, yes, but in Jamaica, not Haiti. We had a relatively large research operation in Jamaica, and, subsequently, in Trinidad and Tobago.

I think the initial reports of AIDS in Haitians were somewhat contemporaneous with other reports of AIDS in heterosexuals. By that time it was clear, to us at least, that the disease was homosexually transmitted and could be heterosexually transmitted. The geography never bothered me at all, maybe for two reasons. One, it was clear that there was extreme heterogeneity of the geography in gay men, in that you had thousands of gay men in New York and San Francisco with AIDS, and virtually none in Chicago or Pittsburgh who were coming down with this disease. The other reason, as I understood it, was the historical connection between Haiti and some of the countries in central Africa where AIDS was by then known to be occurring.

Harden: What I am asking about is the political fall-out of this. Your point of view is that of a physician and a scientist, whereas there were people in Washington who were firing cleaning women because they had come from Haiti ten years before. These kinds of attitudes were becoming mixed up with the science.

Goedert: The problem came up most concretely for me with regard to the self-exclusion of blood donors. What do you tell potential blood donors about who should or should not be giving blood? For example, I think to this day that you still do not say, “Don't give blood if you are homosexual.” You say, “Don't give blood if you have sex with another man.” The reference is to the activity and not the person. This was more difficult in terms of calling Haitians particularly a risk group. With the discovery of

the blood test, we developed a number of collaborations with [Dr.] Sheldon Landesman in Brooklyn, where there is a sizable Haitian community. In collaboration with him, we found that the prevalence of HIV infection in the Haitian community was not insignificant, but it was substantially lower than that found in drug abusers and gay men, on the order of 6 percent. Irrational discrimination against homosexual men and against Haitians did occur. It was more irrational against Haitians, but they were more easily identified because of their language and their race than were homosexual men.

I have never been very closely involved with the Haitian population, or Haitian studies, other than in our Mothers and Infants Cohort Study. Again that is out there in the field. Unlike the situation with the gay men and hemophiliacs, where I have been in clinics and laid on hands, I have spent almost no time out in the field with the Haitians or other subjects in the Mothers and Infants Study.

Harden: Another paper you published that is timely now has to do with observing a connection between tuberculosis and AIDS fairly early on.

Rodrigues: You also mention the development of the phrase "lesser AIDS." I think you were reacting to a problem that you saw in terms of the definition of the disease.

Goedert: The definition being potentially "too restrictive," that is not quite the right word, because I think we have always recognized the need for a surveillance definition in which you could keep track of the trends and the direction in which things were going. But I think the phrase was suggested to me by our colleague [Dr.] Ron [Ronald] Grossman, who is the collaborator for our Gay Men Study in New York. He had seen many of the conditions known to be associated with immune deficiency, particularly in cancer chemotherapy patients, or patients who have received corticosteroids. But it was also clear that these conditions were not life threatening, per se, unlike AIDS conditions. I think tuberculosis was and, by and large, still is a completely treatable, if not curable, condition. The other conditions like herpes zoster and thrombocytopenia are distinctive enough that not many mistakes are made in their diagnosis, as is true for Kaposi's sarcoma or these other kinds of unusual opportunistic infections. The concept was to group together readily identifiable clinical diagnoses that were more specific than simply having big lymph nodes, and more specific, or at least easier to diagnose, than doing a whole battery of immunologic tests and saying somebody had "AIDS-related complex," based on immunologic studies whose scope we still do not entirely understand.

The idea was to try to have a sort of second-order mechanism for surveillance and for grouping conditions together to try to quantify the clinical outcomes of HIV infection, or what they might call now the spectrum of disease. Now, the spectrum of disease usually refers to all the individual conditions, but at the time the number of affected people in any individual study was small enough that it could be recognized at the bedside that there were at least twice as many people who had a clinical manifestation that fit into this spectrum. This goes back to before the virus was discovered. The aim was to try to express the idea of having ARC [AIDS Related Complex] or a clinically defined group of conditions like "lesser AIDS." I think it seemed useful.

Harden: In using a phrase like "lesser AIDS," versus "full-blown AIDS" and linking it to HIV infection, was a part of what you were doing trying to define whether or not people would progress inevitably to death? Were you tracking people to see what happened and who might recover? When did it become clear that, if a person got HIV, he or she would eventually die?

Goedert: I do not know. I think I have always been in the middle as to what the prognosis is. The people in the hemophilia community are only now coming around from the position that hemophiliacs are different. The realization is that, yes, hemophiliacs are different, but only because they are younger. That belief was based on the observation that few hemophiliacs had developed full-blown AIDS compared to the enormous numbers of hemophiliacs that were infected.

On the other end of the spectrum, immunologists, in particular, virologists, and maybe some of the clinicians, felt that this condition had to be inexorable and unstoppable. It seemed clear to me that there was a group of people, and I suppose my estimate of the portion has gone down from one third to 10 percent, that appeared to be doing not too badly immunologically for a relatively long period of time–what are now called "long-term survivors." It is certainly true with almost all infectious diseases, and even with some malignancies, that a minority of those infected, but not an infinitesimal minority, does fairly well for a prolonged period of time. They are able, in the infectious disease world, to develop tolerance or enough immune response to control the infection and have a reasonably normal life expectancy. But I think I was out front in this.

The paper that I published in *Science*, was published for one, and only one, reason. It was the first clear evidence that of those people who were infected, many were going to get AIDS. Even in the gay community at

that time, if you looked at the number of cases divided by the number of infected people you came up with 8 or 10 percent. In our cohort it was clear that 35 percent had gotten AIDS just three years after enrollment, if the proper actuarial technique was used. There was also this rank order in the three-year prognosis based on how long the virus had been in the community, with New York doing much worse than Washington, D.C., which did worse than Bob Biggar's group in Denmark. It was clear from whenever that was–it must been 1985 when we wrote that paper–that at least a third, and probably fully half of the people who had been infected, were going to get AIDS. But, again, from 1985 to the present day, it is clear to me that there is a portion of people who remain clinically well. That is what you would expect from the natural history of infections in human populations and in animal populations.

We continue to expend a lot of energy and a fair amount of in-house money [at NIH] looking for the immunogenetic factors that may account for the difference in disease progression and/or disease resistance. We view that as one of our highest priorities because it may have substantial implications for understanding not only the biology of how a person tolerates or deals with that kind of infection, but also some potential implications for the development of a vaccine or for learning what parts of the immune system must be stimulated in order to get some control over the infection.

Rodrigues: I want to ask you about the study that you did with twins. It seemed very intriguing. Have you continued research along this line, or has that particular project come to an end?

Goedert: No. It has not come to an end. It is most definitely ongoing. There is a rather interesting story about how that got started. I was invited by the Pediatric AIDS Foundation to go to a meeting in California on risk factors for pediatric AIDS and different kinds of immune response. We had reported, for example, that prematurity and low levels of anti-gp120, which is the part of the immune response that might be important in protective immunity, appeared to protect infants from getting infected by their mothers. Because of the time difference between California and the East Coast, the first morning I was there at a hotel on the beach I woke up very early. I took a long walk on the beach. I was trying to put together the things I had heard from the day before and make some kind of sense out of them. It was a good time for thinking; the sunrise was not quite over the Pacific, but coming over the mountains in Santa Barbara.

There had been one anecdote of twins being born that someone had mentioned, where one had been infected and the other had not. It seemed

to me a possible way to distinguish when the infection occurs; whether it has already occurred before the woman goes into labor, in which case the chance of infection should be random for the first-born and the second-born twin; or whether, as I suspected, again wrongly, the virus was transmitted during separation of the placenta, in which case the second-born should be at higher risk because they are in the womb longer, they are exposed for a longer time.

Harden: Is it clear then that the virus does not cross the placenta to infect?

Goedert: Let me tell the whole story.

Harden: Okay.

Goedert: The question was, if the order of infection was random you could say the virus must get across the placenta in a random order. If it was a non-random order of infection–if the second-born is at higher risk, or the first-born is at higher risk–then the transmission of the virus is non-random and it must occur during labor and delivery. Or else there is something funny about twins that we do not understand in terms of where the placentas are attached or whatever.

I recruited a young colleague at that meeting who was French. I thought we needed some French input to get the big European cohort studies and Project SIDA in Zaire involved. It was clear we needed to get a big network since even the biggest studies would only have a few twins. So that is the origin of the Twins Registry, the one study I have worked on in which 99 percent of it was conducted by FAX machine. Without the FAX machine that study would never have been done. We literally faxed out invitation letters with forms, and people faxed the forms back in. Every day was like Christmas. I would come in here and there would be a FAX waiting for me, or maybe two, or three, or four, with more data. You never knew what was going to come across the FAX machine.

The startling finding was not that the order of infection was non-random, but that it was obvious from the start that the first-born twin was at much higher risk. That was because of the physiology of the second-born coming through the birth canal much more easily after the first-born had gone through. It was just intuitively obvious that the kids must be getting infected literally as they were coming through the birth canal.

But you could not disprove–and there were actually some more subtle suggestions in that analysis–that there were probably some children who were infected before the woman went into labor; birth weight

discrepancies, the lighter child being infected, and so on. The study is ongoing.

Harden: You also looked at Caesarian section and found that that did not make any difference either.

Goedert: There was a slightly lower risk of infection, and, in subsequent analysis, the risk has been found to be significantly lower in those that were born by Caesarian section. Even in twins born by Caesarian section, the first-born is at a higher risk than the second-born. We attribute this as most likely due to what we call ascending infection, in that most Caesarians are not done electively. The amniotic fluid has already broken through and the children are already exposed. The child who is in contact with the cervix and close to the birth canal is already exposed to that. There is some evidence from the perinatal herpes virus literature that if the babies are exposed for at least four hours they are likely to get herpes, if the woman has active herpes. We think that there can probably be some ascending infection up into the uterus if the woman is in labor for at least four hours, which is not uncommon at all.

But there was a little lower risk in the first analysis and, in subsequent analyses, the risk was appreciably lower with Caesarian section for both the first-born and the second-born twin.

Harden: That is an interesting study. Is it ongoing?

Goedert: Yes. We have had an extremely good response. We now have, I think, 200 sets of twins and two sets of triplets enrolled. We have the luxury now of just analyzing those who are prospectively identified. There are some statistical reasons why it is hard to deal with those whom you find out about because one is infected. You never have any negative-negative sets if one twin had to be infected in order to come to medical attention. But we have, I think, 115 sets of twins in which we can just analyze those that are identified because the mother is infected. You get a better handle on the absolute risk because you have, in theory at least, the universe of twins that were born to infected women.

Harden: We are coming to the end of our questions relating to your papers. But before we stop, Dennis, do you have other questions you want to ask?

Rodrigues: When we were going though some of your abstracts, there was one that we read a number of times and we were not certain if we understood it. It had to do with the implications of the antibody test in terms of refining our understanding of what was meant by “safe sex.” Could you tell us a little

about that study?

Goedert: Sure. I do not know if it can be called a study. It was a Sounding Board piece, which is an uninvited editorial in the *New England Journal of Medicine*. This was at the time that politics was preventing even doctors who wanted to from readily testing their patients for HTLV-III, now known as HIV, antibodies. The rationale for limiting access to this test was, first, the potential for discrimination and other kinds of adverse activity, which was a real consideration. The second was that in theory nothing could be done for the patients who were found to be infected. The pressure, which was very successful in some communities, was to use the test only for donated blood and plasma. The wording was always very careful to specify that the donor was not being tested, the blood was.

Meanwhile, there was a raging epidemic with numerous people going around not knowing whether they were infected or not. It still makes no sense to treat everybody the same in terms of their education. The educational approach at that time, which was rather successfully promulgated by gay men, was the same for everybody–"Everybody should use condoms." There were also some other recommendations, such as finding out if the person had been sick, and so on. It was not clear then, and it is still not clear to me now, what kind of educational campaigns are successful and what are not. We have indirect anecdotes and so on, but, although I do not consider myself a scientist, I do consider myself somewhat of a social scientist. It is very dissatisfying not to have a clear picture as to what kind of education is helpful or successful and what kind potentially may even be harmful. You could, in theory, tell everybody to use condoms and in theory–I do not think it is likely–you could promote sexual activity.

The Sounding Board piece basically said there is an objective way to define truly "safe sex," and that is no sex; masturbation, in which there is no contact with other people; and a completely monogamous relationship with another person, provided both have the same HIV antibody status. It is very explicit not only that both people are negative, but also that both people could be positive. I think it still never has been shown that there are adverse consequences from two HIV-infected people having sex with each other. But in order to do that, you then had to apply the antibody test to this counseling and definition purpose. The points of the article are:

One, you can define clear standards for what is completely safe. You may not be able to achieve the standard, but at least you will know how close you are getting to the goal; and, two, people can be free to have unrestricted sex if they and their partner know their antibody status. It

seemed to me that this was likely, at least in some populations, to have an advantage in getting closer to the goal, closer to the achievement of truly safe sex in a larger portion of the population. It also seems like a clearer message, rather than, "Reduce your number of partners," "Use condoms," or "Use condoms at least if you are going to have anal sex." Or, what about oral sex? I do not know. There are still many things we do not know, but it seemed to me that the antibody test could be used to define sex with a monogamous partner that was truly safe. Conversely, the antibody test could be used to define frankly unsafe sex if the people were known to be discordant.

We have continued to confront this in the hemophilia couples where the men are almost all infected and the women are almost all uninfected. What can those people do? Not much. That is a tragedy. But to tell these people that they can just use condoms borders on perpetrating a fraud. I think when the rubber meets the road, so to speak, ultimately they say, "If you have intercourse, then at least use a condom." Then you are making it clear that it is a second order preventive activity. It is not research–it is opinion–but it is rational opinion, I hope.

Harden: But the kind of research that you did put you in a position to make such kinds of recommendations, or be asked to, at any rate, more than someone who was simply looking at a test tube.

Goedert: Yes. I always enjoyed being close to the firing line, close to the fringe. While I wish there were more people like that, I think the whole system, the whole field, is too timid and too sluggish. At the moment I am frustrated by the vaccine trials. Where are they going? Are they going anywhere? Are we being too timid?

Harden: It has concerned me for some time that subunit vaccines do not seem to be being investigated, not only in AIDS but in some other areas too. Will we ever have any kind of a vaccine given how fast this virus mutates, and what should we be doing? If you feel frustrated by what is happening, what do you think might be effective? Will it be subunit vaccines? Will it be whole virus vaccines, live or dead?

Goedert: I am not a vaccinologist, but I heard a telling comment at a meeting I was at within the last week, "You could learn a lot from your failures, but if you don't try it, you don't have any failures." I am not close enough to the subunit vaccine work to be completely discouraged. The people who are working on it are probably discouraged, and maybe I should believe in their discouragement, but even those people, I do not think, are completely discouraged. I believe that we will have a vaccine. I found very exciting

the recent report of the SIV vaccine that used a deletion mutant. It deleted one of the regulatory genes from SIV and really had a very successful challenge, not only with the homologous strain of SIV, but also with a virulent strain of SIV.

Let us consider the subunit vaccine. We will never know which way to go on subunit vaccines until we try them more. Although I am not a vaccinologist, unless there is good reason to think that the person's risk of becoming infected might be increased, or their infection enhanced, we will never know what does not work until we get out there and try it.

Harden: Let me ask you an epidemiological question. Last Sunday in the *New York Times* there was a discussion of the new National Research Council [NRC] report suggesting that we could reduce the incidence of AIDS to low levels by targeting zip codes where there are a high number of infected people. Have you heard about this?

Goedert: Yes. I did hear about it. It was a spin-off from that NRC report that basically said that AIDS has not had much of an effect on the social institutions in the United States, except maybe in New York. This is a higher-powered microscope look at New York. They say AIDS incidence is not even in all areas of New York. It is only high in some of the zip codes in New York?

Harden: Yes. In fact, in the *New York Times* they published a zip code map of New York, showing that they were probably seven or eight zip codes where the infection rate was extremely high. We are awaiting the arrival of the NRC report to read it in more detail, but the idea is that education efforts and other programs could be concentrated in very highly infected areas, and by this means, the incidence of the virus reduced so low that it would not be a factor in the larger population. Would you respond to this possibility as an epidemiologist? Is it a reasonable tactic?

Goedert: No. I think it is wrong. I think the horse is out of the barn. Do you know if the maps are related to recent infection rates, as opposed to AIDS rates and so on?

Harden: I think it is infection rates, but I do not know how recent they are. I see your point.

Goedert: If you did a map of AIDS cases in New York, you would find all these places in lower Manhattan where all the AIDS cases were in gay men. There are very few new infections going on in gay men. It is not zero. But I assume that is not what the report is talking about. It is discussing some

of the minority populations in the Bronx and the like.

Each community obviously has to identify what populations are at highest risk and develop a culturally appropriate, but pointed education effort to get information to those people. But there is very substantial HIV incidence, which is new infection rates, going on in rural America. To have said in 1982, that all education efforts should be concentrated among gay men in New York, San Francisco, and Los Angeles when there were not only enough infected gay men living elsewhere but there was enough mobility within that population, would have been ludicrous. Think of Bel Glade, Florida. In Bel Glade, Florida, a substantial portion of the infected people was migrant farm workers. Are you going to target your effort to Bel Glade, Florida, and believe you have taken care of the problem? Those people go elsewhere and harvest crops.

No, I do not think that approach makes any sense. If the people in communities in Texas feel that farm workers are a group at high risk of becoming HIV positive or spreading HIV, then they should certainly concentrate on the farm workers and not worry much about the school children who live there all the time. But to think that you could come up with a geographic map and focus on a certain area, that does not make any sense. There is too much mobility. In fact, even in areas like Florida and Texas, migrant farm workers probably go back and forth to Puerto Rico frequently and there is a raging epidemic in Puerto Rico.

Rodrigues: I notice from your curriculum vitae that you made a presentation to the Presidential Commission. Was that the Watkins Commission?

Goedert: Yes. That was on the "What is Safe Sex?" thing we just talked about.

Rodrigues: Thank you.

Harden: Would you like to add anything about where you see this epidemic going and what your prognosis is for the future?

Goedert: On a personal level, AIDS has been great for careers, and mine in particular. But on a public health level it has been a disaster, and continues to be so. There are many frustrations and I think the institutional sluggishness is a serious frustration. The timidity of people who get involved is a frustration. The politics are necessary to a point, but it is again a major disappointment that politics so much impedes efforts to try and improve what we see as our mission [at NCI]. That is improving the health of people, reducing their risk of disease, cancer, and death.

Harden: Will it help reduce the sluggishness of research to move all NIH AIDS grants through the Office of AIDS Research? Or do you think it will add another layer of bureaucracy?

Goedert: I think it is worth trying. Those of us in the Cancer Institute are very fearful that we will get left out. I think it will depend on the vision, open-mindedness, and willingness to take chances of the person who takes that office. The office, quite frankly, is set up as a consequence of political pressure. If it is used as a tool of the interest groups, it is asking for trouble. It is not the most expeditious way to get the job done.

The reason I am in cancer epidemiology is to try to prevent people from getting cancer, and that means that our success is in cases we never see and diseases you never see. The Hippocratic Oath, and simple decency, calls first for taking care of people who are sick or dying, but it is clear that the interest groups have that as almost their sole interest. I am here to try to prevent many, many cases from occurring. I do not think you can do the most good for the most people by focusing a grotesquely disproportionate amount of your resources and efforts on treating people. Treatment research only helps people who have or get the disease, but preventing the disease, in this case preventing HIV infection, will do much more good for many more people. How can infection be prevented? That is what vaccine research, epidemiology, and behavioral research will answer. But it is the people who have the disease that mobilize the Congress and the money. It is now true for breast cancer, of course, and I understand it completely. I have dealt closely with people with all those diseases.

I think that the person who takes that Office [of AIDS Research], will only be a success, in terms of ultimately dealing with and controlling this epidemic, if the person has enough wisdom, a broad enough view, and enough strength of character to resist the political expediency of pouring more and more money into treatment of the comparatively small number of people who are now sick, as opposed to the much larger number of people who are at risk.

Let us hope that whoever gets in there has enough wisdom to help us. One of our immediate concerns–it has been immediate for a while–is to understand the cause of cancer and, ultimately, how to prevent it. We are using this as a way to understand the cause and prevention of AIDS-associated cancers and, obviously, cancer in general, without HIV infection.

Harden: One starts to see all sorts of areas of research coming together in cancer,

AIDS, and the whole immunological understanding of the body. Immunology seems to be taking over everything in one sense as a fundamental discipline.

Goedert: Yes. It is quite fascinating in terms of neurologic diseases and the like.

Harden: Thank you, Dr. Goedert. We certainly appreciate your time and your comments.