

This is an oral history interview with Dr. Samuel Broder, the former director of the National Cancer Institute (NCI), on the response of the National Institutes of Health to AIDS. The interview was conducted on 2 February 1997 at the Hyatt Regency Hotel in Bethesda, Maryland. The interviewers are Dr. Victoria Harden, Director, NIH Historical Office, and Dr. Caroline Hannaway, NIH Historical Contractor.

Harden: Dr. Broder, we would like to start the interview by asking you to tell us a little about your background, where you grew up, where you went to college, where you went to medical school, and how you got into medicine.

Broder: I grew up in Detroit, Michigan. I went to the University of Michigan as an undergraduate, and then I went to the University of Michigan Medical School. I graduated from medical school in 1970. I went to Stanford University in Palo Alto, California, right after graduation, did my internship and residency in internal medicine, and came to the National Institutes of Health (NIH) as a clinical associate in the National Cancer Institute (NCI) in the early 1970s.

Harden: What was it that made you go into medicine? Were there any particular family influences, for example, that made you want to become a doctor?

Broder: That is complicated. I think basically I was interested in a combination of science and scientific activities and an ability to help either people individually or from a public health perspective. I acquired that interest probably when I was in my early teens. It is hard for me to pinpoint any one force that did that. It just seemed like a very logical thing to do, and things unfolded thereafter.

Harden: When you came to the NIH in the 1970s, with whom were you working and what were you doing?

Broder: I worked initially with Dr. [Thomas] Tom Waldmann in what was then called, and probably still is, the NCI Metabolism Branch. I moved briefly to the NCI Medicine Branch and then moved back to the Metabolism Branch. In approximately 1980, an opening occurred as the head of the clinical oncology program at NCI. It seemed like a good opportunity, so I became the head of the clinical oncology program.

Harden: That is a rapid rise. Tell us about your earlier research. What were you doing in those years before you became head of the clinical oncology program?

Broder: I was interested in immunodeficiency disorders and was particularly attracted to the relationship between immunology and cancer. Tom Waldmann's group had a number of very interested and focused individuals who were studying diseases like ataxia telangiectasia, the Wiskott-Aldrich syndrome, hypogammaglobulinemia of different types, intestinal telangiectasia, and other things like that. They seemed to personify what I was interested in doing in that most of the people in Tom Waldmann's group were doctors, M.D.s, but they were interested in generating knowledge and learning from patients, both as individuals and as part of the clinical trials activities. In fact, that was actually a very interesting time, because [Dr. Robert] Bob Good in that era, had extolled the virtues of studying "experiments of nature." The theory was that there were certain clinical syndromes which, despite their rarity or seeming uniqueness,

actually taught broad lessons in medicine and science; and that these often resulted from inborn errors of the immune system, or sometimes from certain acquired injuries to the immune system. These clinical syndromes “performed”, if you will, experiments of nature that were more interesting than what a scientist in that era, or maybe in any era, could have designed.

Harden: This was the period when molecular immunology was flowering. Do you recall feeling as though you were learning something new every week?

Broder: I think there was a lot of excitement. The molecular revolution actually had not quite taken off when I first got to the NIH. It was in its infancy, and probably the questions being asked were, at one level, removed from the kind of elegant molecular biology that now informs immunology, informs everything.

But I think, ironically, I did catch the wave of the National Cancer Program, which then was still very new. This program was very controversial, and I think, in some ways threatening to some members of the scientific community, both inside the intramural program and throughout the country. But, actually, the National Cancer Program was an engine that drove almost all biological research and provided unbelievable benefits to the NIH generally and to intramural scientists and to those who received grant support.

I think it was a very interesting time, because the public’s commitment and vision in favor of cancer research were applied across the board to virtually every Institute within the NIH. Many of the ideas that we take for granted (cloning and sequencing genes, expressing novel, new proteins, understanding

the molecular basis of genetic regulation, and so on) were derived from the commitment to study things in the context of cancer research. I think that was a bargain for the public at large, and I think we are still seeing the aftershocks and residuals of that era. There is still much misunderstanding and perhaps even occasional anger about the National Cancer Program.

I joined the NCI at a time when many ideas could be pursued freely, particularly in the clinical arena, without necessarily worrying about clinical costs and the limitations of third-party payers. This was a marvelous, and alas, now vanished time.

Harden: You were always involved in clinical research?

Broder: That is correct.

Harden: I would like to hear your comments on being a young investigator in the NIH intramural program. What was unique about this? And what were the limitations?

Broder: I can look at it only from the standpoint of what I like to do and what I thought was being done in the intramural program. In the intramural program, scientists can make a serious commitment to clinical activities at the same time that they have their own laboratory activities. Even more important, they can use the clinic as a vehicle for generating hypotheses that can then be taken back to the laboratory. I think there are some profound misunderstandings of how important this is, primarily amongst scientists who spend their entire lives in a conventional laboratory and may not appreciate how important is the clinic can

be in generating knowledge for the laboratory to pursue. Being able to make observations in patients and then using those observations, based on the skill and acumen of a great clinician, to go back into the laboratory and to answer research questions, is a wonderful feature of the intramural program. However, I fear that the importance of the intramural clinical programs may now be underappreciated. In other words, the people who founded what is the modern version of the NIH took great pains to locate laboratories in juxtaposition to a hospital ward or a clinic. Sometimes a laboratory would actually be on a ward--a research laboratory, not a clinical laboratory--and that juxtaposition between scientists and clinicians, allowing a clinician to see patients and walk a few steps back and forth to exchange samples of tissue or blood, was invaluable for progress. The free flow of knowledge and the encouragement of ideas based on that principle were unusual and perhaps unique.

Programs in other parts of the country and in other academic centers could perhaps do the same thing, but I think they tended not to. Even when I arrived at the NIH, the seeds of managed care were already planted, and while they had not completely taken root, other academic centers lacked the freedom to do what NIH could do. We are now obsessively focused on third-party payers and making sure that revenue targets are met. As the 1970s and 1980s unfolded, we saw a compartmentalization of clinicians versus laboratory scientists. Part of this was based on the reality that laboratory science became extremely specialized, requiring skills in molecular biology not available to the ordinary

physician. But many of the individuals at the NIH, nevertheless, made a very effective transition into the new world of molecular biology. I had the good fortune to work with many such people, people like Tom Waldmann and a number of other people who were very effective at bridging the gap.

I think that that this bridging function was extremely valuable, and my suspicion is that much of it may have been lost. My fear is that the intramural program does not function at that same level in terms of the interplay between the lab and bedside, and probably no place in the country now does. I think the NIH leadership clearly has not assigned full value to this function historically, in part because of practical necessity (costs), in part because of a lack of an appreciation or respect for the process.

Hannaway: To follow up on that, do you believe now that the emphasis on laboratory research has become predominant at the NIH in terms of where discoveries will be made?

Broder: I think that is basically correct.. I do not want to be misunderstood on this point. It is a basic principle of anyone who has ever led the NIH and anyone who has ever held a senior position at the NIH, that basic, fundamental, unrestricted laboratory research has an indispensable and cardinal role in the activities of the NIH. I certainly do not disagree with this philosophy. However, the process of generating ideas for science does not follow a simple trajectory, involving a simple process in which a scientist thinks of an hypothesis, generates all the laboratory data that might be necessary, identifies a gene and molecular pathway

that is relevant and then, by essentially a black box, knowledge gets applied in the clinical arena. I think it is quite the opposite in many situations. Sometimes an astute clinician, or a set of clinical observations, drives the basic research in fundamental ways.

It was once very common to see individuals who could traffic in both scientific and clinical ideas. When I first got to the NIH, this was still very common. It is becoming less and less common and less and less respected or valued, in my view. The NIH is potentially allowing a two-class system in the intramural program: there are the *crème de la crème* basic scientists, and then the clinical scientists are an afterthought or are tolerated as a necessity. Perhaps this critique is not totally fair, but I think there has been drift in that direction.

Harden: I know that [Dr. James] Jim Wyngaarden was very concerned about the situation with clinical investigators when he was director and was trying to encourage more people going into clinical research. Perhaps it is just very difficult to do clinical research, find the funding, and have the expertise in the laboratory.

Broder: I think that is true. Institutions are often defined by how they reward individuals, and I am not talking about simple financial reward. I am talking about a culture of respect and giving positive reinforcement. I think that people who can function in basic and clinical research perhaps receive less respect than they did in an earlier time.

I think that, on balance, for example, the NIH of today might find it difficult or impossible to respond to the AIDS epidemic in the same way that it

did in the early 1980's. Getting answers very quickly would be very difficult, in my view. Providing the necessary resources and administrative flexibility might be very difficult.

I do not think it is an accident that much of the critical work for perhaps the first three to four years of the AIDS epidemic originated within the NIH intramural campus.

Harden: I recall seeing an NCI memo dated 1981 or 1982 to [Dr. Vincent] Vince DeVita saying, "This new disease looks really serious. I think the Cancer Institute needs to commit money." This memo shows a grassroots response to AIDS—an investigator bringing it to the attention of the NCI director, rather than the other way around. Would you agree that this is what happened?

Broder: You asked an interesting question, because you are describing a situation in which the National Cancer Institute is responding to what looks like an infectious disease in a public health emergency. In fact, that is a strength of the program. The National Cancer Institute was criticized for doing that. But at the beginning of the AIDS epidemic, —NCI resources had to be placed in the service of identifying a cause of AIDS and possible prevention and treatment.

There is a potential lack of corporate memory. Some scientists and organizations, that might have made a contribution, did not respond to the AIDS emergency. I am not being critical. I am merely stating a reality, that a scientist in a laboratory doing wonderful work may not feel that he or she has any obligation, in such situations. It may not appear to be an important problem to

that person. The NIH, and its unique team of scientists and clinicians, and especially a core of individuals who could wear both hats, made a profound difference. In my opinion, there were no counterparts to Bob Gallo or Tony Fauci, outside the NIH.

Hannaway: Can you remember when and how you first learned of AIDS. Do you have a recollection of that?

Broder: Well, we had a case on Tom Waldmann's service, in 1981. This was an individual who basically was a walking synopsis of what AIDS turned out to be. It was not then even called AIDS. There were various names being given.

Hannaway: GRID.

Broder: The GRID syndrome, that's correct. There were all sorts of complicated names attached to it. I do not think the name AIDS had actually come into play at that point.

We admitted this man, who was referred to the NIH because he had a profound immunodeficiency, a very dramatic reduction of lymphocytes, a very strong susceptibility to opportunistic infections of various types—viral, bacterial, pneumocystis, a number of things that were not very clear--and in some ways, did not fit the definition of any then-known immunodeficiency disorder.

Harden: We have talked to Dr. Waldmann.

Broder: So he must have described the same thing.

Harden: Yes. He has described it.

Broder: So you know I am not making it up!

Harden: No, no. The only problem was that the medical records for that first patient were lost, misplaced, something happened to them. But we have heard about this patient from a number of people.

Broder: You see, it is part of the conspiracy to downplay the contribution of the NIH intramural program!

Harden: Dr. Waldmann said that people are going to think that.

One person with whom we talked said, "I remember there was a large group of people in this room. Everybody wanted to see this patient that Dr. Waldmann had."

Broder: There is no question that this was an unusual patient. His medical history showed that he had visited Haiti, he ultimately had a lymphoma of his GI tract, and many unusual infections. Basically, all I remember saying was that we had never seen anything like this before, and I hope we never see anything like this again.

Hannaway: But had you read newspaper accounts or heard from colleagues about AIDS?

Broder: Oh, yes, sure. It was not called AIDS, but as part of the work-up, we discussed anecdotal reports of a new immunodeficiency disease in otherwise healthy gay men. The junior staff had done a very good job of reviewing the literature and came across some unusual cases, sporadic cases of gay men, primarily in New York and San Francisco, who seemed to have very unusual and devastating things happening to them, especially a kind of global immunologic failure.

There were two indicia that something very strange was happening. First, they were young men starting to get ill, and their doctors were having to call the CDC [Centers for Disease Control] for the release of pentamidine, which was then used for *Pneumocystis carinii*. Ironically, one of the world's repositories for knowledge about *Pneumocystis carinii* was in the intramural program of the National Cancer Institute, where Vince DeVita was one of the world's authorities. Same goes for Tony Fauci, whose lab was about 4 floors above the ward. So there was an enormous realm of expertise. [Dr. Philip] Phil Pizzo was here and was able make a number of contributions. There was an enormous wealth of expertise all within a few floors in one building.

Harden: Do you remember the conversations of people talking, "What on earth is this?"

I do not know whether, how...

Broder: Sure, sure. There was an enormous sense of pressure and urgency, because there was so little known and so little we could do.

As additional cases became known, there was a substantial level of stress and a certain level of public distrust and confusion, all of which made everyone's life more difficult.

The situation temporarily gave a level playing field to all sorts of crazy people who, in the Andy Warhol sense of the term, could obtain not only 15 minutes worth of fame but possibly build a career, promoting ideas without a scientific foundation. This greatly confused the public and to some extent damaged science. In part, the sheer complexity of AIDS, and the inability at

that time to determine its cause or treatment, made things much worse. The only way you can block a very bad idea is to put forth a good idea. At the very beginning, scientific community was not able to do that. We really did not know what was going on. So the only honest thing we could say is, “We need more research.” Many of the theories put forth at the time essentially blamed the victim, and greatly complicated many issues related to public education about disease transmissibility.

Some of the issues of lifestyle became a big issue, and Tony Fauci once, when it came to maternal-to-fetal transmission, asked a critic, “What lifestyle did the fetus undertake to acquire the disease?” I do remember feeling a sense of sadness that a number of scientists, who had great power and great prestige, were delighted to stay completely out of these issues in that era.

Harden: Did you see any homophobia among the scientists at the NIH who stayed out of it or got into it or...

Broder: No. I know of no scientist who refused to enter the AIDS research arena on the basis of homophobia.

My only point was that there were a number of scientists who basically said, “I am doing my own research. You do your thing, but I am not switching to this. I am not going to spend any time on AIDS.” I do not know if I am the only person who has expressed that view.

Hannaway: No. A few people have. Some have been quite dismayed, I think, by some people wishing to stay away from AIDS research.

What we wanted to ask you about now is that, after the AIDS retrovirus was identified, you decided to pursue research into treatments for AIDS in your laboratory. Could you describe how you came to this decision, who was in your laboratory, and how you initiated and organized this research?

Broder: This is a complicated question. It was clear that we needed a focused laboratory that was used to drug discovery, and was willing to work with live AIDS virus. The only institute in the NIH that historically had focused heavily on new drugs is the Cancer Institute. Other institutes certainly played a role, and other institutes have made wonderful contributions to the therapeutic armamentarium. But the Cancer Institute is the only group at the NIH that actually had become a “pharmaceutical company” working for the public, in difficult areas where the private sector either could not or would not make a commitment. Ironically, one of the drugs synthesized for the National Cancer Institute was by Jerome Horowitz under an NCI grant working at what was then called the Detroit Cancer Institute, I believe, and is now called the Michigan Cancer Foundation. This was AZT, and it was initially created and tested as a possible anti-cancer drug.

Hannaway: During the 1970s or...

Broder: During the 1960s and 1970s....

I turned my laboratory to trying to look for drug discoveries in that arena, knowing that we could have at our disposal all of the things necessary for early drug development, including a ward right down the hall, with the backup

of the entire infrastructure NCI had established for new drug discovery and development. In effect, we had a “skunkworks.” We did not cure AIDS, but we did deliver many specific drugs in real time: real drugs, not theoretical things, not promises to develop a drug in the future, not the basis of an RFA or an RFP- - real drugs. Some of them were patented on behalf of the government, some of them not, some originated in collaboration with private sector partners, others not. But a large number of candidate therapeutic drugs emerged from the NCI programs. Some were successful, others not. However, even those that were not successful stimulated important further research and, in my opinion, were an antidote to the sense of therapeutic nihilism that was very common in that era.

We had superb clinical investigators like [Dr. Robert] Bob Yarchoan, who was available and ready to do the things we needed to. We had Hiroaki “Mitch” Mistuya, who was exceptionally gifted, and could grow anything in tissue culture. He was able to set up mass screening systems that were very effective and reliable. That attracted the attention, of course, of what was then Burroughs-Wellcome in developing AZT. Then we were able to develop analogs, (some of which are still out there), or at least stimulate the development of other analogs. [Dr.] Jan Balzarini joined me from Belgium. He was an exceptionally good medicinal chemist/pharmacologist. And we were able to tap on many of the people like [Dr.] Dave Johns, [Dr.] John Driscoll, in fact all the people in the intramural program. They were able to do structure activity relationships with us. There was a two-year period of time where everything

sort of clicked in and the bureaucracies were not there, to do what bureaucracies usually do. I do not think it could be done now, quite frankly.

Hannaway: Was Dr. Mitsuya already in your laboratory?

Broder: He was absolutely already there.

Hannaway: Was he a postdoctoral fellow?

Broder: He was a postdoctoral fellow at that time. He subsequently has become a permanent staff member of the NCI.

Harden: And this window is, you are saying, 1984 to 1986.

Broder: I would say from about 1984 to about 1987. But there was a two- to three-year window of time where the bureaucracies were not well established yet. Quite frankly, among the reasons why I think bureaucracies stayed away is that there was a strong presumption that the project would fail quickly or self-destruct.

Harden: I would like you to elaborate on this because of two things. I am very interested in how scientists thought about AIDS when it first appeared. Were they all thinking within the same paradigm, or were, for example, basic scientists thinking about the disease as a molecular phenomenon while physicians were thinking more of the whole patient?

Broder: I do not think there was one simple viewpoint. In my case, I was influenced by the fact that I was trained as a medical oncologist and, therefore, in some ways was able to take advantage of similarities in the way a retrovirus replicates and the way a tumor cell replicates. I was also willing to accept that it is better to make some progress quickly than hold back and wait for a cure before acting or

before trying to implement a new therapy.

A starving man or woman cannot turn down a slice of bread because it is not a full loaf, and I think that, on balance, many of the scientists involved, perhaps from a combination of well-intentioned but naive analyses of the situation, were really saying, “A cure or nothing. Give me 20 years and I’ll give you a cure.”

In addition, there was a lack of an appreciation, an ineradicable lack of appreciation, for the role that certain types of clinical advances play in the basic research agenda. Once there was at least a recognition that one could make certain partial advances with a single agent, AZT, then one could bring in things like didanosine, or the other products. One could bring in non-nucleoside inhibitors. One could be more confident that viral protease inhibitors would work, and were worth pursuing.

Hannaway: Did Dr. DeVita support your ideas of going for the slice of bread if you cannot have the whole loaf?

Broder: Yes. But he also did more than that. He had a belief that you can do things without having to wait for perfect knowledge, and he was not afraid to act. There was a destructive level of skepticism at one point. Some scientists forgot that skepticism is a tool of science; it is not a replacement for science. It is a tool that allows you to analyze, to weigh and consider, not to be fooled, not to let your emotions run away with you. But what was happening, in my view, in some portions of the scientific community was that skepticism became

the format of science: it was very unhelpful. There was a curious belief that nothing would work. When we had our first reversal of dementia, which subsequently became a common thing, especially in children, some scientists said that they would not believe it. We would show them PET scans. They just refused to believe it

Hannaway: Did Dr. Bruce Chabner, who was the chief of the Division of Cancer Treatment at the time you started this work, believe that AIDS drug discovery was an important part of his division's mission?

Broder: Yes, and he made major contributions in his own right. He was interested in a drug called trimetrexate which turns out to be a very good agent for certain opportunistic infections—this drug was originally developed for cancer, but it has value in other clinical settings.

Harden: In 1986 the Technology Transfer Act became law. It represented a tidal shift in attitudes towards patenting within the government. Do you want to comment on it?

Broder: The federal Technology Transfer Act of 1986 and subsequent iterations of it proved to be very valuable from a scientific point of view. This act provided a framework for working with industry and for making it the policy of the NIH and other federal laboratories to concern themselves with the practical applications of research, and getting the fruits of research to the places where the public good could be served. The Act provided an incentive and a legal framework for getting products developed and for collaborating with the private

sector in ways that would otherwise be impossible. .

Harden: Going back to 1984, was there much interaction between your laboratory and Dr. Gallo's laboratory? We noticed that you published several papers with him in that period, and you were reviewing treatment avenues in one of them. Could you just elaborate a bit on how his work in etiology and your work in treatment might have fit together in the context of the intramural program?

Broder: There were many interactions, on many levels. This included making sure that the Gallo lab received tissue samples and peripheral blood specimens, which accelerated their discoveries in AIDS. The Gallo group made a number of seminal contributions, and it is my view that their location on the main campus, within easy reach of the Clinical Center, made their lives a lot easier. It is worth noting that there were substantial criticisms about all of our efforts at that time, based on a lack of awareness of precisely how much was actually getting done.

Harden: This would be from outside.

Broder: Yes. I did not stop what I was doing in the clinical oncology program. I still was supposed to run the cancer intramural treatment arm and function as the clinical director, and no one said, "Okay. Well, you do not have to do that job." This was an add-on. And Gallo had other things that he was doing, too. And it could have all gone nowhere.

Harden: That is a theme that we have heard again and again, too, that AIDS research in the early years became an add-on and that people simply stayed later and

worked nights and weekends.

Broder: Right. For a substantial amount of time, there were certainly no additional resources available.

Harden: Would you comment on a strong misconception by AIDS activists during the early years of AIDS that science was just another political force, and that if they yelled loud enough or obtained enough money, a cure would be discovered.

Broder: This issue is not simple, and I think it cannot be reduced to a simple analysis. Activists or patient advocates are human beings, so they are subject to the full range of human frailties as well as noble features. There is a constructive form of advocacy and a destructive form, and some of the premises are built on the principle that if we yell loud enough, we'll get more money, and money will translate to progress. And that is partially true. There is no way of getting around it. It would be unrealistic to say that is not true.

My concerns over the advocacy in that era, or advocacy in general, is usually not focused on whether patients want more resources. Of course patients want cures, not excuses. I agree with that philosophy. Patients want their government agencies, particularly the NIH, to solve problems that concern their health or the health of their loved ones. I do think that there were many areas of misunderstanding. I believe the patient advocacy community was correct in their concerns that there was an unwarranted detachment in some elements of the scientific community who conveyed a sense of indifference, perhaps not intentionally so.

The “obligation” of any patient is to get better. Doing something for science, or for a greater good, is something that we cannot compel in our society. Patients do not have such a duty, nor can any centralized government authority say otherwise. Some members of the scientific and clinical community just assumed that patients would be willing to enroll in placebo-controlled trials, and they did not initially do enough to work with patients, to listen to their needs, and to look for constructive ways to develop new drugs, using placebo-controlled trials when necessary, but exploring a range of other approaches when not absolutely necessary. One of the really powerful memories that I have is when the AZT randomized clinical trial was completed. At one point in time, there were approximately 19 deaths in the placebo arm, and there were zero or, maybe at most, one death in the AZT arm at a certain interval of time. I remember that Vince DeVita had been hospitalized for some emergency surgery.

I had to track him down while he was recovering from the surgery to show him the data. We were then in the process of reviewing what to do. And, there was an enormous air of uncertainty and doubt about what to do at virtually all levels of the scientific community involved. I remember Vince clearly and calmly saying that we should stop the study. He knew when to do a study, and when to stop study. He is a great thinker on these issues. There were some members of the scientific community who were not quite so in touch with reality. Whenever clinical researchers are dealing with a potentially lethal disease, they need to

carefully assess these issues, and make sure that they do what is necessary to explain what's at stake to the patient community.

Hannaway: I would like to come back to your early contributions to AZT research. Your laboratory was important, of course, in developing a precise anti-HIV screening assay known as ATH8, and Dr. Mitsuya, of course, was involved in this work with you. Could you discuss the development of this assay a little for us and explain how it worked in some detail.

Broder: We made a decision in the early 1980s, that we would begin screening for compounds that had several properties: speed, reliability, simplicity. Hiroaki Mitsuya made several contributions. He developed a very rapid system, backed up with other confirming, longer tests, for checking whether a drug would work to suppress the AIDS virus in tissue culture. And he developed a sensitive line that died upon contact with the virus, to actually see the cytopathic effect of the virus, under very rapid conditions, adaptable for selecting candidate drugs that might go into the clinic. His techniques were robust, and as events have proven, predictive for success in the clinic. For a time, his work was the foundation for a large number of ideas that went into clinical trials.

He also was courageous, and kept the morale of the lab at a high level. In working with live AIDS virus in that era, you did not know whether you would be infected. You did not know what the issues were. It was a real concern then.

And I think Mitch was very dedicated, worked very long hours, and, out of respect for others in the lab, would work after hours so that other people would

not have to fear the work he was doing. He did not complain, he just did what he had to do. And we could take his discoveries right to the clinic. Even those few people who were screening for new anti-AIDS drugs had essentially no effective clinical arm.

Hannaway: So they could only work in the lab.

Broder: They could only work in the lab and then publish some paper somewhere and hope that somebody would pick it up.

Hannaway: Were there any technologies, in addition to being so near the clinical arena, that helped in development of these assays?

Broder: Well, a lot of the technologies were dependent on the Gallo group, because one of their earliest things they did was to develop new viral isolates. There were various isolates. Some isolates grew only in certain types of tissue-culture conditions, some isolates grew in T cells, some grew in monocytes. We could conduct a whole area of research based these tissue-specific isolates.

And we learned things about AIDS drugs. For example, some of the nucleoside analogs we used are inert in their own right and have to be anabolically phosphorylated or activated inside a cell before they begin to work, How they are handled (activated) in monocytes or macrophages is different from how they are handled in T cells. We were learning how to manipulate this system and how to get the maximum activation, if you will, how to pick rational combinations based on biochemical pharmacology. AZT, for example, works especially well in dividing cells. Another drug, ddI, works particularly well in

non-dividing cells or resting cells, and, therefore, could block the initial entry into cells.

Harden: You obtained potential anti-retroviral drugs from pharmaceutical companies. Was this your initiative? Was it their initiative? Could you go into some detail about how this process worked.

Broder: Yes. One of the things that was very clear to me early on was that we would need partners in the private sector, and that we would eventually need them, if nothing else, to circumvent what would be, an inevitable bureaucracy. Scientists from the Burroughs-Wellcome company and I got together largely through the help of [Dr.] Dani Bolagnesi. They were willing to do things, to develop products, and not just to talk. They were willing to exchange information and provide drugs that could be tested. And they were pretty clear that they would make a commitment to try to develop and commercialize a product that looked good. Even they had trouble with their own internal corporate bureaucracy, however. It turns out the private sector has its own share of bureaucracies. At one point, the company could not obtain its own supply of thymidine, a starting block for the synthesis of AZT. We at NCI were able to send them a large shipment.

Hannaway: Where had you obtained it from?

Broder: The NCI had a repository of thymidine from another era. We were one of the world's few places where you could get it. But Wellcome scientists were bummed out. I mean, if they were honest, they will recall that they were unable

to produce it. There were going to be dramatic delays. And then, voila, a shipment of thymidine arrived in the company loading dock. New drug development is complex, expensive, and not something that just any group at NIH has the infrastructure to do.

Harden: I want to pursue a little further the question of private and public collaboration, because this became the bone of contention in the lawsuit over who was to have the patent on AZT. And just for the record, I would like to get more details of your version of how you became involved with Burroughs Wellcome in AZT research.

Broder: Sure. Dani Bolegnesi, a Duke University professor, helped to arrange a meeting. I do not remember exactly when it was. But early on in the process, I went down, talked to the company about our capabilities. I exchanged some of the early results we were obtaining. I explained what our capacity was in terms of clinical trials and essentially offered a collaboration with them, with the promise that we would, whatever came up, develop drugs as fast as we could and that they would get a product out of it. There was no other way to encourage pharmaceutical companies. They were not the only company that I visited, but to their credit, they were the first to make a serious commitment.

Harden: Would you have done it differently after the Technology Transfer Act was passed? Would you have done it differently to try to tie down these legal things after what happened?

Broder: No. I think this is one of those areas that, again, cannot be viewed easily in the

optic of hindsight. AIDS was a public health emergency, and it was essential to get things started. AZT is out there. It is an approved product. I view that as successful example of a public/private collaboration.. It laid the foundation for almost every other product because, in my view then and now, the failure of AZT would have had very dramatic effects, would have induced people to say,. “It is all a waste of time. Why are you wasting the government’s efforts?”

There were many people who were very skeptical, who cautioned me almost to the point of warning me not to continue in this area, (or at least not to be so visible in this area), that I was making a bad career move. Most of the people who were involved were adopting a sense of that, “we will do an orderly process of science, we will do it step by step, we will do rational drug synthesis,” whatever that means. The AZT collaboration stimulated a lot of science, and laid the foundation for better drugs in the future. And it also provided patients with a measure of hope, at a time when there was none. I felt very confident at the time that there would be all sorts of people not connected to the science or clinical aspects, well-meaning and sincere government employees, perhaps working in the Office of General Counsel, perhaps working elsewhere, who would have found thousands of reasons why what we were doing was not appropriate, and required a lot more paperwork. And those forces tend to become very quiet after a project seems to have worked. They do not come forward at that point.

Hannaway: But they are prominent before that.

Broder: Because once there is a success, they see the department (DHHS) has embraced the results and everybody's happy. But beforehand, they would have clearly, in my view, clearly introduced barriers. We would have had, at a minimum, two separate teams of lawyers talking to each other forever. I had been in government long enough to know that. There would be the lawyers from the government and the lawyers from the private sector. They operate under a different sense of time and urgency.

Harden: You began phase 1 trials on AZT in July of 1985.

Broder: That is correct.

Harden: And we'd like to have you talk in some detail about the process, what you were seeing in phase 1, how Burroughs-Wellcome moved on into phase 2, and I believe they were quite concerned about their people being infected.

Broder: Oh, they were extremely concerned. They refused to accept live virus, and at one point refused to accept patient samples. That was a little unusual. They basically put the entire onus for the phase 1 pharmacokinetics and related issues on NCI.

Harden: Maybe you'll walk us through the whole clinical trials process using AZT as an example.

Broder: Yes, sure. It was very clear--and I cannot remember the exact time--that AZT was elevating patients' T-cell counts and having other positive clinical effects. Other drugs and drug combinations also began showing positive effects. A combination of AZT and ddI and a protease is an excellent regimen.. And

there is a study in the *New England Journal* that ddI alone, ddI alone actually had as good a mortality rate as AZT or AZT and ddI in certain categories of patients. I think AZT is important both for what it did clinically--there is no question about it--but also for the principle that it established, AZT laid the groundwork for defining surrogate endpoints in other studies, for illustrating that anti-viral agents could work in patients, and for providing a template for moving quickly from a laboratory observation to a proof-of-concept clinical study, and from there to a randomized prospective clinical trial.

AZT proved that we could block viral replication in a human being. AZT could block maternal-to-fetal transmission. That is a simple statement, but it was a radical idea in the mid-1980s. AZT proved that you could reverse dementia, particularly in little children, even with cerebral atrophy. I think that AZT changed the tone, and pessimists were becoming less and less rewarded for their pessimism.

Harden: What about the criticism later? I never know whether it was just shortsightedness or frustration when a later study showed that AZT was not the be-all and end-all, and suddenly people were saying, "We should never have gone with this. We should have worked on something that worked." Would you comment on these tribulations?

Broder: You will find no statement from me or anyone in my laboratory, or probably anyone in the NIH, that AZT was a cure or was anything other than a first step, albeit an important first step. We always chose our words cautiously and

specifically. It was simply a starting point. But without AZT, and all of the issues that I discussed earlier, we would have been very hard pressed to make any progress in the therapy of the AIDS virus.

The scientists at Merck and Abbott and Roche, and elsewhere were following the AZT story intently. They've said so. They were able to argue successfully with their senior management.

Harden: Would you comment on the suggestion by Peter Duseberg and Robert Rood Bernstein that AZT is the cause of, not the cure for AIDS?

Broder: Well, subsequent events have shown that to be completely wrong

Harden: Why do they continue to press their case?

Broder: I do not know. You'd have to ask them. But nobody in the scientific community believes that. And the advent of protease inhibitors, in combination with drugs like AZT, simply provides a further refutation. There are people now routinely getting better, and they are getting better for long periods

Some people had hoped that AZT would be a cure. (No one at NIH ever said that it would be.) And, therefore, when it was not a cure, that reality affected people. And then there was the overreaction the other way. There is, to this day, a group of individuals who argue that HIV is not the cause of AIDS. They argue that the NIH has not been telling the truth. The capacity of anti-viral drugs to prevent premature deaths and alleviate suffering in patients with AIDS, to block the transmission of AIDS from mother to unborn child, and a host of other scientific observations can mean only one thing.

Hannaway: That there is a virus. You characterize Burroughs-Wellcome's development of AZT as a successful commercial venture.

Broder: Yes, no question.

Hannaway: And you said that it encouraged other drug companies to deploy resources in this area.

Broder: There is no question, in my view.

Hannaway: However, some have said that Burroughs-Wellcome profited, over-profited, let us say, by the price that they put on AZT. I wonder if you would comment on this general issue.

Broder: Well, that is a controversial issue, and I think people of goodwill have to agree to disagree. When I was the director of the NCI, we had a reasonable price clause put in to various Collaborative Research and Development Agreements (CRADAs). That was considered very controversial and was removed by Dr. [Harold] Varmus when he became NIH director. I do not object to that, and I think that that is perfectly fine and perhaps, in retrospect, is the correct thing. But it is simply an expression of the fact that you cannot please everybody; we thought that if you had a reasonable price clause put in, it might alleviate the public's concern about these issues, and then the public would feel that its tax dollars were being used more effectively. But another argument, which I have to say I cannot disagree with, is that that such a policy will discourage innovation and collaboration with NIH. And I think people of goodwill have to just accept that as a reasonable point for disagreements, and I am comfortable

with the removal of the clause.

Hannaway: And there was a great debate in 1987 with Senate subcommittees and others-- the complaints over the costs of AIDS drugs.

Broder: Yes. That is true. And these issue have to be addressed with respect. I am comfortable with the way the NIH is currently solving the issue. That is fine. But what I am saying is that there are other paradigms for using the NIH's prestige to make sure that the public does not feel that it is paying more than what is fair for drugs that emerge from the NIH programs, and I think that a reasonable price clause is acceptable and is one way of dealing with this. But it is not the current NIH policy, and I am very comfortable with this fact. These are not easy issues.

Harden: In the wake of AZT's success as the first anti-HIV retroviral, a lawsuit was brought against Burroughs Wellcome by a company that wanted to produce a generic version of AZT on that basis that you and your NCI co-workers should have been named on the AZT patent. Burroughs-Wellcome, however, claimed that NCI had no right to the patent. You were deposed even though neither NIH nor NCI were parties to the suit. We have looked at your deposition and wondered how you kept your cool through some very tough questioning by the attorneys.

Broder: I think that the lawsuit was an interesting example of how bureaucracies deal with things. The government was not prepared to defend its position. It did not want to. The Commercial Litigation Branch of the Justice Department seemed

very unhappy with the whole litigation and did not put forward, in my view, a spirited defense, or sufficient energy and resources.. Now that I am in the private sector, I understand a little bit more about these things.

The adversarial process in a legal setting is predicated on the assumption that you'll allow parties who are equals to contest one another. The government, for whatever reason, did not choose to act as an equal in the litigation. The interesting thing is that Burroughs-Wellcome did not win. That is a misnomer. The Court of Appeals for the Federal Circuit actually upheld one of the counts, or at least, rather, sent it back for further trial. It was just that people did not want to pursue it. If you read the decision, Burroughs-Wellcome had declared my laboratory a "pair of hands," but the Court of Appeals took the unprecedented step of saying, "They definitely were not a pair of hands," in their decision.

Harden: The lawsuit represents another example, I think, of how AIDS forced scientists to learn how to do their research "in a glass house," where people were watching every move and often demanding documents via the Freedom of Information Act process.

Broder: Let me add just one more thing. The Supreme Court actually was asked to take this case, and they wanted to know what the government's views were. The government asked for the case to be dropped, and I am told that this was against the advice of the NIH. Why they took this position is still not clear.

But in the last analysis the legal aspects are a secondary issue. The drug

is out there. AZT is out there. In fact, this whole episode supports my point. If you have people who aren't doctors and scientists brought into an important public health issue, it doesn't necessarily advance the interest of solving the problem.

Harden: Is the legal problem of possibly having to defend yourself in courts of law and having to spend time responding to Freedom of Information more of a problem for government scientists than it would be? I mean, do you think that this situation would inhibit drug discovery and development in the public sector as opposed to the private sector?

Broder: I do not think so. But I think it is a factor that, on balance, by and large, the adversarial system depends on equal participation.

Hannaway: Some other scientists we've interviewed have said that getting embroiled in these things distracted them completely from science.

Broder: Well, I think that is true.

Harden: Would you like to make any further comments about any of the drugs that you've worked on

Broder: All I can say is that, with comparably small resources, my laboratory produced three drugs that went through the Food and Drug Administration (FDA) approval process within a short period of time, and we helped support a lot of others. I think that dollar for dollar, the taxpayers got their money's worth out of that intramural commitment. And I think that that would not have happened in any other setting. But, more important, by far, is the fact that the public got

its money's worth from the entire intramural AIDS program. That especially includes the NIAID group: Tony Fauci's group, Cliff Lane's group, and the whole range of people who worked on AIDS both from a clinical and basic science point of view. And I think that a lot of the people in a lot of different functions had a very critical role. The nursing staff played a critical role, a lot of people are unsung heroes, so to speak.

Harden: Would you like to comment on how AIDS changed your career, changed your life?

Broder: In some ways, the development of drugs and responding to a public health problem like AIDS was a very satisfying experience, a once-in-a-lifetime opportunity. I told people in my lab at the time that this was a once-in-a-lifetime thing, that they had to look at it that way. Most scientists can work their whole lives and not see any practical application of their work.

Hannaway: One more general question, and you are uniquely qualified just to comment on this. We are interested in seeing how the NIH interacted with other government agencies, and specifically in this instance, the FDA. I mean, you are one of the people who had the most interaction with the FDA because you were interested in drug treatment, and you were very knowledgeable. Would you provide an overview of the NIH-FDA interaction in developing AIDS drugs?

Broder: By and large, the individuals at the FDA had among the most unfair and painful jobs in government, in my view. And I do not always agree with the FDA and I have clashed with them before I left government and since I left government.

But by and large, I think the FDA is made up of very fine people who want to do the right thing and do not always have the resources to do it, and certainly do not get any public recognition for what they do but will be blamed when things go wrong.

I think there was an enormous outpouring of anger and resentment against the FDA by the many members of the affected communities, and the FDA became a scapegoat for a lot of anger and anxiety. The FDA building was trashed and occupied, and throughout it all, the agency staff responded with dignity and professionalism.

Harden: Thank you, Dr. Broder, for talking with us.