Robert B. Nussenblatt
April 25, 1990
Oral History Interview

This is an interview of Dr. Robert B. Nussenblatt of the National Eye Institute (NEI), of the National Institutes of Health (NIH), at Bethesda, Maryland. The interview takes place on April 25, 1990, in Dr. Nussenblatt's office at the Clinical Center at NIH. The interviewers are Dennis Rodrigues, program analyst and Vicky Harden, director of the NIH Historical Office.

Rodrigues: First of all, to set the stage for things, we've been asking why people decided to go into medicine? What was your motivation to become a physician?

Nussenblatt: Probably the major reason for going into medicine is the fact that there really are no two "rights." That is, there isn't a game of sophistry that's played in medicine. It's one real goal: the ideal of treating patients. I find that ideal very attractive and one that's worth devoting one's life to. So, it's a very simple goal.

Rodrigues: Could you tell us more about your training?

Nussenblatt: All my training was done in New York State. I went to school in New York City. I went to the State University of New York. I interned in internal medicine at Bellevue Hospital in New York City. I did a first-year residency in medicine there, and then continued on at Bellevue and New York University Hospital in ophthalmology. I finished my ophthalmology training in 1977 and then came here to the NIH as a clinical associate in the Public Health Service and have stayed here ever since.

Rodrigues: During that period of time what were your research interests?

Nussenblatt: Well, my research interests, in a generic sense, have really always stayed fairly stable. They revolved around questions of immunology and inflammatory diseases. The internal medical background that I had helped me put some of the ocular problems that we've seen into perspective. When I was in internal medicine, the interests that I had, revolved around the rheumatologic diseases and immune-mediated diseases. In ophthalmology, there is a separate area of ophthalmology that deals with inflammatory diseases of the eye, or uveitis is sometimes the term that one uses. So this goal has kept constant over the years. Certainly, or at least I hope, our ability to ask and to answer some of the questions, has become more sophisticated with time. The goals however have remained fairly constant.

Harden: How have those claims shifted from internal medicine to ophthalmology?

Nussenblatt: Probably not for specific reasons. I can't say that they're absolutely logical. I think one of the problems or aspects of internal medicine, at least in the way that I perceived it, was that though I enjoyed very much the excitement of Bellevue, it was quite clear that the practice of internal medicine would not be the same on the outside. Additionally, internal medicine required you to sub-specialize, and I didn't like the idea of not being involved in the whole area--the whole discipline. Ophthalmology was something that I found very attractive when I was a student. Actually, I had intended to go into ophthalmology, but at the same time intended to stay in internal medicine longer than people usually do. What I found attractive about ophthalmology was the ability to deal with the whole discipline, and also the combination of both surgery as well as medicine. It offers a great deal. It's a very gratifying sub-specialty.

Rodrigues: Now, could you take us up to the point when you first became aware of this disease that was eventually recognized and called AIDS?

Nussenblatt: The first patient to my recollection that we saw through the Eye Clinic was a patient that was originally referred to Dr. [David] Cogan who is a professor emeritus at Harvard and has been here at NIH now for many, many years. He is one of the great ophthalmologists of our century, who has trained many of the leading figures in ophthalmology from the United States. I've had the great fortune and the great benefit to have interacted with him. He is a man with many great talents. Initially, when he came here he was involved in neuro-ophthalmology as well as pathology, but his abilities span almost every area of ophthalmology. An interesting patient came to the NIH who had a poorly-defined illness that manifested itself in the eyes. Ultimately, it was determined that he had cytomegalovirus retinitis --CMV retinitis. That, to the best of my recollection, was the first patient that I saw, who had this sight-threatening problem, and ultimately had AIDS. That was a fairly uncommon problem for ophthalmologists. I think I had seen probably two patients before who had CMV retinitis. Its usually seen in patients who are extremely ill or who are immuno-suppressed for a variety of reasons, either because their disease itself causes an immunosuppression or because of therapy that they receive, whether it be for transplantation purposes or for other reasons. I had seen, as I said, two patients. I remember one in particular, since he was a physician from the eastern shore who had very bad CMV retinitis, Wegner's granulomatosis and was being immunosuppressed for that problem. But this was an extraordinarily unusual disease, that could be reversed. If the immunosuppression stopped, then you would get rid of the CMV retinitis.

Harden: Now, this patient came to you all from someone else who was treating the more generalized disease here?

Nussenblatt: That's correct. Indeed, we saw him through the consult service. We followed him and then, with time, this disease or this problem became recognized as a uniform ailment. Then ultimately, but not early on the term AIDS was applied to it. It was just an immunodeficiency problem. This patient lost his vision because the CMV retinitis could not be treated at that time, then just marched across his retina and unfortunately took his vision.

Rodrigues: When was this?

Nussenblatt: It was in the early 1980s. I can tell you that it was during the time that [Dr.] David Bachman was with David Cogan--Dr. Cogan. I think you're right. It was probably in 1981 or 1982, sometime then.

Harden: Which case was this one? We had been talking about your earliest cases and I remember a reference to this. So, even though it's very hard to remember how you were thinking at that time; could you tell us what you were seeing and how you evaluated what you were seeing in the whole patient?

Nussenblatt: It is difficult to give you the whole story. Certainly this presentation was odd, in that he was clearly not being immunosuppressed by physicians and he had other opportunistic infections. I remember he had thrush. So, he was clearly ill for unknown reasons. The AIDS virus had not been discovered at that point. We certainly suspected that he had an infectious process and it looked pretty much like CMV retinitis, but we weren't absolutely sure. But it certainly seemed to fall into the category of the infectious process.

Rodrigues: I assume then that not too much time passed before you began to see other cases.

Nussenblatt: Yes. Indeed.

Rodrigues: Were you directly involved with some of the people in the Clinical Center who were admitting these patients tests?

Nussenblatt: Our greatest and longest collaboration has been with Dr. [Anthony] Fauci's group. With Cliff [Dr. Clifford] Lane, and [Dr.] Henry Masur, as well. Henry, of course, is, perhaps strictly speaking, not part of that group. But that was the group that really we interacted with and we've continued to interact with them over the years. I had a working relationship with Dr. Fauci because of my interest in inflammatory diseases and his great interest in immune-mediated diseases. We had talked to each other when he was a lab chief, dealing with questions of Wegner's granulomatosis. So, this was sort of a natural continuation of that

relationship. When it became obvious that more patients were going to be coming, we began to formalize the way in which we were going to see these patients. On my side, the person who accepted a very large part of the responsibility was [Dr.] Alan Palestine, who, until recently, was here as a section chief in our laboratory. He's now in private practice. Alan took the bull by the horns and helped establish a uniform, logical way in which we were going to evaluate these patients. Someone else who played an early role, again from our side, is [Dr.] Merlyn Rodrigues, who is an ocular pathologist. She's now at the University of Maryland. Another person who was very instrumental early on was [Dr.] Abe Macher who is a pathologist. He's no longer here at NIH. He's a pathologist and infectious disease expert as well. He had an interest in ophthalmology because of his brother, who was an ophthalmologist. We then began to see these patients on a fairly regular basis. One of the goals was to know what these conditions were in the eye. Was it all cytomegalic virus retinitis or was it something else? In one of the early projects that we had, we had the opportunity to examine the eyes of an AIDS patient who died here at NIH. There was a very large study that was published in the early 1980s, demonstrating that the patients who had these ocular lesions had--almost all of them had CMV retinitis and, that, in fact, we could correlate our clinical observation to what was occurring pathologically. Another observation was that those patients who had CMV retinitis had exceptionally low T-cell counts. So, if the total T-cell number were below 100, we knew that they had a very high possibility of developing CMV retinitis. Those were, perhaps, the earliest observations, other than just the anecdotal one of this patient, that I mentioned to you before.

Harden: I have a question about CMV. Is CMV a virus that is so common, that normally it's around and one fights it off immunologically, or is it a more rare kind of a virus?

Nussenblatt: CMV is ubiquitous, and certainly anyone who's in a hospital environment is infected with the virus. As long as you are immunocompetent, nothing happens. You have to be extraordinarily immunocompromised in order to develop problems with it, so it's really a ubiquitous organism.

Harden: Opportunistic infection.

Nussenblatt: It is indeed. Other disorders that we saw--and this has seemed to have changed now, maybe because of the kinds of patients seen at NIH, was Kaposi's sarcoma. We saw Kaposi's on the eye, around the eye, and made some of the early observations dealing with that. We also dealt with the problems of how to treat it, what to do. Other conditions include ocular toxoplasmosis, which is fairly rare in AIDS patients. We really don't know the reason for that. It's much more common

in the central nervous system, in the brain, than it is in the eye. As time progressed, other things were observed, but the predominant disorder that we saw in these patients, and the one that was sight-threatening, was CMV retinitis.

Rodrigues: This is sort of an aside, but are there ocular manifestations before the patient actually progresses to the AIDS, like people who are infected with HIV [Human Immunodeficiency Virus], such as ARC [AIDS Related Complex] patients, or do you see ocular complications later in this state?

Nussenblatt: There are early changes within the retina; however, they're much more common in patients who have AIDS. They are cotton wool spots--microinfarctions of the retina that appear to be fluffy white. When one looks at the back of the eye, there's a fluffy white nature to them. There's also a vasculopathy--vascular changes that can occur in patients who are HIV positive. Sometimes it's difficult to differentiate those changes from that of CMV retinitis. In fact, only time can tell, that is, if it begins to expand, we feel pretty secure that it's CMV retinitis. Those are much less common, however, in patients who have ARC as opposed to those who have AIDS.

Rodrigues: One of the things that I'm curious about is the process by which different institutes dealt with this problem. Everybody at that time, during the early 1980s, had a pretty full plate of activities and there weren't excess resources sitting around waiting to be utilized. When a new problem came up, decisions had to be made about shifting personnel and resources. Is there something you can say as to how decisions were made? For instance, you just indicated that a number of people were now having to deal with these patients. Presumably, they let go of other responsibilities that they had prior to that. Who made these decisions?

Nussenblatt: In all frankness, I'm not even sure that a conscious decision was made, at least within our institute, to drop other priorities. One of the interesting parts about working at NIH is that people are really devoted to looking at interesting questions. What happened, in all honesty, was that people just worked longer and included it into their schedules so that they didn't have to let go of other projects. I do not remember off-hand, at least with the people who were close to me, anybody dropping other projects in order to become involved in AIDS. They simply worked longer. When it came time to do animal work, for animal experiments, they were simply put off until after clinic hours. If they had to come in on the weekends, they did that. The eyes were accessed whenever we could get them, and that would be in the wee hours of the morning or late at night or whenever the case may be. So, people just make time and they really don't work the eight to five or eight-thirty to five shift. They simply are here as long as it takes to get these interesting projects going. In terms of a decision--one of the

other interesting aspects, from my point of view, and one of the reasons why I think this is a unique a place that has to be nurtured and kept, is that the decision to become involved in this was made very early. It was purely scientific and medical. It had nothing to do with politics; nothing to do with making someone happy. It was a scientific decision that this was an interesting area, it was an important, and that it was clearly going to be an important area because it was an unknown. The emergence of a fairly rare infectious entity inside the eye, which suddenly becomes so much more common, clearly told us something very profound about the way the body deals with the eye. That decision then was made by the people who were involved in the work itself. It was not imposed upon us in any way. That's been really the attitude all along through the years.

Harden: We have heard what you said and we have spoken to some other people who said that it was an interesting problem. I'm sure you have read a number of the popular books about AIDS. Government scientists, in particular, but scientists, in general, have been criticized for stepping back and saying it's an interesting problem. AIDS activists are saying one needs more dedication, than that you were talking about in the beginning on going into medicine requiring dedication. Perhaps you would comment on how these two things scare research physicians.

Nussenblatt: In terms of the complaints that have surfaced, I can't really answer them, because I think that they swirled about at a very different level than what I am interested in. When I say it's an interesting problem, that in no way suggests that, that is a cold, uncaring point of view. If anything, it was an interesting problem for us because it potentially could give us information to help people. In the end, that's really, the goal--to develop new ways that we can help people. However, one does try to take advantage of nature's quirks and certainly from a research point of view, one wants to be on the look-out for these observations and to take advantage of them. In some ways, the role of a researcher is somewhat different from the role of somebody who's going to be treating a patient in a local hospital. Their roles are different, and I can fully understand the frustration of the lay community, when they say that more money and time should be spent. But sometimes we don't have the ideas and that's a simple reality. Sometimes we're waiting for nature to give an answer to us and sometimes she doesn't want to do that. So, it can be very frustrating at times for us, as well.

Rodrigues: Picking up on that--has AIDS taught us something profoundly new? Beyond what we've learned about HIV and the advances that we made on that particular problem, do you feel that AIDS has expanded our understanding beyond its own immediate sphere?

Nussenblatt: The answer is "Yes" in perhaps at least two areas that come to mind. One is that it has enhanced our understanding of viral diseases of the eye and how, in fact, some of these mechanisms may come about, not only in the AIDS patient but in others. It was our awareness and suspicion that virus may play a role in even immune-noncompromised individuals-- patients who do not have immunologic problems. The other area that is important is the better understanding of the way in which the HIV enters into a cell. There are certain concepts that have developed concerning our ability now to alter cells in a positive sense--to use this very nefarious methodology of molecular biologic techniques, for the benefit of individuals. So, from a very specific ocular point of view, it's been very helpful, and also in terms of developing new ways in which we can treat certain diseases.

Rodrigues: One of the things we've also been looking at is the different activities that were going on preceding the emergence of HIV, that were particularly helpful in being able to quickly come to grips with this new viral entity? Were there any efforts that you were working on, or that you were aware of, that played a big part in your ability to understand what the nature of this disease was?

Nussenblatt: Well, I think I would, say that somewhat differently. I don't know if it was so much the area that we were working on as opposed to the ability to interact very rapidly with a variety of individuals. By that I mean, there was a very close-knit group that came from very different specialties that were able to work together, and I think that dramatically helped our ability to come to an understanding of what was going on, as opposed to a specific area of research. I can tell you, however, much later on, there were unusual entities within the eye that sometimes occur in AIDS patients and new surgical technologies helped us identify that. In fact, this entity is a bacterial infection that can be cured with simple antibiotics. So, the new technology helped us immensely in our ability to make the diagnosis and then treat a patient.

Harden: Could you talk a little more about the bacteria and the technology?

Nussenblatt: Well, yes, though it should be put in perspective that we have been really discussing very early aspects of AIDS history, or ocular AIDS history, and this is something that happened more recently, only a few years ago. We saw patients and we've reported this in the American Journal of Ophthalmology. There are patients who came to us with a very unusual entity inside the eye. At least in our minds, it didn't look like the more common disorders that we see, such as CMV retinitis or toxoplasmosis, though the initial patient had been treated for those and he did progress. He had the problem in both eyes, but one eye was not doing well at all. We elected then, to do a retinal biopsy. We were able to take a small piece of his retina, with the eye remaining intact. We didn't have to remove the eye.

The very small piece of retina gave us an enormous amount of information. It was a very small piece of retina, perhaps one by two millimeters, two by two millimeters, with which we were able to obtain evidence to show that it was a gram-positive bacteria. Ultimately he was treated with a standard antibiotic and he was cured of his problem in his other eye. In fact, he probably had this systemically, because he felt much better after therapy. We were then able to recognize the same entity in one of his sexual partners, and we were able to treat him as well. So, that technology helped us immensely in identifying the problem and, ultimately, in treating it.

Rodrigues: Were there particularly unique problems in dealing with those AIDS patients?

Nussenblatt: I think there was. I think that there was a fear, of how problematic dealing with the AIDS virus was going to be. We ultimately reported from here that, we can find the AIDS virus in tears as well as in the cornea. We did that with Dr. Gallo's group and [Dr.] Zaki Salahuddin. So, we had a real concern about whether, the AIDS virus could be spread through touching the eye. There was also the need for greater sensitivity, I think, on all of our parts, in terms of interacting with many of the patients. The patients that came to us were frightened, and needed tremendous amount of support. I think that's changed dramatically over the years, at least here, where I think, we have an extremely good rapport with our patients. I think, and hope in any event, that at least from the eye point of view that, the community of individuals who are at high risk from getting this kind of problem, know that they will be treated in a correct and ethical manner. It was an evolutionary process as we learned about their needs. For me, I think that that was the most important, because the area of ocular inflammatory disease is such that these are generally chronic problems. Unlike some of the other areas of ophthalmology where you might intervene with a surgical procedure, and never see the patient again. Patients with uveitis come back again and again. One of the things that we have to do is to develop a good rapport with the patient. Their input is certainly as important as ours. The same was true for the AIDS patients who had CMV retinitis. They clearly have to know what the problems are and have to trust us as we have to trust them. It took time to develop that trust.

Harden: It must be one of the most terrifying things to encounter, when you already have a generalized disease, to realize that you may not be able to see. I think that you must have to intervene at a critical time.

Nussenblatt: It's horrible. I think we do, and I think that it took time to fully appreciate this reality and for us to maturate in our minds. You know, as an individual with AIDS becomes more debilitated and more bedridden, the only thing for them to do is turn then to reading or watching television, whatever the case may be. And

then with the idea that they may become blind on top of that, it seems like the ultimate horror that can happen to them. They risk losing their ability to become self-sufficient, even in terms of taking medication, and so forth. We've learned to take better care of individuals who have AIDS, and their life span has been extended. There is a very strong possibility that between ten to twenty-five percent of the individuals with AIDS will get CMV retinitis. So, the answer is "yes".

Rodrigues: So, if I understand this correctly, one way of looking at it is that although we've been able to extend the life of these patients, our ability to protect them from different types of complications, such as CMV retinitis, is not on a par with some of the other problems. In other words, although they may be living longer, they're still going to be susceptible to a variety of other problems that are going to make life very difficult.

Nussenblatt: Well, yes. If I rephrase that in another way--what we knew was a complication before, still is. What may have been in somebody who only lived three months, a peripheral problem, because of their increased life span now becomes a serious one.

Harden: And there is no therapy for CMV?

Nussenblatt: Yes there is. We can halt it. We were the first to report it in a study. That was in the American Journal of Ophthalmology some years ago. That was again, I unfortunately can't tell you the patient's name, but this was in conjunction with Cliff Lane, Henry Masur and Dr. Fauci's group, in which we began using DHPG, or Ganciclovir as it's called now. We had never seen a reversal of CMV retinitis. We had tried a variety of methods. The CMV retinitis marches through the retina causing a necrotic lesion, which has a front which moves as in a wave. Indeed you can see this border of very active disease. We tried to put down a border of laser and did a variety of other things. It just didn't work. I remember very vividly when we first used it. Alan Palestine was in the clinic and he called me and he said, "You've got to see this." The CMV lesion in the eye had disappeared. In fact, it was an extraordinary experience because that had never been seen before, at least here. Initially, we weren't even sure we could believe it. But, in fact, higher dosages of Ganciclovir arrested the problem very nicely. However, in an underlying immunosuppressive problem, if you stop the medication, it will come back and, unfortunately, if you reduce the dosage, which one has to do because of the problems of side effects, a very large percentage, and some might argue that in even all of the individuals, the disease relapses. We have a second medication and that's Foscarnet. We've just finished the first

randomized massed study to be done in CMV retinitis with Foscarnat. So, we can stem it, but we can't cure it.

Rodrigues: You mentioned earlier about some of the political fire storms that were raging about AIDS. I think you said at one point that that was at a different level and didn't really concern you. Looking at the institute in general, and the way the program revolved, did you think the level of political concern about the disease has been helpful or has it harmed the effort?

Nussenblatt: My answer really is a very localized one. It's dealing with our level. I can't speak for other areas. I don't think it's necessarily harmed. I don't really perceive as being harmful to us the awareness of the problem, whether that's translated into the ability to recruit patients or in monies. I think that by being in the Eye Institute in some ways, we were protected from the main thrust of many of these problems, since we weren't really considered to be particularly relevant at that time. We were a small institute; we were on the periphery of things. Perhaps the problem of CMV retinitis wasn't absolutely recognized at that time. We now recognize that CMV retinitis is an excellent way to evaluate new drugs, because we can visualize whether the medication is having an effect. It's much more difficult to do that in other areas of medicine. But, at least then, I don't think that we were in the mainstream of what was going on. So, we were protected, from a large part of that.

Harden: We certainly appreciate your taking the time.

Nussenblatt: My pleasure. It's an interesting experience.