INTERVIEWEE: Dr. Albert Heyman
INTERVIEWER: Dr. James Gifford
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HEYMAN INTERVIEW NO. 1

JAMES GIFFORD: Durham, North Carolina. December 18, 1985. This interview presents Dr. Albert Heyman. Dr. Heyman is professor, Division of Neurology, Department of Medicine, Duke University School of Medicine. The subject of this particular interview is Alzheimer's disease and the history of work on Alzheimer's disease at Duke and the success of Duke in becoming an Alzheimer's disease research center. Your interviewer is James Gifford. Dr. Heyman, perhaps we could begin by having you say a little bit about your own personal and professional background.

ALBERT HEYMAN: Yes. I came to Duke in 1954 from Emory University. At that time I worked with Dr. Eugene Stead, who was professor of medicine and subsequently the dean at Emory. I had been an intern and had been a house office very soon after he came to Emory and became interested in research under his encouragement. At that time—it was during World War II—and he found an opportunity for me to work with the Public Health Service in Atlanta, more specifically the Georgia Department of Health. During the war, there was considerable amount of venereal disease in the South, as there was in many other sections of the country, and they needed someone to do some research and work in that area. I got interested in neurosyphilis and did a lot of work in that, wrote a number of research papers. That's how I became interested in neurology. Since much of neurosyphilis is concerned with blood vessels of the brain, my interest expanded

to include cerebral vascular disease at that time. This was particularly true since the advent of penicillin reduced the problem of neurosyphilis to a considerable extent. There was also another factor at that time; that was the development of new, relatively simple ways of measuring cerebral blood flow, and I had done a number of research studies on that as related to cerebral vascular disease. So when I came to Duke, 1954, my main interest was in stroke and has been until the present time.

GIFFORD: Now, during the time you've been at Duke, your research has been on stroke and also on hyperbaric medicine.

HEYMAN: That's right. Soon after the hyperbaric chamber was brought to Duke, we tried out the—we attempted to determine the value of hyperbaric therapy on cerebral vascular disease and did indeed do a number of research investigations on that particular problem. Hyperbaric therapy was not particularly helpful in stroke, although some people still are trying it out and don't accept the original negative findings. It was about that time that the gerontology program was applying for renewal of their grant. It was suggested by one of the members, one of the psychologists, Dr. Larry Thompson, who was in the gerontology program, that hyperbaria might be effective in elderly demented patients. Since I had reasonable amount of experience with hyperbaria and also knew something about the nervous system and dementia, he asked that I help with this project, which was funded through the gerontology unit. We treated—oh, it was also claimed by other investigators, in a paper which appeared in *New England Journal* about 1975, that hyperbaric therapy was effective in dementia, and our program was to determine whether indeed this was so. We did try out—we did treat a number of patients with hyperbaria and found that this treatment was not effective. That paper was published about 1973,

but the work had been going on for at least three years before that time. It was through that first research study of dementia that I became interested in dementia of the aged and learned to know something about dementia of the aged as a result of that negative investigation.

GIFFORD: Now, Alzheimer's disease is something that has been treated at Duke for some years. Can you say something about what had gone on at Duke prior to the recent application for funding as a research center?

HEYMAN: Well, as I mentioned, the gerontology program was very interested in this, and Dr. [Carl] Eisdorfer and his colleagues had done a number of studies on dementia with various drugs, none of which, as you know, was very effective. It was about 1977 or '78 that I again became interested in dementia and Alzheimer's disease. Just how that came about, I am not certain; but we were involved in a study of brain damage following stroke, and obviously impairment of intellectual function often resulted. So because of my prior interest in dementia and the current interest in cerebral vascular disease, it occurred to us that perhaps a study of Alzheimer's disease would be useful. I had gotten together a number of colleagues at various universities, and we established what we called a collaborative case control study of Alzheimer's disease, and that would have been about 1978 to '80. We thought at that time that we'd have some difficulty in finding sufficient cases of a younger age group. We were particularly interested in patients between the age of fifty and seventy, because we thought that that group may have disease in a more aggressive form. So this was the first NIH [National Institutes of Health]-supported Alzheimer's disease study. It soon became apparent that we didn't need four different universities working on this, because we found that we had enough

cases on our own. So the study, which began as a collaborative one, became basically our own study; and I suppose we entered our first case about 1977, '78.

GIFFORD: Now, some years ago, I used to hear Alzheimer's disease referred to as a post-senile dementia, and there was apparently not a great deal of attention given to Alzheimer's disease among younger patients. When did that change?

HEYMAN: I suppose it changed with increasing attention. One of the early papers (*sound of rustling papers*) on that subject was the result of a symposium held in Washington in 1978. At that time, it was recognized that Alzheimer's disease consisted of perhaps two types, a younger set of patients in whom the disease developed early on. Dr. Seymour Crofferman, who is now here at Duke in the Division of Epidemiology and Oncology, participated in that conference and wrote and presented a paper whether Alzheimer's disease was one disease or two depending on whether it occurred early or late. And at that conference we presented some of our interest in cerebrovascular disease and dementia. Our interest at that time resulted in a number of papers on Alzheimer's disease. We did a genetic study in which we were interested in determining the frequency of familial type of the disease, the presence of Down's disease in the families of patients with Alzheimer's. We had done some studies on lecithin therapy. We did an important, if I say so myself, epidemiologic study in which we looked at all the possible factors in Alzheimer's disease which could be determined by an investigation known as case-control study. That particular one was interesting because no prior case-control study had been done; and we took a group of patients who had this disease, looked at their neighbors and people who live in their community, and see whether there was any differences in the risk factors, whether one smoked more, drank more, effects of coffee,

aluminum, other things. So that brought people's attention to the fact that there may be other factors which could be related with or associated with Alzheimer's disease. So that particular study went on to about 1981 or '82, and indeed in the Alzheimer's disease support group, which was established at that time, we had written a short a paper for *(loud noise; unintelligible*) research at Duke on this illness. I should emphasize that one of the spinoffs of the research study here at Duke was the formation of the network, of the Alzheimer's disease network. It was obvious that there was nothing we could do for the patient himself in terms of therapy. It was also obvious that the families needed help, and we enrolled—or we asked for the assistance of the Gerontology Division in this regard, and they sent us one or two social workers who would help. And Lisa Gwyther was one of them, and she has established a very important network in the state which led to the establishment of Alzheimer's disease chapters in the state, and I think that that was as important as anything else in making the disease known throughout the state.

GIFFORD: Now, when did you first become aware of the potential program for establishing Alzheimer's disease research centers?

HEYMAN: Well, we had been thinking of that in various ways, but there was no—very little basic science going on, and it was about in the summer of '83 that it became apparent that we were getting new staff here who had an interest in Alzheimer's disease, and Dr. [Charles] Nemeroff had called me and asked me whether I would be interested in doing some work or I'd be interested in working with him in some way. (*rustling of papers*) There's a note there that he—acknowledging his interest, and he expresses the fact that he was coming here to Duke and asked me whether I would meet with him. And, of course, I did, and met with him and a number of other people who were

interested in the possibility of doing a basic science and clinical science study. We had nothing in mind about an Alzheimer's disease center at that time because there weren't any such in the early days, in August of '83. It was then that—let's see. It was about November that the first announcement of the newsletter came out that Congress was interested in providing money for the establishment of not more than five specialized research centers, (*rustling of papers*) as it says here, on Alzheimer's disease. I first learned about that when Dr. [Allen] Roses, who sent me and Dr. [Harvey] Cohen and Dr. [Donald] Schmechel a little note asking had we known about this new thing. I had not known about it.

GIFFORD: (*sneezes)* Excuse me. (*pause in recording*)

GIFFORD: Okay, Dr. Heyman, you were speaking about the newsletter notice about funding that you received from Dr. Roses.

HEYMAN: Right. I wasn't aware of that and wrote to him and thanked him for calling our attention to these plans for establishing research centers. And had told him of our interest in such a thing and thought the idea was feasible and that we ought to meet. And that was the beginning of the proposal that we eventually had put through.

GIFFORD: Now, this came out in November of 1983.

HEYMAN: Right.

GIFFORD: What did you and other members of the Duke faculty do to prepare an application under this program?

HEYMAN: Well, the same thing that one usually does. You look around the university and try to find who's interested and who's involved, who has either done previous work or would like to do future work; and gather together people who you knew had some

interest. Dr. Schmechel had worked with me seeing patients, and he was obviously one of the people who had an interest in Alzheimer's, because he had done some studies of some therapeutic trials. Lisa Gwyther, as I mentioned earlier, had been the social worker seeing patients, and then Dr. Roses found a number of other people involved. I had worked with the statistician before on some other papers; he, of course, was involved. Dr. Burger, one of the pathologists, was involved in some of our previous work. So Dr. Roses found most of the people in the basic sciences, and I found some of those interested in the clinical work. So together we put together a proposal, which was submitted, and eventually after second application, we did get the grant, as you well know, in October 1985.

GIFFORD: Now, the first time around, as I understand it, you came close to being funded but were not. What inhibited being funded in the first round?

HEYMAN: Well, the NIH—what did they call the—? NIH review listed a number of things which we had not given sufficient attention to or had not been able to do this to put together a sufficiently attractive proposal. They listed the absence of adequate statistical help, which was corrected. They listed the need for a neuropsychologist, which we're still working for in terms of a full-time person. Let's see what other things they were concerned about. About pathology, also. They wanted a full-time person or a person who would devote a major time to pathology. There may have been some other things which was available on their original critique. When that came through as indicating the fact that we hadn't met their needs, we—or at least Allen made arrangements to correct those things.

GIFFORD: Now, what was the place of the rapid autopsy protocol in all of this?

HEYMAN: I'm not certain exactly when that began, but certainly that was an important part of the proposal because there was an obvious need for obtaining fresh brain tissues after death. A number of chemical substances in the brain quickly deteriorate after death, as you know, and there was a need for obtaining fresh postmortem tissue. And that idea of obtaining that was emphasized by Dr. Roses and more importantly the logistics of obtaining it, because people had been aware that you needed fresh tissue and indeed had answered it by taking biopsy tissue, which is not feasible, at least in this country. So in lieu of biopsy tissue, you get brain tissue as close after death as you can.

GIFFORD: Now, between the time that the first application was approved but not funded and the second application was approved and funded, there was a site visit. What happened at that time?

HEYMAN: The usual things that happen at site visits. They had read the previous proposal, had read the critique from the previous proposal, and were aware of the fact that the proposal, as they thought, was lacking several things. However, it was the obtaining of funds for improving our potential that I think may have made a difference. Turn that off a minute. Let's see. (*pause in recording*)

GIFFORD: Now, what was the reaction of the site visit committee to the fact that rapid autopsies had, in fact, been performed?

HEYMAN: Well, as you would guess, they were pleased and quoted that as a major strength in the new application, the fact that there were actually three or four—I forget how many—rapid autopsies already done, and they looked upon that as a major strength in the new proposal. They were also impressed with the fact that there was statistical help, that there was a pathologist, and those things were—and also a prior background. I

may have here some of the—here we are. The strengths of the new proposal was, as they have listed, "Strong leadership in research activities, clinical activities, at Duke. A strong ongoing clinical program in Alzheimer's disease. A strong data management and statistical expertise. A strong—a rapid autopsy protocol. A well-established information outreach program—" which the outreach, as I mentioned—

GIFFORD: That's Liz Gwyther's program, basically.

HEYMAN: That's right. The information program was partly hers in distributing information, but we had in our stroke program for years a strong databank under the—in stroke, and this had been well established for a number of years. Much of our stroke work was based on a databank in which you bring patients in, put them on databank, follow them for a number of years. And of course the thing that was also a major strength was the research proposals which were in the new application. So there were half a dozen parts of the new grant which influenced their final decision. (*telephone rings; pause in recording*)

HEYMAN: I think you've got the idea that—

GIFFORD: Yes, I see the basic process and formation. Let me ask you what you see as the unique elements in Duke's application as contrasted, perhaps, with others. What is it that Duke brings to the ongoing task that may be unique?

HEYMAN: As you mentioned, the rapid autopsy is unique. One of the things that I'm pleased with is that we've got a major interest in the pre-senile Alzheimer's disease.

GIFFORD: Which?

HEYMAN: Pre-senile, in the younger age group.

GIFFORD: Oh, I see. Pre-senile. Okay.

HEYMAN: So that many of our patients have the disease in their fifties and sixties, and that's the group we've been tackling. We have used our experience with the databank in getting all the information down on patients and doing a follow up. So we follow patients now for seven years at least or until the time they die, so we have a longitudinal study, closely follow a group of patients, and we have autopsies on a significant number of those people who did die. So there are lots of people who get autopsies, lots of people who are studying Alzheimer's, but very few of them are studying this distinctly unique group of young people. And indeed one of our patients is thirty-five years of age, which is very unusual. So that you ask me what's special; that's special. Lisa's close connection with the network is an important thing. There are very few places that have the close linkage with the community outreach and the research. Let me think of some of the other things which made them change their mind. Certainly we have a strong statistical group here, and I have been working with them for, gosh, easy ten years in our stroke study. Dr. Roses's genetic background is a key factor since much of the cause of disease is thought to be related to a genetic factor, and there aren't many places in the country—for that matter, the world—which are doing the kind of work he is with recombinant DNA as related to Alzheimer's disease, so that's certainly unique, and that's certainly one of the strong research proposals. The other research proposals in the grant, of course, Dr. Nemeroff, Dr. Davis, Dr. Schmechel, all were significant factors in making a decision. One other thing that we had done that was interesting, that we had an interest in epidemiology of Alzheimer's disease, and several of our proposals was related to the amount of Alzheimer's disease in the community, which is new, also, in terms of combining that with a clinical and basic program. The fact that there's a gerontology unit

here interested in dementia is another key factor. So here you have gerontologic experience, epidemiologic experience, good genetic laboratories, outreach programs. I think all that added up to a proposal which met their approval. So it was relatively easy to see that.

GIFFORD: Thank you very much, Dr. Heyman.

(*end of interview*)