Interview with Zaven Khachaturian, Ph.D.

Interviewed by Kate Nagy on July 11, 2022.

Editor's Note: The content of oral history interviews is personal, experiential, and interpretive because, by its nature, it relies on the memories, perceptions, and opinions of individuals. Interviews should not be understood as statements of fact or opinion endorsed by the National Institute on Aging. Questions were provided to Dr. Khachaturian prior to the interview and may be referenced but not directly reflected in this transcript. Transcript has been lightly edited for clarity and length.

KN: Okay, so tell me about where you grew up. What were your parents like?

ZK: My parents were the victims of the first genocide perpetrated by the Muslim Turkish government against the Christian Armenians around the First World War, and subsequently they were displaced. There was a major ethnic cleansing, and close to a million and a half people were driven from their homes. [My parents'] home was Cilician Armenia, which is [near] the northeastern corner of the Mediterranean Sea, and they were driven from their home into the deserts of Syria and Iraq and somehow they wound up in Syria during the French Mandate for Syria and Lebanon. This was a mandate by the League of Nations – Syria and Lebanon became a protectorate of France. They wound up there, and I was born in Aleppo, Syria during this period, which was from 1923 to 1946.

My father worked for the French army as a technician and my mother had been -- had worked with her five sisters doing lace work and needlework to support their brothers to go get an education.

We lived in Syria until -- this was during Second World War, and we lived there until the end of the Second World War when Syria declared its independence and we moved to Lebanon *en route* to Madagascar, where the French army was being pulled. But for some reason we stayed in Lebanon and that's where I got most of my education. My mother was a housewife; my father had started the contracting business doing heating and plumbing contracts for new constructions in Beirut at that time. I had an older sister, four years older. She died with childhood diabetes at age eight because at that time Syria and Lebanon were very poor; they weren't -- there weren't that many resources.

I went to get my primary and secondary education mostly in Beirut. I went to an Armenian Presbyterian Congregationalist Communities school, which is affiliated with the Armenian Evangelical Church. It was called Armenian Evangelical College because it had the first two years of college as part of it. The school was based on the British educational system. In fact, at the end of high school it included the entrance matriculation exams for Oxford and Cambridge. It was a no-frills school focusing on just the basics. We learned five languages: there were formal classes in Armenian, Arabic, French, English, and at home I learned to speak Turkish. Mathematics was from arithmetic to calculus. Science included chemistry, physics, biology, social sciences, geography, history of the world, cultures…and so it was a very solid education.

I left Lebanon in 1955. I received a permanent resident visa and migrated to the United States primarily to continue my higher education. It would have been very difficult in Lebanon to get the quality of

education or the quality of higher training that I was looking for, although the American University of Beirut was excellent -- I just did not have the scholarships or the means to allow someone with limited resources to attend, so the United States was really the choice.

I came to the United States in 1955, essentially to go to college, but I arrived in July of 1955 – I was too late to apply for college, so I continued high school for another year in Hamden, Connecticut. That was essentially to improve my English. The following year I was accepted to Yale and attended Yale. I had become interested in Yale when I was in Beirut during my ninth grade and I had started corresponding with the admissions office about the requirements, what's needed and so on. My particular interest in Yale was twofold. One, my grandfather's younger brother had gone to Yale and had gotten educated there and then had gone back to our homeland to teach at an American university [there]. Jesse Matossian was his name; he was a professor of psychology and biology at the American university in Aintab, Turkey. Aintab is the town where this American college was. My other reason was that my maternal uncle, a physician, was at the Yale Medical School and practiced medicine, so I had their place to stay. He became my guardian. So I wound up at Yale for that reason.

KN: And is that who you stayed with when you spent the year going to high school before going to Yale?

ZK: Yeah, that's why I went to high school in Hamden, which is a city outside of New Haven, but Yale was always the target.

While I was at Yale I was on scholarship, mostly. First I received a full scholarship. Later on, I had to work my way through years at Yale, and that involved working as a lab assistant for one of my professors, and I also worked as a dishwasher/busboy at a restaurant on weekends. That amounted to about 25 to 30 hours of work a week, so I didn't have much time for the frivolities of a college life, but I did not mind it that much because I enjoyed my work in the in the laboratory.

At the end there were two professors that were very influential in shaping my thinking. One was a professor in psychology by the name of Neal Miller who was a major theoretician on learning and memory. Neal Miller was a major influence. Besides the regular classes, I became a special student in his lab and did my first experiments under his direction. My other mentor was a man by the name of John Flynn, who was a very interesting person in the Physiology Department. John Flynn was doing work on brain structures related to emotion and working the circuitry -- how aggression, emotion affects…[undecipherable]

So from Neal Miller I developed my interest in the theoretical aspects of learning and memory, which later on became very relevant for my work with Alzheimer's, which essentially dealt with learning and memory, and from John Flynn I learned the idea of how to become a scientist, which meant how to frame a question; how to build your own equipment; how to learn to do brain surgery in small animals; how to build electronic equipment -- he was an all-purpose scholar, a rare breed. Formerly, he had been a Jesuit priest and had been studying the philosophy of Thomas Aquinas. For some reason or another his superiors did not like the way he was pursuing [his studies] so he left the priesthood and became a scientist, and he was a very great influence on me in terms of how to become a scientist.

You had asked the question: What were the beginnings of my interest in research and in particular how undergraduate education had influenced my thinking? You also asked what made me go into science or

scientific research. I've reflected on that, and partly it's due, I think, to the fact that in my early childhood I was in a very poor country. There were no resources; electricity and running water were luxuries that were not available. I grew up without any toys, so the few toys I had, I had to make myself or my father made it. That gave me the mindset of learning how to convert scrap material to be discarded into useful projects, so that began a mindset of learning how to make things work or finding out how things work that I think continued through my early education. The interest in learning how things work, and also relying on fantasy, relying on imagination, daydreaming -- daydreaming was a major event which meant making mental connections between disconnected things, which later on became very useful for thinking through problems in the abstract.

Abstract thinking became a part of my experience growing up in in Lebanon and Syria which later on I found in retrospect to be very useful. I could think about problems differently than most people. I could see connections, relationships most people don't see. I think I will come back to that theme, which is an important part of the scientific enterprise. An important part of creativity is to create something which doesn't exist by bringing new or different relationships, and I think that's a skill set that we should try to teach. Now we're not advocating that we take away toys from children in order to achieve that skill -- that's a bit harsh -- but there might be other ways to teach people to think differently and I think [that's important].

That brings us now to my education. Subsequent to my undergraduate training at Yale I had become very much interested in brain mechanisms of learning and memory. The learning and memory, the behavioral aspects, came from Neal Miller, Psychology Department. The underlying physiology, the molecular biology came from John Flynn. So that combination, the relationship between brain mechanisms and behavior – clinical features -- became a continuing interest, and I pursued that first at Yale -- I stayed after my undergraduate degree at Yale for another year in the Physiology Department working for John Flynn as a technician. But by that time the interest of the Department of Physiology had moved from electrophysiology into more hormonal endocrinology, so I went to Case Western Reserve, where a psychiatrist by the name of Fritz Rowland was very much into the mainstream of what I was interested in -- that is, brain mechanisms of learning. He was interested in the electrical activity of the brain related to memory, emotions -- the whole clusters that I was interested in. In my graduate training, the two great influences were Fritz Rowland and then a man by the name of Henry Gluck, who was one of the most brilliant people I've ever met. They were my mentors.

At Case Western Reserve in the early 1960s, the mantra in the medical school was the integrative aspect of the nervous system. The neurobiology program there looked at the nervous system as an integrating element, where the idea was to look at the neuron or the neural system as a system that integrates information mechanisms from diverse sources, so that became an important part of my thinking later on that was reflected in how I went about building the program at NIA. That aspect of looking at the neuron not only from the anatomy but from the biochemistry, the physiology, the electrophysiology -- in other words that receives, integrates information from multiple sources at multiple levels -- later on, that would all comes under the term “systems biology.”

KN: Now, at this point were you working on a Ph.D. or on a medical doctorate?

ZK: A good question. I was working on a Ph.D. originally. When I was at Yale I started thinking about going to medical school, but my experiences in the Physiology Department with Flynn and the kinds of

work he was doing -- I became more interested in the research aspect than the medical practice, so my interest shifted from medicine more into the biology and physiology of the issue.

At Case Western Reserve my training was in neurophysiology, behavior -- the relation between brain and behavior. The training and the faculty were from the Departments of Psychology; Physiology; Electrical Engineering; and Mathematics, so all those disciplines came to play a role into this systems approach -- that is, you look at a problem like the neuron or the brain not as a simple entity but something that interacts, integrates multiple things. It's like a city. A city is made up of people, but they speak different languages, they have different attitudes, there is an infrastructure, transportation, sewage, water -- all that integrates into a viable, lively lifestyle.

The same kind of a model [exists] with the neuron and the brain, where it's multiple levels, which makes it more difficult to study than a simple one-to-one relationship between A causing B and C causing D. That's a linear relationship. In systems biology you have very complex interactions where in order to gain an output you have to have A and B and C, maybe D, and have an output that coincides in time, and if they don't coincide in time the thing doesn't work. It's a different mindset than the typical mindset in a reductionistic kind of a science, which was the struggle in putting together the NIA program about it, and it continues to be. We'll talk some more about that.

After Case Western Reserve I went to Columbia to [study] in human learning and memory and did some work on newborn infants to learn what is the earliest stage at which a newborn can learn to detect a meaningful signal. In graduate school at Case Western Reserve my interest was the role of attention in learning, and I continued that at Columbia with newborn children to see what is the earliest thing they could learn, and the measurement was how their heart rate changes. That problem of measuring heart rate in newborn children became a completely different problem than I had started; it became an electrical engineering problem, a computer problem. How do you detect or recognize changes in what's called the QRS complex of a heartbeat, where the electrocardiogram has measurements of different components of the heart? The challenge was trying to devise a computer detection system that would recognize the abnormal one and be able to correctly time it so that I could measure whether the newborn infant was recognizing this early sound, and that that led me into becoming quite proficient in designing electrical circuits and designing computers' processing systems, so I became an electrical engineer in the process.

This, again, served a useful purpose in my first faculty position at University of Pittsburgh, where I continued my interest in learning and memory, but from a different angle. In my early work I discovered that attention plays an important role, but I became interested in the question of how attention plays a role in terms of selecting what's important and what's not important. The brain receives input from various sources, but for some reason it can focus on few things that are of importance for you at any moment in time. But what happens to all that other information that's not relevant? How does the brain filter out what's not relevant?

A good example of the problem is a cochlear phenomenon where you're having a conversation in a crowded, noisy environment. All of a sudden, you hear your lover's name. All of a sudden, your attention changes. How does the brain detect that, make that shift, with all that noise, all that noisy environment? This is a very important problem to solve for learning disabilities, and it continues to be an important problem for Alzheimer's, so I was trying to understand what are the brain structures involved that allow you to do that, and what happens to if you can't do that. The problem is still relevant

today! I can go back to the lab, pick up where I left off, and the problem will still be around, but that's another story. We won't go there.

By now, this brings us to 1972, the Nixon era. Getting a grant from NIH was increasingly becoming difficult. Although I had received some support from NIH at that time, I became interested in the question of who makes policy decisions, how they make decisions, and why they make their decisions. I became more and more interested in the question of who at NIH or in the government makes these decisions and how they make them, so I became a student of science policy. As a faculty member at the University of Pittsburgh I could take courses in different departments, so I started taking courses in the history of the U.S. Public Health Service; a course in the legislative process; a course in planning; a course in the budget process; health laws…I became a student of the Public Health Service and how NIH came about. I had a mentor by the name of Allen Pond who had been Assistant Surgeon General starting with the beginnings of the Department of Health, Education, and Welfare, which was the predecessor organization to HHS. He had been an assistant to Mrs. [Oveta Culp] Hobby, who was the first Secretary for Health, Education, and Welfare during the Eisenhower Administration.

Allen Pond became my mentor about [matters related to the] Public Health Service and NIH. About this time I learned about a program at NIH called the Grants Associates Program, which was a one-year fellowship where five or six people were selected and were given carte blanche to come to NIH. It was a program run by the Director's Office in Building One. At that time Don Fredrickson was the [NIH] Director. It was run out of Don Fredrickson's office, and basically a Grants Associate was assigned a senior person from one of the NIH Institutes as the mentor and took assignments in various Institutes or Centers within NIH as well as outside. For that year I took a series of assignments to learn more, but I came already pretty well prepared because I had been studying NIH, so I was in a unique way to learn about the assignments.

One of my assignments was with Paul Rogers, who was the Chairman of the Subcommittee on Health and Environment -- the Subcommittee within the House that passed lots of the public health laws. I took an assignment there and worked with Paul Rogers, and through that I got to know Ted Kennedy, who was the counterpart on the Senate side, and that gave me a lot of opportunity to make connections.

One of my other assignments was in a newly-created Institute: The National Institute on Aging. The legislation for NIA was in 1974. It became an Institute in 1976, formally, and the first Director, Robert Butler, came about 1976-77, which is about the time when I was at NIH. One of my assignments at NIA was to develop a strategic plan for the Brain Aging and Alzheimer's Program, which was of great interest to Butler. Butler was a psychiatrist who had some smattering of research experience early in his training, mostly at NHLBI, at the Heart Institute, which had an aging program. He had worked [on] brain perfusion. Then he went into clinical practice, but he retained a strong interest in the brain and neuroscience. To make a long story short, my assignment was completed, and he liked the plan and the ideas I had for starting a new program, so he asked how would I like to come at work at NIA and develop the program.

Meanwhile, I had been on sabbatical from the University of Pittsburgh. My plan was to go back to Pittsburgh. My family had stayed in Pittsburgh, so I was commuting back and forth between Pittsburgh and Washington, but the idea of starting a *de novo* program for an organization about which I had been studying the history and the politics -- here was a golden opportunity to start something new from the ground up. Not too many people get such a chance. The worst that could happen is, I would totally fail,

and it would be one big disaster and I'd go back to Pittsburgh -- no, no loss -- and learn a few things. The other one is that I might have a mild success and I could be famous and rich, and everybody will cheer me as the champion of brain aging and Alzheimer's!

I was interested and my wife agreed to move to Potomac, so in 1978 we moved. Then I began the challenge of building the Alzheimer's program. Now, there were several challenges and it's at this point, if you allow me, I would like to show you some slides.

The story -- the whole Alzheimer's movement, the scientific aspect -- began in 1978 with the beginning of the NIA and at the same time a year later the Alzheimer's Association was created. I'll come back to that. Those two events -- the creation of the NIA and the Alzheimer's Association – were really the beginning of the Alzheimer's movement.

During this period we've had a few successes and a few failures, so let's look at what were some of the major problems that had to be surmounted in getting this thing going. Well, first was the lack of funds. I think as you noted that in 1978 the total budget for NIA was about 19 million dollars, and for brain aging, Alzheimer's, neuroscience [the budget] was practically zero – maybe there were a handful of [funds], so having no funds was a major handicap. The more important handicap was the need for a critical mass of people, the resources. There were, worldwide, probably a handful of people that knew anything about Alzheimer's or were interested.

The modern era of Alzheimer's [research] actually began in 1961 in Britain with a psychiatrist by the name of Sir Martin Roth who had assembled a group to revive the interests that had been begun in the turn of the century by Alois Alzheimer to study the relationship of this particular form of dementia and its underlying biology. About the same time in the United States the first [NIH] grant on Alzheimer's was awarded to a neuropathologist by the name of Bob Terry in 1961 by NINDS.

KN: I'd like to interrupt with a question.

ZK: Sure.

KN: Did scientists really understand that Alzheimer's disease as a pathological entity as described by Alzheimer in 1908 and "senile dementia" as seen in elderly people were the same entity? Because Auguste -- the woman in whom Alzheimer discovered the pathology -- was a young woman. She was my age.

ZK: No. The answer is no. There were handful of people who knew the history. That's why I'm going back to Sir Martin Roth in Britain to start the process, because he was the first one to revive that interest in looking at the condition. He was approaching it from this psychiatric perspective, but he also had an interest in the brain pathology, and at that time electron microscope had become available and was being used. People in Britain began to study the pathology using not just staining, which is what Alzheimer had done with the light microscope. They were getting more into the details of the structural changes. That interest was revived by Bob Terry, who was a colleague and collaborator with [Robert]

Katzman (we'll come back to Katzman). So Bob Terry in a way was the father of the Alzheimer's program within the United States.

Going back to 1961, what Katzman and Terry did was revive the idea of looking at the problem [of Alzheimer's dementia] from not only the clinical but biological aspects, so that the combination of looking at the clinical and biological became the prototype for later building the program. But as I said, there were only a handful of people around the world that were interested or knew anything about it.

So the idea in 1978 was to start creating the people that would be interested to create the resources and infrastructures to do that. The scientific community had very little interest; in fact, they had complete apathy. Nobody would get into an area where they were not going to get a grant, and it was not a hot area of science. In fact, in those early years, if you went to a NIA/NIH study section meeting, when they received a grant [application] that had aging research on [Alzheimer's disease], it would become a joking matter. It would be laughed at as being an idea in pursuit of some money. The idea was that it is an Institute that nobody wanted, and they have some money and these jokers are coming with grant applications to get money for something that's not going to go anywhere. So that was the general attitude.

The other important problem for developing the field, which is the thrust of your question, is there were no promising scientific leads. How could you get the top neuroscientists to become interested in a problem that not too many people recognize? You don't see [persons with Alzheimer's disease] in a teaching hospital; nobody knew about what they could study, so developing a promising lead was an important need.

The other problem was the clear definition of the aging and disease. At that time Alzheimer's was considered synonymous with aging and aging was considered synonymous with senility, so the challenge was to disabuse the scientific community, the medical establishment, of the "conventional wisdom" that these aren't two separate entities. One can age quite healthy without disease, having the disease has nothing to do with aging -- it's an independent process. That was another big challenge.

Another important challenge, and this comes into your bailiwick in the Office of Planning and Evaluation at NIA, was the vague terminology of the first legislative mandate. The first legislative mandate for NIA said, "Thou shall do research on age-related conditions" and that was it. That created a big problem, because virtually everything NIH was doing – cancer (NCI), heart and lung (NHLBI), NINDS -- had age-related implications, so you had a built-in conflict. So one important task was to clarify the legislative mandate.

Another element was amongst the leadership, going from Fredrickson down to the other Institute Directors. They were not fond of having another Institute come, so from the beginning NIA was considered a bit of a joke, an unwelcomed person to the dinner table. They couldn't get rid of it because it was mandated by Congress, yet they didn't know what to do with it. And Butler did not enamor himself with most of these people. They considered him a lightweight. That's the general environment in which the program development had to take place, and all of this had to be addressed -- and they were, and each one of these can be a story in itself.

Now, the initial step was to develop a long-term aim for the national program, and as I said, that was done before I came on board for Butler, and he liked it. That included the idea of organization of a program that was different than what was at [the] Neurology or Mental Health [institutes]. The

organization structure was different: it had elements of trying to engage an outside group to become an advocacy group. Creating an advocacy [group] was important because, as I indicated, I had studied the history of other Institutes, the successes of other programs, and it had become apparent that major successes of earlier work such as cancer and child health relied on a strong spokesperson. In the case of cancer it was Mary Lasker; in the case of child health it was Florence Mahoney. We needed to have a champion, but besides having the people like Mary Lasker and Florence Mahoney, the movement creating the national program required an advocacy group. And that was one of the ideas: to create an organization like the Alzheimer's Association.

The other important challenge was to recruit key leaders from neuroscience to become interested in problems of aging and neuroscience. That meant by going around from one [extramural] laboratory to another, one university to another, trying to take the problem of what we wanted to solve to key leaders to become interested. Another important [step] was to address the question of overlap between neurology and mental health.

These were various strategies that were developed through the early years in order to get the program going. The idea was to assemble a cadre of key investigators in neurobiology.

One of the early hooks came from the Katzman - Bob Terry laboratory. At that time they had begun to recruit basic biologists to study the biochemistry and the neuropathology of the disease. Amongst these was Peter Davies, who had come from Britain. He had discovered that there is a particular enzyme that's missing in the brains of Alzheimer's [patients] that's required for making one of the key neurotransmitters. That work by Peter Davies about the absence of the enzyme involved for the synthesis of acetylcholine was an important hook and that began to give the beginning of a telling of a scientific story.

Another challenge was to make the distinction between biological aging and chronological aging, so that was an important scientific goal.

Another important question for taking the scientific problem to the key leaders in the field was question: how come a neuron that's designed to go for 120 years – because a neuron, unlike other cells in the body, can repair or restore itself and theoretically it can survive to a very old age – what's required to maintain the healthy brain for 120 or more years? Rather than asking the question of why pathology occurs, the flip side was the key question: what is required for maintaining health? That became an important challenge, to convince people that this is an important scientific question that they can be interested in.

The other challenge was to find the mechanistic link between aging and dementia because dementia occurs late in life but we're saying aging does not cause it, so what is the relationship between those two? In order to [identify] that mechanistic link, about 1980-82, I began to develop a hypothesis that the regulation of calcium ions within the neuron within aging brain is a critical variable -- that changes in it can lead to the problems you see in dementia and aging. The calcium hypothesis began to be formulated as a program development tool to get people interested in mechanistic explanation [for the development of Alzheimer's disease]. Until that time, most neurobiology of aging research was being done in a descriptive way; people would get older animals and compare them with younger animals, so it was more of a superficial description rather than getting into the nitty-gritty of the biology. That was necessary in order to get the top neuroscientists from other fields to become interested.

The calcium hypothesis was based on the progress reports we had received from a few of the grants that we funded and was put there as a speculative hypothesis. Through the years at NIA, and even now, it has been revised several times and has received quite a bit of confirmation and support that it's a good hypothesis. But it was one of the tools to achieve the goal that I described about what's required to bring the top scientists into the field.

The clinical challenge -- this is what I discovered was the scientific challenge, but there was also a clinical side -- one of the big challenge was to dispel the myth of senility, because that was a killer. The myth of senility said that, well, dementia is really part of aging and aging inevitably leads to dementia, at least so there's not much you can do about [dementia]. It was a nihilistic approach. The conventional wisdom was, “Okay, it's aging, there's nothing you can do.” My answer to them was the story that I told people and continue to do: John, who is 100 years old, goes to the doctor and he says, “My left knee hurts.” The doctor says, “Well, John, you're 100 years old. What do you expect?” But John reflects a minute and says to the doctor, “But, Doctor, my other knee is 100 years old. Why doesn't it hurt?”

That story tells the essence of the problem -- that aging was this dismissive kind of an idea, that it was minimized. The fact if that we don’t understand it, therefore we attribute it to aging. Fighting that [attitude] was an important part.

As part of that, also related to the attitude in Congress, was the idea of changing the terminology from “senile dementia” to “Alzheimer's disease.” At NIA we made a concerted effort abandon the term “senile dementia” and adopt the term “Alzheimer's disease,” abandon the notion that there was a senile form, a pre-senile form of the dementia, that it's one disease that we're dealing with. The reason was that we wanted Congress not to consider [dementia as a] vague, ephemeral, or a fully defined psychiatric condition [indecipherable], [but to think of it as] their disease. “Disease” is a lot more sexy construct than “dementia,” which they didn't quite understand.

Those early years were [busy with] those kinds of efforts, and the Public Information Office at NIA played a very important role during this period in educating the public. Jane Shure was the Director of Public Information and Marian Emr was a science writer that had a particular interest in Alzheimer's. They were terrific partners with me and with Butler in getting the message out. I can't tell you enough about the importance of the Public Information Office at NIA, the important role they played in changing the hearts and minds of the field. When I would receive a progress report that sounded like it had a good story, immediately I would go to Marian Emr and she would construct it into a nice story that would be fed to either the *Washington Post* or the *New York Times,* or sent to CNN, and there would be a story generated about the thing and that was an important part for, really, the Alzheimer's movement and for changing hearts and minds.

The third important clinical challenge for NIA was creating a diagnostic criteria that could allow accurate detection of the disease. That took quite a bit of effort. In 1983, 1982-83, I organized a series of workshops, and one of them was eventually published in The Archives of Neurology[1] that provided the very first attempt to look at the question of diagnosis from multiple angles: not only from the clinical point of view but from the neurochemistry, the imaging, biomarkers, neuropathology, psychiatry, neurology, geriatric medicine, neuropsychology. The workshop, which is I think is an important one, should be part of the archives that you're creating about the history of Alzheimer's disease; that article should be included there because it was first mention [of] the concept of biomarkers, which now has

[1] *Arch Neurol.* 1985;42(11):1097-1105. doi:10.1001/archneur.1985.04060100083029

become a very popular topic. Imaging was mentioned as important, which has become very important. A lot of the material covered in that 1983 workshop -- which eventually was published in 1985 -- really set the stage for creating a more systematic evaluation.

Now, the other problem for the disease -- part of the program development not too many people know or appreciate -- was the need for what we started talking about: going back to the origins, where the efforts of Alois Alzheimer were to look at the clinical problem and then look at the underlying biology. That process -- linking the clinical features to the biology -- was really fundamental for developing the program yet couldn't be done, because unlike cancer, unlike heart disease, you could not go to a teaching hospital and study its phenomena because Alzheimer's patients were not in teaching hospitals, they were in nursing homes and nursing homes were not suitable for clinical studies. So we had to create the infrastructure for enabling systematic clinical study, followed by biology and including biological assessment. That required creating the Centers Program.

Now, creating the Centers Program also required not only [establishing] the criteria for diagnosis so that you could have everybody doing more or less the same thing so that you're not comparing apples to oranges. There needed to be some standard for evaluation, so we had to create standardized tools. Then I spent a lot of time and effort promoting the development of clinical assessment tools and neuropsychological assessment tools – not only developing them but standardizing them; not only standardizing them but making it so that it's culture-free and can address the diversity of the subject. A lot of the programs that are mentioned on this slide were done to address that.

The centers program was to allow the longitudinal study; the assessment tools were done to standardize the evaluation. The CERAD [Consortium to Establish a Registry for Alzheimer's Disease], which was a Consortium to establish an Alzheimer's registry, was created to standardize the language, the cultural aspects, to look at the problem from multiple points. The ADCS [Alzheimer's Disease Cooperative Study] was created -- that's Alzheimer's study consortium for clinical studies in order to allow clinical trials in a longitudinal way.

The first few years were spent not only taking the scientific problem to the field but also creating infrastructure. Creating infrastructure and ability to do certain research really goes unnoticed; people don't appreciate it because it's not easily demonstrable, and nobody gets the Nobel Prize for creating these infrastructures, yet it's crucial for allowing [researchers] to do certain kinds of study which could not otherwise be done. We would not have, today, clinical trials or any kind of attempt to do therapy development if we did not have the assessment tools, the groups that have the knowledge for doing clinical trials, or if that had to be built from scratch.

Now, the organization of the program, the core scientific question for the NIA program for linking brain aging to Alzheimer's was this slide, which was borrowed from a neuroanatomist at UCLA by the name of Arnold Scheibel and his wife, Madge Scheibel. They were interested in developmental neurobiology. These are slides showing the development of a neuron from the fetus into old age. I have reformatted this slide to use it as a metaphor for aging and Alzheimer's. In the right hand slide at the extreme is the healthy old neuron with which looks like an uprooted tree with lots of dendrites and lots of synapses. As I indicated earlier, the aging brain can maintain that neuron for 120 [years] or longer by continuously repairing, restoring the structure, so the same nerve cell can continue to operate.

It's something like doing historic restoration. The White House has been around since the 1800s and we keep it occupied by periodically painting and updating the plumbing and electrical and windows and so on, so that it's a modern functioning structure, no matter how old. The same thing is true with the aging neuron. The question is, what's required in order to maintain that continuous [function]? That was the logic for organizing the NIA program, and the answer was that we needed to look at the problem from multiple points. That is, we need to study the parts that go into maintaining [the organism], from subatomic particles or atoms, molecules, proteins, genes, neural systems, organs, and so that is a hierarchical organization of science that goes into understanding how the neuron functions. That's what I meant by saying that the NIA program was organized in a vertical way to go from basic science all the way to behavior -- that it integrates into the scientific program people that are doing molecular biology, genetics, protein, chemistry, genetics, anatomy, physiology, neuropsychology, and all the way to clinical applications.

Ultimately what we want to solve is the memory problem and learning problem in all the individuals, and in order to do that, science typically reduces the complexity into lower, lower levels, and the idea of organizing the program at NIA was different. Where at Neurology or Mental Health they would organize these scientific programs into silos, where one silo dealt with the molecular biology, genetics, another one with the clinical aspects, but the two were never really integrated, at the NIA we took a different approach.

KN: Was NIA considered unusual for organizing their program that way?

ZK: I don't think people within NIA or outside appreciated that it was an internal organizational management logic. That was not obvious or apparent, yet it was the driving force, since the other difference between NIA and Neurology and Mental Health was that because they were well established, they did not have to do much work to attract grant [applications]. In fact, their attitude was, “There are plenty of good grants! We don't have to go work, cultivate the fields. Good stuff is coming, all we have to do is select the ones we want,” and that meant the projects that were given high priority by study section.

At NIA I took a different approach because I had a very specific plan, specific goal. I was more proactive. I would go out and cultivate people with specific questions, specific projects and bring them in and that was the distinction. In fact, I would get into discussions with my colleagues at Neurology about why I'm breaking my back going all over the place trying to develop projects when all I have to do is sit at my desk at Building 31C and good stuff will come my way and all I have to do is just pick and choose! Well, I wasn't satisfied with that, and it was more of like trying to build a football team, where you recruit, or an orchestra, where you recruit different instruments, different things. There was a score, there was a plan of what was to be done – and the next slide will show you that.

The plan was to the answer the question, “What's required for the neuron to continue functioning for 120 years?” The logic was that there are three major systems to maintain. One is the ability of the neuron to have an adequate constant supply of energy. The neuron is a big consumer of energy. The nervous system represents 20 percent of the body weight, or a small percent, yet it consumes 90 percent of the energy that the body requires, so it's a major consumer of energy. If energy deprived, it deteriorates and becomes dysfunctional. Stroke is a good example, where energy supply is deprived for a short period and the ischemic cascade kicks in, and the neuron dies.

The second important feature for the neuron is the ability to recycle to make new membranes and new proteins and to restore the functioning that has to remain intact. The third system that's required is the communication. It has a very intricate signaling system. Those three systems have to work properly to maintain healthy functioning.

This slide shows the energy supply and communication and there are the essential elements, so the question is in what way aging affects this and in what way disease affects them? The notion was that under ideal conditions aging should not affect that, that [the neuron] will continue functioning quite well and if there is any kind of a problem it's due usually to disease, so the idea was to separate the notion of inevitability between aging and disease, that they're separate, that there's a specific biological reason why the nervous system fails. It's not just mere passage of time.

And then to look at the facts of genetics. How does somebody's genetics affect one or more of these? How does nutrition, diet, affect one or more? How does the endocrine system? how does the immune system? And then to look at the effects of toxins. Virtually everything that we support now fits into this diagram that was developed way back in 1978. This this slide is from 1978, and it was used as a master plan for recruiting people to address one or more of these elements. When I went to recruit people to deal with research on neurotransmitters, I recruited people [who represented] not only one, but multiple perspectives. When I looked at the question of toxins or infectious agents I brought in several people for counterbalance. For example, with the Infectious area, we recruited somebody like Dr. Prusiner, who got the Nobel Prize, and counter-balanced them with another person that had a different perspective. When we recruited in genetics, [we] recruited somebody like Allen Roses, who gave us some very important insights about APOE, counterbalancing with some others. So that is one of the areas that had a cluster of people looking at that particular problem from different angles. This is what I called the systems approach: to look at the problem of the relationship of the disease from multiple angles, and that was the key element to the development of the Alzheimer's program and to the success, in some ways.

The other areas of neurological disorders or psychiatric disorders like depression, Parkinson's, Huntington's, were known and were hot topics way before Alzheimer's came on the scene, yet today Alzheimer's is on the forefront. Why? Because of the way the NIA program was organized and managed. The Alzheimer's program was underfunded through the early 1990s. Until the 2000s it did not get the big boosts until 2009 with the NAPA [National Alzheimer's Project Act] increasing the funding for it. Within NIH Alzheimer's was not a hot topic. Harold Varmus and Bernadine Healy gave lip service but did not put any resources or did not highlight it until Congress came with NAPA and began to add substantial funding for it.

Okay, what are the remaining challenges? What are some of the problems we need to solve?

One is the continuing saga of the relationship between aging and neurodegeneration. The problem that we began with: Still there is no clear explanation for it. The other major unanswered question, even today, is the mechanistic relationship between the biology and the clinical behavioral program. During the last 40 years we've learned quite a bit about the biology of a lot of the hallmark lesions like amyloid, tau, we know the genetics, we know the molecular biology -- but we do not know how those biological signals lead to the clinical behavioral problems.

This problem was highlighted with the recent FDA ruling about the amyloid reducing compound [aducanumab, or Aduhelm™], where the FDA approved conditionally the use of a surrogate biomarker for detecting or for approving a treatment, but they made it conditional, saying that it's not enough to show the drug's effect on a biological marker; you also have to show improvement on clinical or behavioral features of the disease. The reason is this. The scientific field is very much interested in the biology. They get very hot and bothered about understanding the mechanism or the structure of amyloid or tau, but they forget the fact that no patient goes to the doctor saying, "I got lots of amyloid, lots of tau in my brain." They go to the doctor because they can't find their way to the bathroom. They get agitated. They can't sleep. Those are the problems we want to solve, and the relationship between all the biology and all the sexy whistles and bells and the genetics have not explained the clinical behavior.

Let's go back to the slide. The relationship between the atoms, the molecules, and the behaviors is not linear. Understanding all these structures does not automatically mean you can solve the behavior. That is non-linear. That's a concept from complexity sciences; it's called emergent behavior. That means different ways you have to approach the problem. We have known the gene for Huntington's chorea for over 30 years, yet we don't have a solution for it. Knowing the genetics or the protein structure of a disease doesn't automatically mean you're going to have a treatment for it. You have to approach it differently, and that's the big challenge for the for the field and for the NIA: to address the non-linear, non-consistent relationship between the biological and the clinical features.

You have many people with these lesions, yet they don't have the clinical features. The converse is also true: you have people with no biological [problems] yet they have the clinical features. Which is the one you want to solve? The scientists are very excited about the biology, but that's not what the public wants. That's what we need to solve.

The other important challenge is the specificity and selectivity of the pathological interactions. The disease does not occur all over the place; it occurs only in particular [brain] structures, in particular neurons. We need to understand why that selectivity occurs, why some parts are spared, and others are more vulnerable. Heterogeneity is also another big issue. That is, the disease is not a single disease but multiple conditions that come together, and those multiple conditions are due to complex interactions between genetics, family history, lifestyle, and comorbid conditions. This issue has been around for a long time, and we tried to address it very early on in the history of NIA, particularly with respect to vulnerable populations. We have known for a long time that some populations are at greater risk than others. African-American, Native Americans, and Asians are at greater risk, and women are at greater risk, because they have some comorbid conditions. Vascular conditions are much higher prevalence in these populations, which makes them more vulnerable. We need to understand the biological basis of this heterogeneity, why some populations are at risk while others are spared. There's a lot of hand waving and a lot of lip service to the issue but the scientific questions, the underlying science for the issue gets lost, and that's one big problem that needs to be solved.

Patterns of progression and the sequence of biological and clinical progression in the prodromal period – that is the period before the symptoms appear -- is an important one. That is, the disease doesn't start at the point where you diagnose it, but it has started 20, 30 years before. We have no way of detecting who those people are. How does it progress from the pre-clinical prodromal period to the clinical period? Now that's an important challenge for the field for the future.

The other challenge is the fact that there is no such thing as pure Alzheimer's. When you look at Alzheimer's, it's mixed pathologies. It's always a mixed bag of things. The more correct term now is rather than call it a disease we should call it a syndrome, that is, it's a mixed bag of various conditions together. We need to understand that more carefully.

These are some of the unknowns that must be addressed for the future. We need to tease out the multiple risk factors: age, family history, genetics, lifestyle, comorbid conditions -- how do these various conditions interact? What is the relative contribution of each condition? Also, in different populations these have different impacts for example the genetics in African Americans is completely different, and it creates a different pattern of interaction with these other conditions. That complexity again needs to be sorted out, and we need to develop the tools the infrastructure the same way that at the beginning of the Alzheimer's Movement we put quite a bit of focus on creating the infrastructure and the technical capabilities to address these problems.

I did an analytical report for the OECD [Organization for Economic Co-Operation and Development] in 2012 to identify what's needed for a global approach to address this problem. That report suggested that there needs to be an international effort to create a very large longitudinal cohort study where you recruit not thousands but *millions* of people from diverse backgrounds for longitudinal studies in order to sort out these complex interactions between premorbid conditions, comorbid conditions, family history, genetics and so on.

We need to understand the complexity of etiology. The disease is not a single-factor disease. It's not a single etiologic factor, but multiple, so we need to bring into the field the complexity sciences, which has the tools for looking at the problem from a different angle.

We need different models for disease. Progress in other areas of medicine has relied on models; the models we have are totally inadequate. The rat models, the mice models are very simplistic. The evidence for that is the fact that virtually all of the therapy development for the last 40 years has relied on these simple animal models. They have not worked; they have not led to any effective therapy development. That means we need to do things differently. That means we need to have a different conceptual model of how we study the disease.

There is a need for additional biomarkers for identifying the disease in the various early stages before the symptoms appear. The reason for that is that the earlier we can intervene with the disease the more likely that we can change the course. We may not be able to treat or cure the disease, but we certainly could change the trajectory of the disease. A number of years ago I did an analysis based on the data from the funding of various projects with NIA that a delay of five years in disability can reduce the numbers in half. That's a very dramatic effect, and now there are signs that this is possible, given that the results of lifestyle multi-modal interventions through the FINGER study or U.S POINTER study, funded by NIA and the Alzheimer's Association, indicate that these are very promising interventions. So there's a light at the tunnel. But there are still also some major challenges that we need to overcome.

KN: I'm very cognizant of your time. I feel like I've attended a university class this afternoon, but would you be willing to email me your slide deck and we will drop it into your into your interview?

ZK: I will. I'll be glad to send you -- I only showed a few of them. I'll send you the full monty!

KN: That would be great. This has been fascinating; this has been a really great perspective. I've really appreciated hearing from someone who came in on the ground floor, so to speak. I have just a couple more questions if that's okay.

ZK: Sure, go ahead.

KN: You worked with some of the greats in aging research. You worked with Robert Butler, Nathan Shock, Franklin Williams, Florence Mahoney…. What can you tell me about working with them?

ZK: I was fortunate to have met the greats and to have rubbed shoulders [with them]. For me it was humbling, given the fact that I came from a very poor country and really had no expectation of ending up rubbing shoulders with the rich and famous, but I think in each case I learned something, and it was very positive. I had a particularly warm relationship with Robert Butler, who was a very enthusiastic, very positive, charming character, almost roguish. He was a great champion of aging research. He was the right person at the right time for the for the field, and he was a strong supporter of what I did. It was a bit unusual situation in that when I accepted the challenge of building the NIA program I asked one thing from Butler: that he give me a free hand. I did not ask for anything else. He kept his promise; he allowed me to operate without any interference, so that I could interact with various people.

At that time NIH was very sensitive to program staff interacting with legislators, but because I had spent time on the Hill during my Grants Associate period I had a lot of contacts on the Hill ranging from Mark Hatfield to Paul Rogers. I knew the people and the staff and continued interacting behind the scenes, giving them material, ideas -- in some cases I wrote the legislative language for the NIA. My writing was used verbatim in some cases. Both Butler and Frank Williams gave me a free hand, and as long as I did not embarrass them they were they were okay with that.

Along the way I met a lot of other important people. Besides the people on the Hill, I had developed a network within the Office of the [Health, Education, and Welfare] Secretary because during my early tenure I was sent to the Office of the Secretary on a detail. My detail was in the Secretariat during the transition period between [Secretaries Joseph] Califano and Patricia Harris. I had the desk for the public policy, coordinating health policy -- that's for all NIH and FDA issues. That gave me an insight to how policy was coordinated within the Office of the Secretary, whether it be linkage between legislative and budget and judicial and so on, so I got to make a lot of content. All those helped me to do the planning and to the writing up for the additional funding.

I played an important role in the reauthorization of the NIA legislative mandate. As I indicated, the first legislative mandate in the 1974 version was very loose -- no mention of Alzheimer's, nothing at all. But the 1985 reauthorization specifically talked about the Alzheimer's Centers and gave a broad mandate to NIA for the Centers program and put the Alzheimer's program at the center. That sort of broke the conflict with Neurology and with Mental Health because now we had very specific mandate. You're in the office [note: NIA Office of Planning, Analysis, and Evaluation]; you should have in your files the language for the reauthorization that specifies the Centers program, and I think that would be an important historic fact.

Along the way I got to know people like Zach Fisher who was a New York builder and philanthropist. I worked with him and developed plans, and Fisher's workshops were important.

I also became the Director of the Office of Alzheimer's Disease Research, which was created by James Wyngaarden, who was the NIH Director after Fredrickson. I was responsible for coordinating the NIH-wide Alzheimer's program.

KN: And that was an OD level office?

ZK: It was it was a something similar to the Office of AIDS Research or the Office of Nutrition, but it was housed at NIA, so I had the dual role of the Director for that as well as the Director for the Neuroscience program. That meant I became the spokesperson for NIH on all Alzheimer's-related matters. That meant continuous interaction with the press, with the White House, with the legislators, so I was writing and responding to all Communications, from no matter where it me to my desk to draft a response. That gave me a lot of contacts all over the place.

KN: When did you leave NIA?

ZK: I left in 1995, largely because my next wave of development was to go beyond NIA and create public-private partnerships with industry. At that time NIH was not terribly interested in having any kind of programs with industry or outside entities, and the new NIA Director, Richard Hodes, who came from Cancer [NCI]– he came to the field with no background in aging or Alzheimer's. In fact, he had very little background -- I don't think he was a branch chief. He became the Director of an Institute and did not have that much of an interest in aging or Alzheimer's research. He was more interested in the management. NIA was in a period of tremendous upheaval, and he basically focused on solving the administrative problems, and he was also getting outside pressure from the aging community about too much emphasis being placed on Alzheimer's. There was the terminology used: "Alzheimerization of aging" was the terminology. There was a growing conflict within and outside, a lot of unpleasant experiences, and I did not feel I was going to get the support I needed to continue the growth of the field into the next era. I felt that going outside of NIA would be more productive, so I became an advisor to the Alzheimer's Association and began developing the Ronald and Nancy Reagan Research Institute for them to do the next phase of the development of the program.

Then, in fact, some of the programs I started [at NIA] were terminated, which was a bit short-sighted in retrospect. One program was the satellite program [for the Alzheimer's Centers] for addressing the question that minorities were not being recruited for study. This was way back in the late 1980s, early 1990s. I created a satellite clinic program in the Centers to create satellite clinics in places like Harlem, in Indian reservations, or underserved neighborhoods linked to the Centers particularly to address the question of diversifying the recruitment. Now it's the hot topic. Yeah, I was addressing that issue way back in the Dark Ages!

I tried the Office of Alzheimer's, which was to coordinate all NIH research [on Alzheimer's]; that was abandoned. Then the CERAD program, which was to standardize assessment, was abandoned. There were a lot of missteps that I wish hadn't happened but did.

KN: Any final thoughts?

ZK: I don't have any. As I indicated, I think the future is promising. I think that the I think we have all the pieces to solve the problem; we have to find a way to connect the dots.

KN: All right, well, thank you so very much for the benefit of your time and your thoughts.