NIDDK

Oral History Project

Interview with Dr. Allen Spiegel

Conducted on June 25, 2019 by Kenneth Durr

KD: This is an interview with Dr. Allen M. Spiegel. Today is June 25, 2019 and I'm Kenneth Durr. Dr. Spiegel, thank you very much for taking time today.

AS: My pleasure.

KD: I want to start way back. I understand that you're an immigrant. I want to get a little bit of that story and how you ended up in New York.

AS: I arrived in Boston actually, not Ellis Island, at the age of three, in 1949. I'm going to use the word "allegedly" here because we want real facts as opposed to alternative ones. So a lot of what I'm going to say about this early history is based on what you receive from your parents. My parents both from Lodz, the second largest city in Poland and both Auschwitz survivors, so not only Holocaust, but concentration camp survivors, sent there from that ghetto, which was the longest standing ghetto and not liquidated until September 27, 1944. They pretty much, alone among their respective families, managed to survive. He was liberated by the Americans because he was on the death march from Auschwitz to Buchenwald. She was liberated by the Soviets because she was quickly sent from Auschwitz to a camp in Czechoslovakia. They managed to reconnect in Lodz. He quickly presciently realized this was not where they wanted to remain and managed to get back to the American sector in Germany.

I was born then in May of '46, allegedly the first child born in this displaced person's camp in Landsberg, Germany. We did come to America in '49, although disembarking in Boston, took the train down to New York and lived in Manhattan in an area that's now been rebranded as Hamilton Heights, 155th and Broadway. He was a tailor and worked in the

garment district. We came under what's called the Truman Quota, so that's relevant to current immigration issues. It was the Johnson-Reed Act in 1927 that precluded most people from Eastern Europe, Southern Europe, certainly Asians, from coming to the United States, and that didn't really change. The Truman Quota just said they would let a few refugees in. One of the other amusing stories which I doubt is true, but your mother says this is what happened, Eleanor Roosevelt used to come and meet and greet these ships bringing refugees and she would give every young child coming off the boat a dollar. But when she saw me, she gave me an extra dollar because my mother said she recognized I was so special. So there you go. Only a mother can tell you that kind of story.

Early days living in Manhattan and going to initially public school, my mother had come from an observant family, whereas my father, absolutely not. That becomes relevant later when I talk about college applications, another current topic. They didn't have $500,000 to get me into Harvard. But the upshot is she insisted that I go to a Jewish parochial school, a Yeshiva, and it was a progressive co-ed one in Washington Heights. She had to work as a cleaning lady to be able to pay for the tuition. But then, in a recurrent motif, I quickly got a scholarship and she was relieved of that responsibility.

A signal event was moving from Manhattan to Brooklyn, and that's significant in several respects. When I told this story at a dinner party for some Einstein donors they all burst out laughing. Shouldn't it be the other way around they asked, because that's usually the upward mobility. But it's astonishing. When I came to New York City in 2006 to become Dean at Einstein, the rebranding and the emergence of Brooklyn as not just hip, but a whole brand, is just astonishing. It wasn't back then. In any event, my father was able to get enough resources to purchase a cleaning and tailoring store in Brooklyn. We lived in Brooklyn for those years and I continued to attend a Yeshiva high school. That school is now defunct. It was in the heart of Flatbush, Church and Bedford Avenues, and its most illustrious (some would say notorious) alumnus who preceded me by a few years was Alan Dershowitz. So there you go.

KD: Were you interested in science when you were in high school?

AS: Definitely. The relevant interjection there is that the Sputnik satellite, which was put up by the Soviets, the space race, the Cold War, created a wave of consternation, almost paranoia in the U.S., which is a little hard to imagine now, despite all the things that continue to go on. One of the beneficial effects, though, is that it spurred more efforts to get students interested in science in specific ways. For me, that manifested as a National Science Foundation program for high school juniors. That summer, the summer of '62, I participated in that program with my first laboratory experience. I wouldn't glorify it with the term "research," but that was at the Albert Einstein College of Medicine, which was then all of seven years old. I would be taking the subway from Brooklyn to the Bronx to do research, working on effect of barbiturates on enzymes in rat testes. It was a rewarding and interesting experience, and it was really my first taste of research and that stuck.

Going forward to college admissions, given my folks with their limited background and resources, it was the opposite of the situations we see now with helicopter parents pushing and driving. I applied to a small range of schools, Cornell and Columbia, because those were within New York State, and there was something called a Regents Scholarship, which would be relevant. I also applied to Harvard and Dartmouth. Don't ask me why Dartmouth. That was nuts. The upshot is I got into all those places except Harvard.

I want to bring back this theme with the Harvard interview. This is now the fall of '62. This is now into my senior year in high school and it's in the Graybar Building on Lexington and 42nd in Manhattan. It's an alumni interview. I didn't have the resources to go up to Cambridge. The attorney who was giving the interview says, "You're going to this Yeshiva, so you're obviously going to need kosher food. Kosher food costs more at Harvard, but your father is a tailor. You're going to need a scholarship." He goes on and on in this vein. Now days you would sue probably or get out on social media and he'd be shamed or trolled, or whatever. I didn't want to give him the satisfaction to know that because of my dad's nonobservant upbringing, he and I were going to the Chinese

restaurant eating pork spareribs all the time. The upshot is I didn't get into Harvard. So what.

I did go to Columbia and that was really an outstanding education and a really rewarding experience. At Columbia, I had further opportunities to do research. One deviation from doing research was working in what used to be called the Catskills, which are now a shadow of their former selves. I was working as a bus boy at a place called Kutsher's Country Club. That was a very well-paying position for a college student. That was the summer after my freshman year. After my sophomore year I had the opportunity through a classmate to work in Germany at a Max Planck Institute. The Max Planck Institutes were renamed after the denazification. This was in Frankfurt, Germany in an institute for biophysics. You may ask, why would you be going back to Germany? There were several reasons, and not Poland, specifically Germany.

It was a very interesting experience. I did get to do and participate in some interesting research and certainly the personal experiences—I remember vividly in the street, an attractive young woman wearing some outlandish outfit and my eyes look at her, another middle age German gentleman's eyes look at her and then our eyes lock together. And he says to me, "Ach ja, was diese Frauen machen," what these women won't get up to. Then we then just started a conversation and immediately he didn't perceive—I don't want to give myself too much credit. I had taken two years of German actually at Columbia. In the DP camp, my parents of course spoke Yiddish, which is middle-high German, so it helps a little bit. I was not by any means fluent going into that class. But I became much more conversant. And he didn't immediately perceive that I was a non-native speaker. Then I divulged being American and his first words were, "I fought on the Eastern Front." This is in the '60s. It's relatively early on.

Long story short, the residue of anti-Semitism and Nazi influence, if you think about it, it wasn't really until sometime into the '60s that, even in the U.S., there was more of this kind of recognition of the Holocaust, not that people weren't aware in Germany. As is

evident, this is obviously a dominant theme in my psyche and even to some extent in my career.

That summer of research ended and then continued in several other forms. I actually worked, not at Columbia, but in a lab at NYU Medical School after my junior year at Columbia, summer program, and that's really very germane. I worked with a man, now deceased, named Mark Bitensky. He had been at NIH in this institute as a research associate. Remember, we're talking about the years of the doctor draft, the derisively termed "Yellow Berets," there was not a yet a Vietnam War in his era. He worked with Gordon Tompkins and Lemone Yielding. This was the laboratory of molecular biology. It still exists and is arguably one of the premier labs at NIDDK. He got me really turned on to research. I worked with him for two additional summers, after senior year at college, and then even after my first year in medical school, and got completely hooked on a molecule called cyclic AMP, the second messenger of hormone action.

I want to telescope ahead here because it's relevant to the NIDDK and indeed the NIH intramural program, and to my own career. He was working on mechanism of hormone action and he was really one of the few at the time who was working on it. An investigator named Earl Sutherland, who shared the Nobel Prize in 1971, purportedly, this is before my time, came to NIH to give a seminar in 1968. He had discovered cyclic AMP back in '55. Very, few people totally appreciated the significance of his work and also technically it was very difficult to perform the biochemical assay to measure the substance.

There were many labs in NIH and I can rattle them off, not just in NIDDK, working on the mechanism of their particular hormone of interest. My to-be mentor, Gerry Aurbach was working on parathyroid hormone, Orloff and Handler of the Heart Institute were working on antidiuretic hormone. Marty Rodbell and others were working on glucagon and catecholamines, Jesse Roth working on insulin, that's a separate theme. They hear the seminar from Sutherland and suddenly the proverbial or clichéd lightbulb turns on in everyone's head. They realize everyone had thought that their hormone works in a unique

way. Because in fact, the dominant feature of these particular hormones is the great specificity in the target cells that they act on, which we now know is due to the receptors, and the physiologic effects they elicit. For parathyroid hormone, specific effects on phosphate handling in the kidney, specific effects on calcium phosphate handling in bone. But it turned out they all realized that every one of these hormones, not insulin, but the ones they were working on, had cyclic AMP as the common second messenger, the common intermediate step in action.

As I would later describe in some of my own work, the specificity is at the front end and the back end, the specificity for the hormone is in its unique interaction with the cell surface receptor. These are cell membrane receptors. Then you get cyclic AMP. It activates a so-called cyclic AMP dependent protein kinase A. That phosphorylates specifically intracellular proteins changing their biochemical action, and it's the specific substrates expressed in those cells that determine the physiologic effects. This was the thing that they needed to comprehend and they all then started publishing papers on the role of cyclic AMP role in their respective hormone's action. This was all started by the work with Bitensky and it was then carried on in medical school. I'm going to weave a number of themes here together. We're now talking the fall of '66.

KD: Were you in pre-med in Columbia?

AS: Yes. I'll backtrack for a moment. I was in pre-med in high school and the reason for that is this is really a unique high school. I say now defunct, but a series of brilliant kids, mathematically, many outstanding individuals, one of whom, Joel Moss who was a classmate, I believe is still working in the Heart Lung Institute. He is the head of the pulmonary branch. He went on to get an MD-PhD at NYU. That's the quality of some of the people in the class. That said, our mindset was very clear. Many of us were pre-med, determined even at that stage, and we insisted that the school provide Latin as a course. Why? Because of the misconception that you needed to write prescriptions in Latin. How crazy is that? That was the mindset. But that worked out well because I managed to read Caesar's *Gallic Wars* and got to early Cicero, so there are beneficial effects.

KD: Did you consider going into a PhD program rather than to medical school?

AS: It's a relevant question. I didn't and I'll be candid. I was very conscious, again, I'm emphasizing this immigrant theme and the sparse resources, I went to Columbia essentially, virtually on full scholarship, along with a 20-hour a week job, right through the four years, prize room in the dormitory in my senior year, which meant I couldn't live in an apartment. The fact is I wanted to be able to hedge my bets. When now as a former dean of a medical school, I stepped down in July of '18, but it's relevant today. You basically see students now getting out with so much debt, although some schools have managed with philanthropic contributions to be debt-free, but as an M.D. you were always guaranteed of at least some reasonable income, and that was true then.

I recall that MD-PhD programs were just in their bare beginnings, so that would have been for me a viable option. That would have been the preferred option is MD-PhD, but I did not go that route. In fact, in my Harvard Medical School class, two individuals in that class who were in the M.D. program went later and got Ph.Ds., so they were not MD-PhDs. One of them, by the way, Bill Wickner, is the brother of Reed Wickner, who I believe is still a distinguished scientist who I promoted to lab chief when I was the intramural director. That's just showing how embryonic the MD-PhD program was back then.

The real reason was hedging my bets. I figured this way I can always go into clinical practice. The other relevance is, sadly, this is why physicians with M.D.s only who go into research, unless they do the Master's in clinical research, which is a good program, they're often not successful in terms of pursuing a research career and getting NIH funding. Often they're forced by deans to do more clinical work, so it's kind of a Catch-22.

For me, I knew that I wanted research as an important part of my career. It's not that I didn't relish patient interaction. Because of the exposure to research that I had, cyclic AMP and the mechanism of hormone action, and also the desire to be involved in clinical medicine, I picked endocrinology as a specialty early on, and that made sense in terms of

the research. The other thing, which is not intuitively obvious now, back then in late ‘60s, early ‘70s, endocrinology was arguably one of the only internal medicine specialties that was really biochemically science-based. Immunology was in its very early stages. Neuroscience was just being founded. Cardiology was “plumbing.” I’m being a little derisive. Endocrinology really made sense. Too much of a hormone, too little of a hormone, the hormones were synthesized; gratifyingly, you could replace the hormone if it was missing. So that was an appealing specialty. That’s where you could almost say it was tunnel vision.

Harking back to the fall of ‘66 and the medical school applications, I applied to Harvard Medical School among a few others and what a difference. I get in in November, in the first wave of admissions. I’m going to relate this to the Einstein situation. The Albert Einstein College of Medicine was founded in 1955. It was founded as part of Yeshiva University because of the virulent discrimination against Jews to go to medical school. Very few were accepted to a very limited range of medical schools.

A visionary president of Yeshiva University decided this is a way to rectify it, went down to Princeton to the Institute for Advanced Study to interview and request Albert Einstein, would he be willing to lend his name, and he said, “I’m a physicist, not a physician. Why would you name a medical school after me?” He said, “Okay, we’ll name it the Joe Blow School of Medicine.” He said, “Who’s Joe Blow?” “That’s why we want to name it the Albert Einstein College of Medicine.” At least that’s the anecdote. That’s indeed what happened. Einstein is everywhere on campus. There’s no copyright on his name or appearance. There are other entities around the world even with the Einstein name. I was consulting on a scientific advisory board last fall for the Albert Einstein Jewish Hospital in Sao Paulo, Brazil. You can pick up that name if you want to lend some panache to it, scientifically, humanistically.

The upshot is the anti-Semitism in that period of time and the discrimination hadn’t disappeared totally, but it was really dissipating. Another manifestation of that is Mt. Sinai. Mt. Sinai is a hospital in Manhattan that goes back to the mid-19th century, founded by the

German Jews who were among the first waves of Jewish immigration. The hospital had a very distinguished record, but no medical school. Why would they bother? In 1969, 14 years after Einstein, they founded what is now the Icahn School of Medicine. The reason for that is the few Jews who got into medical school had very few choices of residency. Mt. Sinai had their pick. As the anti-Semitism started dissipating, they realized they were going to have to be competitive and they grew their own pipeline. This is some of the sociology of what was going on.

At Harvard Medical School my research theme continued. I was very fortunate to work in the laboratory of the person who was the Chair of Medicine, a man named Alex Leaf, very distinguished and interesting individual. He was working on antidiuretic hormone and he was one of the first M.D.s in the National Academy of Sciences. Again, you had elective time, you had summertime, so there were times to weave in, and continuing the same theme of mechanism of hormone action and indeed cyclic AMP.

What's relevant here in terms of my NIH career, it's pretty much a given that if I can get in I'll go to the NIH. The reason I say that is this is the era of the doctor draft. Graduating in '71, as I did, that turned out to be the last year of the doctor draft, but I was still at risk. People interested in research tried to get to the NIH. People interested in epidemiology would try to go to the CDC. Being in the public health service fulfilled that requirement of military service, the Commissioned Corps of the public health service. Fortunately, I was able to get in there. There's a huge hole in the ground now, on Woodmont Avenue at Wisconsin Avenue where there used to be a motel, and that's the motel where I stayed, taking the Greyhound Bus from Boston, overnight, into D.C., coming up from New York Avenue to that motel, for two days of interviews.

I didn't want to take any chances. I had arguably over two dozen interviews in many labs with many institutes, and I was fortunate to get my first choice with Gerry Aurbach in what was then NIAMDD, the names have changed over the years, in the metabolic disease branch. Aurbach was a phenomenal mentor. He died tragically in '93 in Charlottesville,

VA. He was arguably the only graduate of UVA Medical School to get into the National Academy of Sciences.

KD: There is a connection with Aurbach. Your first paper, was it in endocrinology?

AS: Yes. He was either an associate editor or he was on the Editorial Board of *Endocrinology*. That paper on glucagon structure function and activation of cyclic AMP formation in the liver was with Mark Bitensky. That paper was written based on work done those summers after college and first year of medical school and was accepted. That is my first publication. The other twist here is at the Mass General, which I went to for internship and residency, they thought they were the center of the universe, medically, and didn't realize there were other places like Hopkins and Einstein, Montefiore, Jacobi.

There was the Ether Dome, the Charles Bulfinch Building built in the early 19th century where ether was first used in 1854 or so for a procedure. That Ether Dome still exists and that would be where endocrine rounds were given and the speaker, one year I was there as a student, was Jesse Roth, who was then not a branch chief, but he was at the NIH in a section within the clinical endocrine branch. Later, they split off as the diabetes branch. He's such a charismatic figure and I was so taken.

I went up to Jesse hoping to be able to work in his lab. The way things worked, his lab only had associates every other year and it was not my year. I don't want to denigrate Jesse, but it is a great twist of fate that I did not get into the lab. There are terrific people who came out of that lab and we should mention them: Ron Kahn, who I just saw at the diabetes meetings a few weeks ago. Ron was at NIDDK in the diabetes branch for about 10 to 11 years, with Jesse, doing the pioneering work on the insulin receptor. The insulin receptor is a tyrosine kinase. This is different from the G protein coupled receptors that go into the cyclic AMP pathway, an important mechanism of hormone action.

Jeff Flier stepped down just a few years ago as the Dean of Harvard Medical School. He came out of the diabetes branch, did very important work on some of these extreme forms

of insulin resistance, which then Simeon Taylor carried on, Phil Gorden and others continued to work on. There's a rich history there. I'm not saying one couldn't do well in Jesse's lab. He was very controlling. So it's not coincidental that Ron left. He went up to Boston and Jeff Flier followed him there. That was the opposite of Aurbach. He was "sink or swim." He gave you guidance and support. He was a remarkable figure and remarkable scientist.

KD: Talk about the two-day interview. How was it structured? How many people did you talk to and how did you feel when you came out it?

AS: You don't get instant feedback. I literally washed up in the Greyhound Bus station washroom on New York Avenue, came straight up to campus. There was no metro. How would I have gotten up here? I certainly couldn't have afforded a taxi. There must have been some way that I got up here and went through the first day of interviews. There were all sorts of people who were quite good. It wasn't random. I was picking people in areas that were of interest.

Aurbach is a very mild mannered, laid back guy. It wasn't a given, but I had a good feeling about that. Nonetheless, I did repair to that motel, spent that night there, and the next day took the Greyhound back. This was during the course of my residency. You apply early on as a medical student, but you actually have to go through the interview process at a later stage. I was very gratified to get word that I managed to get into the Aurbach lab and met a series of distinguished individuals. A person who followed me by a year was Ed Brown. Ed Brown left after about four or five years and went to the Brigham Hospital in Boston where, in '93, he made the seminal discovery of what's called the calcium sensing receptor in parathyroid cells, which is a very important discovery and relevant to the work initially started in the Aurbach lab.

I described the medical school phase and some of the research there, applications to the NIH and matching internship and one year of residency, you were allowed to short track at Mass General. That was a demanding and rewarding experience. At the same time, I

was quite clear, I was eager to get on with subspecialty training. Here's where again a number of happy circumstances came together. At the Mass General, the head of the endocrine unit was a man named John Potts, still alive and well advanced into his 80s. He had worked with Aurbach when he had been at the NIH, in the Heart Lung Institute, on the sequence of parathyroid hormone. That structure determination is important right through to clinical medicine. One of the treatments of osteoporosis is a synthetic version of parathyroid hormone that builds back bone, Forteo. It's a Lilly drug. I'm not plugging it. I don't have any stock in it. That's an example of how important Aurbach's pioneering discoveries were.

The idea was that I would do my two years in the Aurbach lab, come back to Mass General and do an endocrine fellowship, and we'd see what would happen from there. Well none of that happened because just then an inter-institute endocrine training program was created at NIH and I was one of the inaugural fellows in that program. So I was able to do my internal medicine boards in 1974, and then my endocrine and metabolism boards in 1975. That was a very gratifying experience.

I told you the anecdote with Earl Sutherland and the various NIH intramural scientists. If we now just look at the collection of endocrinologists and endocrine researchers in NIDDK, also the Child Health Institute, Griff Ross, Mort Lipsett, not alive, someone who is still alive, Lynn Loriaux, who came out of that, they focused primarily on steroid hormone pathways and extraordinary clinician scientists.

Within NIDDK, Saul Rosen, Bruce Weintraub, Jesse Roth, Phil Gorden, Gerry Aurbach and his associates, Rodbell was a pure PhD, but relevant here, he was not part of the clinical group, but he was relevant in the sense that he was working on mechanism of hormone action. His discoveries were important to me personally. One is tempted to say these were the days of the giants, but they really were. To sit in the eighth-floor solarium in the old Building 10 and have clinical rounds with these individuals was unbelievable. It was the top of the top.

Furthermore, the opportunities, because of the Clinical Center and the nature of the patients—within short order we saw three patients with a very unusual kind of pineal tumor, so called suprasellar germinomas, and that led to a paper with Phil Gorden and others. I was a Clinical Associate taking care of a young 14-year-old girl who was admitted to the Child Health Institute with primary amenorrhea. She never had her periods. As I took her history it became clear that she also had something called diabetes insipidus, inability to concentrate her urine, so she was constantly drinking and peeing. To me that spelled more than just primary amenorrhea. Indeed, she had what we call panhypopituitarism as well as diabetes insipidus. This spells some trouble up above the optic chiasm where the pituitary is. It turned out to be one of these tumors. By that time we recognized it sufficiently to know it's exquisitely radio-sensitive. She had one of the first what we now call CT scans. They were called EMI scans, which is the company that was also the Beatles' publisher, Eastern Music Instruments. The EMI scan, Hounsfield shared the Nobel Prize for discovery of things related to CT scanning. That showed calcification. Then she was radiated and she was saved, and in fact, had children later. Her parents, mother crocheted a little blanket for our newborn as a gift of thanks.

I never portray myself as a clinician. In fact, my typical statement which is a bastardized version from something I heard from Ira Pastan, who is still working at the Cancer Institute, although started at NIDDK. The clinicians think I'm a biochemist, biochemists think I'm a clinician, my mother hopes I'm a doctor. That was the schizophrenia of trying to be a physician scientist, albeit, not an MD-PhD. The upshot of that is being in the inter-institute endocrine training program.

The doctor draft ending in '71, the powers that be at NIH recognized that this endless stream of people coming, giving them Brown and Goldstein, Bob Lefkowitz who I ended up collaborating with extensively when he was at Duke, he had been with Jesse Roth in the diabetes branch, Stanley Prusiner, many of them Nobel Laurates who came out of this program, that was going to end. Ultimately, I was offered a permanent position, essentially in 1975. I told John Potts, sorry, I'm not coming back to Boston.

By that time my wife had a position at the World Bank. She's a librarian. She actually worked at the main library at Copley Square in Boston. It was then that I got my first medical school loans. We got married at the end of my second year at Harvard Medical School. I had been on full scholarship throughout and the loans are just a minute fraction of the kinds of current medical student loans, even with the changing dollar. They figured since she's working, the classic story. She came down with me to NIH to work at the Georgetown University Library and then was able to get a position at the World Bank and worked at the World Bank two and a half years into my being Dean at Einstein. It's part of the reason we kept the house in Bethesda.

We scraped together the bonus that was given to people in the Commissioned Corps, for the first time in '75, purchased a small Cape Cod on Radnor Road in Bethesda, about a mile and a half from the NIH campus, and that's where we lived for quite a number of years. That was the beginning of a 33-year career at NIH and NIDDK in different positions.

Within the first few years, given Aurbach's mentorship, I was able to establish my own research program. The initial papers hinged on discoveries of Rodbell. Rodbell had been working on mechanism of hormone action, cyclic AMP formation, once they got wind of the Sutherland discovery. But he made a crucial discovery, which is that most people who are doing the assay for cyclic AMP, the substrate is ATP. The ATP they would purchase from Sigma Chemical Company was contaminated with the related purine nucleotide GTP, several orders of magnitude lower in concentration. But it turned out, Rodbell, he was a sophisticated biochemist, they purified the ATP. They added the hormone in the usual way, no cyclic AMP whatsoever. What's going on here? They then recognized that they needed to add something back and that something was GTP.

Through pure enzymology kinetics they realized there is an absolute requirement for GTP in certain hormones' action, and he postulated existence of a GTP-binding protein that couples hormone receptors to the enzyme that generates cyclic AMP. A diagram for a symposium to honor Rodbell winning the Nobel Prize in 1994 shows his drawing of these

three components of what is termed signal transduction. Rodbell shared the Prize with Al Gilman, who sadly died of pancreatic cancer just a few years ago. He had been many things. He had been the Dean at UT Southwestern. He was the first to purify the first G protein, the one that is involved with stimulation of cyclic AMP. He took the Rodbell kinetic discovery and manifested it in real physical terms as a purified protein. This was critical work which just opened up enormous fields, which are still ongoing. Lefkowitz eventually shared the Nobel Prize in Chemistry with his former post-doc, Brian Kobilka at Stanford, for determining the three-dimensional structure of G protein-coupled receptors (GPCR).

In essence, the paradigm is the hormone binds to a seven-membrane spanning cell surface receptor a GPCR, or heptahelical receptor. That couples to a so-called heterotrimeric, three different subunits, G protein. They're a family of different G proteins, which in turn lead to different kinds of second messengers, not just cyclic AMP, and in turn different physiologic effects.

My early work involved some of the basic studies, picking up on some of the Rodbell things, on the G proteins and working with systems that Aurbach had pioneered in. My own interests were to try to combine this basic biochemistry with clinical endocrinology. One of the key discoveries related to a disease that goes back to one of the pioneers of endocrinology at Mass General in the Ether Dome, Fuller Albright. Albright's hereditary osteodystrophy and, he gave it a terrible name, pseudohypoparathyroidism. This terrible name, it's like they're a deficient in parathyroid hormone, but they're not, they're resistant to it. Back in the '40s, he recognized, without benefit of radioimmunoassay or ways of measuring the hormone, that they weren't deficient, they were resistant. He was an extraordinary pioneer. This was an opportunity for me to jump in here.

It was widely viewed that that disease was a defect in the parathyroid hormone receptor, that's where the specificity is. I'm reading literature and I see there are reports of patients with the disease who have hypogonadism, hypothyroidism. And I'm saying this can't be the parathyroid hormone receptor. It's something common to these different hormones

that act through G proteins. Hence, the speculation, the hypothesis was, maybe it's a genetic defect, a loss of function of the G protein involved in stimulation of cyclic AMP. And that's exactly what it turned out to be.

We're in the midst of the late '70s to early '80s, and I'm at this stage close to splitting off from the Aurbach lab. The then scientific director determines that I'll have a branch of my own, the molecular pathophysiology branch, still with cordial relations with Gerry Aurbach, but fellows of my own, and the work is candidly going well. We're doing basic work on G proteins. We were able to make some of the first antibodies to G protein subunits. There are three subunits: alpha, beta and gamma.

One of these interesting twists, that goes back to work related to what my early mentor Mark Bitensky was doing, not when I was in the lab. He carried on his career. He was working on the mechanism of what's called phototransduction, how the retina perceives light in the rods and cones. There's a whole field working on this, completely divorced from our field, which is working on mechanism of hormone action. What begins to emerge is that these are exactly parallel systems in terms of evolution, that the receptor, rhodopsin, for light perception in rods is a G protein coupled receptor.

Lefkowitz picks up on that and runs with it. We picked up on the fact that the G protein that's specific to the rods, it's got the trivial name transducin, is a three subunit G protein just like the ones that are much more rare that we're dealing with, rare and hard to purify. I would send my technician to Catonsville, to the slaughterhouse where he would get cow eyes. We would wash out the retinas and it was a trivially easy purification to get pure transducin and we made antibodies to it, and then were able to show that these antibodies cross-react with the subunits of the hormone related G proteins. That was an important advance and it helped advance the field in general. At one point I had a technician doing nothing but sending out dry ice packages all over the world to people we shared them with. Somewhat embarrassingly, NIH determined we should patent these antibodies, which was a strange thing to do, but it was basically so that other companies could pick

up and provide these as research reagents, so that was done. Believe me, no mega royalties there, but nonetheless it was a good thing to do.

So a variety of strains of work in the lab related to basic aspects of G proteins, some terrific fellows, a few of whom are still here at NIH. I mentioned William Simonds, Lee Weinstein, who's the head of the branch that I had headed, that Aurbach had headed. He's here as a branch chief. There are individuals like Sunita Agarwal who had worked in the lab on a project I'll get to, and Michael Collins who works in the Dental Institute, who also picked up on projects that we had picked up on and was in the inter-institute endocrine training program. All this time the training program is going on I'm able to be an attending for the patient service and pursue this research.

In roughly 1990, the then scientific director Jesse Roth leaves to go to Hopkins and there is a search and a determination by Phil Gorden, who is the Institute Director, to name a new intramural director, and candidly, in those years it was virtually impossible to recruit someone from the outside. People on the outside had better than government salaries, even research space for a laboratory, which typically the scientific director still had, was problematic. So it was invariably not only an internal candidate, it wasn't even someone from a different institute. So it does show you times have changed somewhat. This has waxed and waned at NIH but that was certainly true then.

I'm going to name names. There were certainly two outstanding individuals who I hope and believe are still alive and well. Gary Felsenfeld is one. He was one of the co-chiefs of the Laboratory of Molecular Biology. William Eaton, Bill Eaton, Chief of the Laboratory of Chemical Physics. These are individuals who really should have assumed that role to be the scientific director. And there are various versions of the story, either they didn't want it or the community was polarized, half saying "if he gets it. I'm…" The bottom line is that Phil Gorden approaches me and says, will you take this position.

I'm about 44 at this stage and I will say two things. I'll make the arrogant statement, which is not intended that way. I knew, this was 1990, there would be a Nobel Prize for G

proteins and I would not win it, so perhaps I could contribute in other ways. At the same time, going back to my internship interview at the Mass General, there were two committees that interviewed the candidates, one headed by Alex Leaf and the other headed by the Vice Chair of Medicine, a man named Dan Federman. Necessarily, I was interviewed by the Federman committee because I had been in Leaf's lab, so that was a conflict of interest. At one point Federman says to me, "Do you see yourself becoming Chair of Medicine one day?" And my response was, "Why? That would be a waste of time." So I was immediately completely insensitive to the fact this was an insult to him; that it implied I have more important things to do in terms of my research, etc. Of course the irony is I didn't become a chair of medicine, but look at the administrative things I took on. I really didn't want this position, but ultimately I allowed my arm to be twisted. So I served as the intramural so-called scientific director from fall of '90 through the fall of 1999.

KD: You came from the metabolic diseases branch?

AS: Yes. These names were renamed. Aurbach was tragically killed in Charlottesville in '93 and at that point the branches were condensed. There was no need for me to have a separate branch. Also another figure to mention is Steve Marx. Steve Marx, I'm four years younger than he is, had been in the Aurbach lab some years before. He was at the Mass General for senior residency and came back to the Aurbach lab. He was in the lab about the time I was. He's significant in a number of respects. He excelled as a physician scientist clinical investigator in the rarified context of the NIH. What I mean by rarified, on the one hand you can work on rare diseases, on the other hand common diseases like primary hyperparathyroidism, excessive activity of the parathyroid glands.

This is a program which arguably represents the best that the clinical center can do. It's a credit to Aurbach who founded this program. What it consisted of is being the magnet, the mecca, for patients with primary hyperparathyroidism, the treatment for which is generally surgical. It's removal of the offending gland or glands. If the surgery failed either right off the bat, calcium stayed high or recurred, these patients were very difficult

to then treat because there would be scarring in the neck. Where was the offending gland, what's going on?

This is germane because we had this bias of referral and we being the metabolic disease branch, a radiologist who pioneered in the localization of the abnormal glands, the late John Doppman in the Clinical Center, and then a succession of outstanding surgeons in the surgery branch of the NCI. Many of these surgeons have gone on to major careers at other academic institutions right through to this day. That kind of multidisciplinary collaboration was benefiting the patients, benefiting the research. This is how Aurbach determined the sequence of parathyroid hormone, human parathyroid hormone.

But ultimately this is where Steve Marx excelled. He began to recognize that many of the patients that we were seeing had hereditary forms of hyperparathyroidism. That's significant because they are very difficult to cure because instead of one single sporadic abnormal gland that had become an adenoma, so called, they had hyperplasia. All four glands had a germ line defect, which led to this hyperplasia. A disease he didn't put on the map but described in its full flower is so-called familial hypocalciuric, hypercalcemia, FHH. The way these things all come together, that turned out to be due to a loss of function mutation in the calcium sensing receptor, which Ed Brown then discovered in '93. A lot of the work on FHH was done here by our group in the clinical center.

KD: Tell me a little bit about when you became Scientific Director? What did you see as your big challenges, your big opportunities?

AS: On the one had the research that I'm describing is ongoing. One of the non-conflicts of interest, but clear benefits of being the intramural scientific director is not only can you, but you're expected to continue research. First I want to credit two individuals, early on, a man named Ed Steers. Ed had been the Deputy Scientific Director to Jesse Roth. He was a PhD who had worked with Chris Anfinsen, a famous lab, but had soured on research and had real administrative skill. He's the first example, which was replicated a few times in my administrative career, of having an individual who was trusted by the

community, who had institutional memory and who I believe or deluded myself into thinking wasn't upstaged by my coming in and being their boss. Ed and I had a terrific relationship. He was also a Lincoln buff, an expert. Until he retired, he was a crucial companion to me in running the intramural program.

The features of the intermural program that were crystal clear is just the quality of the science and how outstanding it was. Now in my neck of the woods up in Manhattan a key institution is Rockefeller University, replete with members of the National Academy, scattered Nobel laureates, etc. The NIDDK intramural program was right at that level. Anfinsen had won a Nobel Prize. Baruch Blumberg who had worked there had eventually won the Nobel Prize, although he was at Fox Chase, Marty Rodbell, many National Academy members and both in terms of basic molecular biology, chromatin structure, DNA recombination, Marty Gellert, the three-dimensional structure of proteins, both by x-ray crystallography, David Davies, and NMR—Ad Bax, Marius Clore, absolutely outstanding scientists. Some of the clinical branches were quite good also. I alluded to our own branch, the diabetes branch had a rich history, the program, even preserving its quality, but the challenges were clear.

We had the election of Bill Clinton and Al Gore reinventing government. We think sometimes, without getting into political things about Republicans cutting things back, we had to eliminate a whole series of so-called FTEs, and that led to some interesting dancing to be able to accommodate that. There were always budget constraints.

The issue of recruiting new individuals, particularly the difficulty of recruiting physician scientists was quite challenging. Jesse, for example, recruited away a man named Alan Shuldiner from the diabetes branch. Alan Shuldiner is now Vice President for Genetics at a company called Regeneron up in New York, a very successful company. He had been at the University of Maryland, splitting away from Jesse, a theme that continues. But we managed to retain people like Mark Reitman who, although had a brief period at Merck, did come back to NIDDK.

The challenge of recruiting PhD scientists however, was not as great a challenge because salaries are lower, because the intramural program was a terrific place to work, and we were able to recruit some outstanding individuals. The challenge of the Phoenix branch, with the Pima Indians, the *Arizona Republic* was publishing articles about the Pimas being "poked, prodded, what good are you doing." That was something that we were very cognizant of. I remember going to Phoenix one July in 105-degree weather to see what could be done in terms of certain things that needed to be rectified. Nonetheless, I don't want to over-dramatize the challenges, it was an enormous privilege and opportunity. I discovered early on that I had arguably some knack for administration and leadership positions. And I would say the key thing is to realize that it's not about you, it's about everybody else that you're serving. If you keep that in mind, I think you can be successful.

KD: Did you work closely with Phil Gorden?

AS: Phil was a source of wise counsel. He had been the Clinical Director coming out of the diabetes branch then he became the Institute Director. I think that began in '86 and he was the Institute Director until '99. We've enjoyed a close relationship over the years. He and Vivian his spouse, we're still friendly with and get together on numerous occasions. There could have been some awkwardness in my ending up replacing him and the circumstances, but he's the kind of individual where that was far from the case.

Back to intramural director, one of the challenges was how best to reconfigure my own lab. We have the Board of Scientific Counselors that would review all of the intramural labs on an ongoing basis and I used that opportunity, and Phil was relevant to this, to begin to provide more independence for some of the people like Bill Simonds, like Lee Weinstein, I alluded to, so that their own careers would be fostered. Again, you don't have to stay at NIH. I had a fellow MD-PhD named Andy Schenker, who went off, first to academia then industry and that's a good thing, too. There was a downsizing of the lab, but to good effect.

I want to touch on a few things during the scientific director phase because they were quite rewarding. One was work published in the New England Journal with Andy Schenker as the first author with Lee Weinstein involved. This was the flip side of the pseudo-hypoparathyroidism study. It also shows the strength of the clinical center and the intramural program. In the Child Health Institute in the Endocrine Branch they were studying girls and boys with precocious puberty, the opposite of that in the amenorrhea situation. There are many potential causes. One cause is another Albright disease, that's called the McCune-Albright Syndrome, a very perplexing disease. They had these *cafe au lait* pigmented spots. They can have bone lesions called fibrous dysplasia, and they have all kinds of endocrine over-activity, precocious puberty, also hyperthyroidism, growth hormone hyper secretion.

Here, too, I speculated, and there was some other work that was relevant to this, that an activating mutation in the same G_S G protein that stimulates cyclic AMP could lead to this phenotype, so called, but not a germline activating mutation. The reasoning was if you inherit this and it's in every cell that may not be compatible with normal embryonic development. But if instead it occurs post-fertilization, post-zygotic, you can get what's called a mosaic and that term is now much more appreciated than it was before. Indeed, this was the first example of a G protein disease that was due to this kind of mutation in a mosaic distribution. That's why the skin lesions would be on one part of the body, the fibrous dysplasia. This was important.

There are other examples. There is another G protein, which is mutated and causes uveal melanoma. This is the disease that Oliver Sacks died from, metastatic to the liver. There are other syndromes you'll see sometimes kids with this huge hemangioma, Sturge-Weber Syndrome. That's a mosaic activating G-11 mutation. This was very important work. It actually spun off into the Dental Institute with Mike Collins and Pam Robey working on the bone disease. He's picked that up and run with it and is doing a lot of terrific work in that area.

The other one comes back to Steve Marx. In addition to the FHH, we had many families with other forms of inherited hyperparathyroidism. One of them, so called familial isolated hyperparathyroidism, that was the only genetic component, has only in the last few years had a mutation described by Sunita Agarwal, it's a so called transcription factor, GCM-2, which is unusual because it's an activating transcription factor and it's inherited and causes these parathyroid tumors. The main one of interest to us was multiple endocrine neoplasia type 1. This is anterior pituitary, pancreatic islet and parathyroid tumors. That's the dominant phenotype. We had many families with these. Steve Marx was doing the clinical characterization.

The paper in the New England Journal by Eitan Friedman, an Israeli fellow working with me at that time, was able to show that a locus on the long arm of chromosome 11, 11q13, where a lab in Sweden at the Karolinska Institute had described a putative tumor suppressor gene as lost. This is the so-called Knudson two-hit hypothesis. It's true of retinoblastoma, it's true of other tumor suppressor genes. You inherit one bad copy.

In the BRCA1 and 2 example, those tumor suppressors, that's it. You just inherit that one bad copy and you're off getting breast or ovarian cancer. In this case, you inherit one bad copy, it's in every cell, and then you lose somatically the second good copy in some cell like a parathyroid cell or islet cell, then you get an endocrine tumor. That led to a hunt for what this gene was. We only knew the chromosomal localizations. This is called positional cloning and there was a big European consortium that formed to try to find this gene.

At this point, Bernadine Healy fired Jim Watson, or they parted ways. She was the NIH Director, he was the head of the Genome Center. She recruited Francis Collins from Michigan, this is circa '93. I was still Scientific Director. Francis's terms of coming to the NIH was he had to have an intramural program. The Genome Center did not have an intramural program. She gave him Building 49 where he recruited an intramural program. Francis was known as one of the masters of positional cloning. I met with him early on. I said, "We can do this together. We've got all this patient material, you know how to do

the positional cloning." We quickly scoped out that the European Consortium hadn't made much progress.

The usual story was this would take a graduate student two weeks, but it took four years until '97. This was a gratifying, multi-disciplinary NIH intramural collaboration with Cancer Institute, our branch, the Genome, NCBI for Informatics. We found this tumor suppressor gene, the MEN1 gene. We called it Menin and that led not yet to cures for the disease, but it certainly led to possibilities of early diagnosis. You have a 50-50 chance of inheriting it from an affected parent. So if you are negative you don't have to be clinically monitored all the time. It's had beneficial effects, plus it turns out to be a fascinating protein with very unusual biology and not in the cell membrane, in the nucleus. So I knew this is not an area of our own great expertise.

We would have these weekly data meetings. Collins made a terrific comment, we saw the protein and it didn't look like anything else in the database. It was not part of a gene family. Collins said, "At least it's not in the middle of a pathway that David Baltimore is studying," and that had a certain significance.

The upshot is two different groups, one at Stanford, one at Dana-Farber later managed to scoop us and find out what this gene really does. It's involved in chromatin regulation, so-called epigenetics. Steve Marx moved on and is semi-retired, and Sunita Agarwal continues intensively working on it, particularly on the pancreatic islet and is making some progress as are other labs around the world.

One other example, Bill Simonds was involved with a different group at the Genome Center. He had another one of these diseases we were seeing called hyperparathyroidism-jaw tumor syndrome, and they found that gene, another tumor suppressor gene. What you get from this is the richness of the research that can be done, the collaborations across different institutes in the intramural program, the Clinical Center as such a major resource. I think that's the present challenge, to take full advantage of the Clinical Center as a resource. I've consulted on that in a variety of ways over the years.

I want to fast forward to the spring of ‘99, and it becomes apparent that Harold Varmus, the then NIH Director is determined to appoint a new NIDDK Director. There is a search and I’m the only internal candidate, and at this point I’m thinking to myself I’ve been at the NIH a long time, and candidly, I had looked over the years at very few positions. Not out of spite, but I thought probably if I’m not selected this is a time to move on. I actually looked at a position at Genentech, which might have been interesting.

Harold calls me into his office. In June of ‘99, I was about to go off to an international meeting on the different inherited endocrine neoplasias, and Harold says, “Allen, because I think so much of you I want to let you know that I’m going to give the job to Person X, who was one of the other three choices.” I responded: “Harold, thank you very much.” Fast forward to September of that year when he called and said, “I would like you to take the position.” At this stage I was already heavily involved in the institute in an administrative capacity. I was under no illusion; this was going to be very different, a different kind of challenge, but I hoped that I would rise to that. So I accepted it with equanimity and took over a few months before Varmus left to go to head Memorial Sloan Kettering in NYC. I find it amusing that when I came to Einstein in the summer of ‘06 as Dean, Harold invited me to tour Memorial and have lunch, maybe making up for the short time we had spent together. He and I are friendly. We see each other at the New York Genome Center.

The challenges of taking over as NIDDK Director were really considerable. First, I’m not a diabetologist. I’m an endocrinologist in the calcium field. It isn’t just a question of a diabetologist. What about digestive diseases, what about kidney diseases, even some hematologic diseases, kidney, hematology, urology. Here too I want to credit some individuals who were so helpful to me.

There are three divisions that are very important: diabetes endocrine metabolism division, digestive disease nutrition division, and kidney, urology, hematology, the latter headed by Josie Briggs, outstanding nephrologist and was a pleasure and always interesting

working with her, stimulating, and she's gone on to different things. She was at Hughes for a period of time. She then was the head of the NCAAM, as it was at that time. She's now semi-retired, editing a Kidney Journal. In digestive disease and nutrition, it was Jay Hoofnagle, a major figure in clinical hepatology and clinical trials. As he stepped back, Steve James was recruited.

In diabetes and endocrine metabolism I'm going to be fairly graphic. I'll try to be measured in my words. There was a very unfortunate episode which really had an impact on the Institute and on that division and its division director, and it was one of the most important clinical trials, the DPP, Diabetes Prevention Program, prevention of Type 2 diabetes in roughly 3,400 individuals at high risk because they had impaired glucose tolerance but not frank diabetes. There had been multiple arms to that trial, a control arm (usual care), another arm was a lifestyle intensive intervention, another was Metformin. And another was the first of the thiazolidinedione drugs, Troglitazone, and that drug turned out to have idiosyncratic liver toxicity, leading to deaths and need for liver transplantation, and involved at least a couple of people in the trial arm.

It turns out the then division director was getting honoraria for speakers engagements from the company that made Troglitazone. A reporter, David Wilman from the *L.A. Times*, won the Pulitzer Prize for his reporting around what happened with this drug, primarily involving the FDA, the drug company, an academic investigator at UCSD, but also touching on our division director. This is one of the really difficult and challenging things about administration. I always say I don't relish wielding power for power's sake or saying you're fired, although it's not a question of personal confrontation, it's recognizing that there is hopefully some higher good, there's integrity and you have to take responsibility. And I said to this individual, "This is injurious to the Institute, it's injurious to you." He left. He went to the west coast to a glucose monitoring company.

I appointed an internal candidate, Judy Fradkin, who has just retired, just stepped down, really outstanding individual. I had great confidence that she would lead that very important division with its clinical trials and basic research. She herself, she'd come as a

clinical associate to what was the clinical endocrine branch working in thyroid. She had attended at Bethesda Naval when it was Bethesda Naval (now Walter Reed Medical Center across from NIH). I really respected her judgment and her wisdom, and that turned out to be well served.

These individuals, Barbara Merchant, who had been my administrative director in the intramural program, eventually became the executive officer, replacing Earl Laurence. I had Griff Rodgers (current Director of NIDDK) as my selection to be Deputy Director. That was a gratifying opportunity to work with him. I think my trust in him has been well vindicated, all of these individuals.

This period of time, from '99 to March of 2006, there are many important highlights. I have already alluded to the DPP. This was arguably one of the most important clinical trials. There were many important clinical trials in kidney, the ASK study and hemo, and many others in digestive disease and nutrition. It's a measure of progress that's made and there really is progress made. The HALT-C trial was a trial administered by Jay Hoofnagle, multiple centers around the country for treatment of hepatitis C with Ribavirin and Interferon gamma, both miserable drugs, both only partially effective in treating the disease, and look how far we've come, but that was the best we had to offer at that stage. Now you can cure this disease in a matter of weeks and it's arguably cost effective.

In the diabetes arena, the DPP was important for multiple reasons. In August of 2001, the Data Safety Monitoring Board made the determination the trial should be ended early and the rationale was that it turned out that the lifestyle intervention unequivocally was effective. Troglitazone had been stopped and those patients were just followed. There has been an ongoing outcome study of DPP. In fact, here is a book titled, "The Prevention Outcome Study: Celebrating 20 Years." There are Medicare approved prevention programs at Ys around the country and churches, and other places.

One can make a strong case that this is cost effective. Sadly, as I now know, in my new career stage, I'm taking on additional responsibility at things like the Research Foundation of the American Diabetes Association (ADA) and that was part of the reason I was just at the ADA meetings. Even though we've made tremendous progress in both Type 1 and Type 2 diabetes, a lot of it through work supported by the Institute, we still don't have a cure for Type 1, we still don't know what the actual environmental trigger is for Type 1, or triggers. In the case of Type 2, we're still fighting this extraordinary tide of the obesity epidemic, which then turns into a Type 2 epidemic, and the huge disparities involved. But the DPP has made a measureable difference and there are other examples there. That trial was ended early and then has led to the follow-ons that I described.

In the case of Type 1, when I came in as the Institute Director there had been special legislation outside of the NIH budget for $30 million of so-called Type 1 money that the Institute administered. We had the opportunity through the advocacy of the Juvenile Diabetes Research Foundation and the ADA to increase that amount, and we seized that, and it was up to $150 million a year. And that still survives to this day, and that gave us the opportunity with Judy and others in the community to all sorts of new initiatives that we couldn't do otherwise—TEDDY, for example, the environmental determinants of diabetes in the young.

If you think about it, we know that there are several genetic determinants of Type 1 diabetes. But monozygotic twins are still discordant in a significant percentage. We know that there's some environmental trigger or triggers, and if we could just know what that is, there might be a way of avoiding it or if it's a virus, vaccinating against it. That's what TEDDY is trying to do. They've made significant progress. There have just been reports, first from Australia, now from the U.S. There's a Rotavirus vaccine and it appears that kids who have been vaccinated with the Rotavirus vaccine have a much lower incidence of Type 1 diabetes. It's an enteric virus. These have long been suspected to be a possible trigger.

As far as a cure for Type 1, this brings me into another major theme of my period as the NIDDK Director. There are always things coming out of left field that you didn't seek or couldn't prepare for, and that's the human embryonic stem cell controversy. At one level it seems so old hat because we have to work of Yamanaka and others, induced pluripotent stem cells, etc. This was a huge issue at the time. Jamie Thompson at the University of Wisconsin first showed in human cells that they could derive from embryos, inner cell mass, the human embryonic pluripotent stem cells. It was said there were a hundred thousand frozen embryos from IVF, why not take advantage of that and do the research, which excited lots of people. This was one of the few examples where the huge bipartisan support for NIH, in Congress, which continues to this day as measured by the increases in the budget, notwithstanding anything the current administration proposes, which we can't take for granted and has been enormously helpful. This was one issue which split along the usual lines.

Little did people know, people seemed to be quite oblivious of the fact that even though federal funding for derivation of human embryonic stem cells lines was forbidden by the so-called Dickey-Wicker Amendment, Jay Dickey, Arkansas, Roger Wicker, Mississippi, then in the House, the latter now I think still in the Senate. Fetal tissue research was going on and was funded for Parkinson's, for other kinds of diseases, and it's only now that that's surfaced again as an issue. It's been banned in the intramural program and they stopped a contract at UCSF.

The way this transpired, Varmus was very supportive of funding human embryonic stem cell research, but he left to Memorial. You had Ruth Kirschstein as the Acting NIH Director, she had been Deputy, and you had this controversy, which was front page at the *New York Times*, day after day. There were two areas that were front and center, spinal cord injury and Parkinson's disease, hence NINDS. At the time, Gerry Fischbach was the Director of NINDS. And Type 1 diabetes for which NIDDK was responsible

At the NIH appropriation hearing in April of 2000, Senator Tom Harkin, poses questions planted by the JDRF among others, about how can we do pancreatic islet transplantation.

In Edmonton, Alberta, Canada they developed a new protocol for islet transplantation, which they get from cadaveric pancreases and it seemed to work. There would never be enough pancreases to be able to fulfill the need, hence the need to turn human embryonic stem cells into pancreatic islet beta cells. So I answered those questions and apparently the audition worked because I ended up testifying before Specter and Harkin, usually along with Fischbach on probably half a dozen occasions, sometimes with Christopher Reeve as a witness and others. I remember Senator Sam Brownback who was a senator then before his somewhat questionable period as Governor of Kansas. These are very challenging hearings because you're part of the administration Executive Branch, but you have people like Senator Specter telling you in no uncertain terms that human embryonic stem cells may be a "veritable fountain of youth."

This culminated in an appearance, August 2, 2001, in the Oval Office, one of a series of meetings that President George W Bush, 43, had for "advice" about what NIH should do about funding human embryonic stem cell research. It was me, the then-Head of the Office of Science Policy, Lana Skirboll, and a true stem cell researcher from the Intramural NINDS Program, Ron McKay, who was working on creating dopamine secreting cells for Parkinson's disease. I was there at the request of the JDRF to talk about the pancreatic islet situation.

In retrospect, this was clearly a charade. I believe that they had made their decision and they were using us partially as "cover." In addition to the President there was Karl Rove, and Andrew Card, the Chief of Staff. I felt gratified, when after showing my printed PowerPoints to the President, he said, "Now I can see why these JDRF folks are so cranked up about this." So I felt I had somehow gotten the message through. Then a voice over my shoulder, Karl Rove says, "What about porcine islets?" I'm a little taken aback and I'm going to talk about porcine endogenous retro viruses. Before I can say anything, the President turns to Rove and says, "Porcine, back in Texas, you would have said pig." What was amazing is that he knew what the porcine means. He's not as stupid as some people thought.

Most, shall I say, elected officials have the gift of making you feel that they're nice people, and he certainly did. He's modest, self-deprecating. When he got the NIH stem cell primer, he said, "This is perfect for me. I'm a C student." It was a 45-minute meeting, but in retrospect, as the meeting closes, he escorts us out and says to the Vice President with whom he is about to have lunch, "Dick, come and meet these nice folks from the NIH." These things are emblazoned in your mind. It's hard to forget. About a week later, August 9, at 9 p.m., from Crawford, Texas, he gives a speech saying that they will allow funding of the existing stem cell lines, but not of any new or derivation of any lines. Then he has a press conference on the porch of the ranch, apparently, on August 10th, and the reporters say, "Are there enough lines to do research on?" And he says, "Sure there are." He says, "The NIH walked into the Oval Office and looked me in the eye," so he anthropomorphized us, and says, "Yes there were." That continued apace in the various hearings.

So where are we now? Sad to say even with the California Institute for Regenerative Medicine, which was a $3 billion proposition 71 bond initiative, which was largely funded because of the concerns of NIH limitations on research and certainly funded major programs, including in industry on creating pancreatic islet beta cells, and there are clinical trials, it's still not ready for prime time. Doug Melton at Harvard University, Cambridge, not the medical school, and this is public knowledge, who has two kids with Type 1 diabetes, he's a premier developmental biologist, has devoted his lab to try to make beta cells, has spun off a company, Semma Therapeutics, which appears to be making progress. So there is progress, but not yet a cure.

Even if you can get authentic glucose responsive beta cells to transplant you will need to find some way to prevent the autoimmune process from destroying those, micro encapsulation, etc. The Edmonton Protocol which led to that first Senate hearing, sadly it turned out that after a few years those islets which we typically injected to embed in the liver, petered out for any number of reasons, including the immunosuppressive medications.

Just as an aside, I should come back to this. During the intramural director phase, I learned of two individuals at Bethesda Naval, as it was at that time, doing their payback to the military for their medical school training. Allan Kirk, a surgeon, scientist, MD-PhD, and David Harlan, a diabetologist, I was able to recruit those two individuals and establish a transplant branch at NIDDK. Varmus was pleased because we opened up a "mothballed" ward in the Clinical Center at the old Building 10, and that really went well for some time. Kirk was doing kidney transplants using immune tolerance protocols, the Holy Grail, so that you don't need immunosuppressant medication. He's gone on to be Chair of Surgery at Duke, currently. Harlan is currently at the Diabetes Center at UMass. During that period of time they did six islet transplants and they were successful in the short term. We had visiting congressional delegations. One of the women islet recipients was brought forward and to my consternation she started lifting her sweater. She was wearing a t-shirt with islets on it, saying, "Kiss my islets." It was interesting.

Back to the DK director phase. This period of time, toward the end of it, I felt for a variety of reasons that I should move on. It was going to be 33 years in '06 at the NIH. There was a peculiar reason, that same David Wilman guy from the *L.A. Times*, he reemerged to do an exposé in 2003, thereabouts, when Elias Zerhouni is the NIH director and gets blindsided by this, about conflicts of interest in the intramural program. Some were atrocious examples in the Mental Health Institute, one or two others. I'm not saying we're holier than thou, nothing involving NIDDK at all. But you would from time to time encounter people, and this is counter-productive, who if you work for the NIH, from the federal government think you're a federal bureaucrat. What's wrong with being a federal bureaucrat? Look what's happening at the Department of Agriculture now? Senator Specter, at the end of a hearing he would always, say, "Rush back to your labs at NIH and continue the important work you're doing." He had real respect. The upshot is on top of it, accused of being venal and these things, that didn't sit well with me.

Be it as it may, I did start looking at some positions. One dumb maneuver was to look at the Presidency of the University of Medicine and Dentistry in New Jersey, which I did make the mistake of going for a second visit. There was a *Newark Star Ledger* piece,

which fortunately didn't mention my name, but said the choice came down to two people, some guy who they eventually picked who was in New Jersey or the Director of NIDDK. The place was rife with corruption, top to bottom. Several people were indicted, imprisoned for Medicare fraud, etc. Fortunately, they've completely restructured that place, made it part of Rutgers, as they should do.

Long story short, the position at Einstein came open and I was encouraged by several people to look at that position, one of whom was an alumnus of our liver disease section, Allan Wolkoff, who's still at Einstein. Another is a fellow named Rossetti, who was the head of the Diabetes Center, who I would encounter at diabetes meetings. There was the nostalgia of having worked in the Einstein lab. Sentimentality only goes so far. The campus is in the Bronx. It's separate from the rest of the university. Outstanding in terms of research within just a few years after its founding in '55.We just celebrated another prize for a long time Einstein faculty member, Susan Horowitz, who was the person responsible largely for bringing Taxol as a chemotherapeutic based on her basic studies of mechanism of action, for breast and ovarian cancer. So phenomenal science there, but clearly it had fallen down over the years. My predecessor was one of the giant founders of neuroscience, Dom Purpura had been the Dean for 22 years, arguably too long for anyone, but he had done remarkable things. I saw an opportunity and did seize that opportunity.

You're pretty much a lame duck at NIH once you declare you're applying for an extramural position. So by March of '06, even though I didn't take over officially until June 1st, I took the shuttle up on a Sunday night and my wife was still at the World Bank. For the first four months I lived in our student housing on campus. We have three high rises. In a way it's a manipulative thing to do. It has a certain cosmetic appearance, but why should we spend extra money for a hotel room or an apartment, and this was right on campus.

At this point I'm going to defer to you and see what else needs to be said. Let me just say that was itself a very challenging period. The financial crisis turned out to have a huge

impact on Einstein in particular and other factors that one couldn't imagine. At the same time, extremely rewarding and I initially intended that this might be a ten-year thing. By then I'd be the ripe age of 70. But for a variety of reasons, we, by the fall of 2015, completely reconfigured the medical school so that the fiscal and legal obligation for the school went from Yeshiva University to Montefiore Health System, which is not only our affiliate, but our major affiliate. I fostered from the get-go a much stronger relationship with them realizing that was going to be central to our success and that has culminated in May 24th, the commencement, for the first time, we granted our own degrees. I managed to get with a lot of help through all the various accreditation, things necessary for us to get independent degree granting.

We are structurally a medical school like Sinai, that is a medical school not part of a university, but within a health system, and that's turned out to be, hopefully will be successful in the years to come, and my successor who took over in July of '18. So in '17, I said I want a year and then I'll step down. Gordon Tomaselli is an Einstein alumnus, Class of '82, was the Chief of the Cardiology Division at Hopkins, outstanding individual. I have every reason to believe he'll be successful. I wish him every success. What I've done is stepped into a part time position on the Einstein faculty with an office way away from the Dean's floor, where I can serve as a mentor for MD-PhD students and still teach in some of our courses, which I had done to a degree. I've never been the clinician, but I do come to some of our endocrine clinics in Montefiore and even Jacobi. Then I can spend part of my time at the NIH as a special volunteer, and then other pro bono things like the American Diabetes Association. So that's the story.

KD: What did you learn at NIH that you were able to take to Albert Einstein? What have you developed from your experience at NIDDK as an asset?

AS: I'm guilty on multiple occasions, both in terms of swimming, to the extent that I was an inveterate lap swimmer for a period of time, playing tennis. I don't take lessons. I have atrocious form and just do it to the best of my ability, which means you may be successful to a degree. Eitan Friedman, whom I mentioned in the study in the New

England Journal and MEN-1, was an Olympic caliber swimmer in Israel, and tried once to show me what to do. I said, "Eitan, I'm just trying to get exercise." Then I got to meet Gary Hall, Jr., who turned out to have Type 1 diabetes at the age of 25, but nonetheless managed to win the 50-meter sprint in Sydney, in the Olympics. I met him at an ADA dinner, and I remember I said to him, "I'm an addicted lap swimmer, but I don't do flip turns." And he says, "Flip turns are over-rated." Only then did I realize in the 50-meter sprint you don't do any turn, you just go.

I've arguably made the mistake of not reading managementese books. Barbara Merchant did buy me a book once, *Who Moved My Cheese?* So out of respect to her, I read it. I've relied first on my own personal sense of integrity. I am a terrible liar. On the other hand, I think I can be persuasive, but only if I have true conviction in what I'm saying. I think Griff told me this, Billy Tauzin, who was a representative from Louisiana and then became head of the Pharma Association; he talked about how you can be successful in Louisiana politics. It's all about sincerity. If you can fake that you've got it made. I can't.

For me, certain intrinsic things, a sense of mission, and I'll come back now in a hopefully not maudlin way, to my background. You had a sense that if your parents are alive and they're here, you have some reasons to be dedicated. I always get somewhat emotional at this part because you just can't take that for granted. So hopefully you can contribute and be useful in some way. At the same time trying to be a judge of other individuals who are relying on other people, best and brightest, that is managementese, surrounding yourself with them, giving them responsibility but holding them accountable.

Running NIDDK as the Director, I didn't sufficiently go into this. I focused on the trials, I focused on some staff, I focused on embryonic stem cells, but this was an enormous learning experience for me. First of all, it went from intensively reading literature in a very, very focused area to being spread over this huge landscape, diabetes, digestive, kidney, urology, hematology, etc., and I took that very seriously. You can't be the master of all those areas. Learning about epidemiology and public health, being the Chair of something bureaucratic sounding, the Diabetes Mellitus Interagency Coordinating

Committee, the various federal agencies, private sector, Kaiser Health, VA, etc. that were involved there. The Diabetes Education Program, Josie had us start a National Kidney Disease Education program. It was a huge growth experience for me and that was very broadening. That's one point.

Another point, and this is going to seem very strange, Einstein, before our being part of Montefiore, and the significance there is if you're a research intensive medical school, that's always a money losing proposition. Bob Alpern was the Dean at UT Southwestern then just recently stepped down as the Dean at Yale, a distinguished nephrologist, he was on my National Advisory Council. He would complain in open session, "For every dollar you, NIH, give me, it costs me...,"despite the indirects. I was very glib, "So don't take it." That's still a right answer because if you're a research intensive medical school that's your mission. So how do you make up those deficits? Cross coverage from clinical revenue. You need to be part of a clinical enterprise and if you're fortunate, philanthropy. Medical school tuition, that doesn't do it. That sits on its own bottom. It typically doesn't lose money, but it sits on its own bottom.

As far as philanthropy is concerned, that was crucial for Einstein. I had done my due diligence. We had a significant endowment before the fiscal meltdown and that gives you from the endowment payout, in our case, arguably with a billion at a five percent level. You can do the math. The upshot is you need heavy duty philanthropy. As the NIDDK Director, one of the things that I was doing was giving talks at various places like Mary Tyler Moore's apartment when she lived on 5th Avenue, helped her promote the stem cell theme. The home of Edsel Ford in Michigan, because of the ADA, the Modells, who were involved in the Crohn's Colitis Foundation of "Gotta Go to Mo's." So here you are interacting with these folks who are of substantial means and you're there as the NIDDK Director there being part of advocacy groups. That gave me the sense, and this comes back to the "sincerity" piece that I would be able to raise money and interact with these folks since if I have the conviction of what I'm asking for.

We were able over a ten-year period, and there were definite hiccups here having to do with the fiscal meltdown, to raise about $500 million and some very substantial gifts from some mega-wealthy donors. Others, we had a faculty member at Einstein who was the most modest individual, taught the anatomy course, lived in the Bronx, had no family, and sadly when he died, I remember visiting him in the hospice setting, he left $8 million for scholarships to the medical students. That was, on the one hand, in some ways, guided by some experience I had as an institute director, but taking it to a different level and dealing with a board. Here dealing with an actual Advisory Council, it's a kind of board that you're accountable. The Board at Einstein is a different kind of board, made up of often super wealthy individuals, mostly men, but not exclusively.

The chairperson of our board for seven years in my tenure was a woman named Ruth Gottesman, a doctorate from Columbia Teacher's College, one of the most remarkable individuals. I was fortunate to have lunch with her this past Saturday. We're still quite friendly. She was actually on the Einstein faculty with founding the Center for Adult Literacy as part of one of the programs that we have. She's an individual of exceptional wealth, but an exceptionally kind and motivated individual. I took a leaf out of her book. She would take the express bus from the Upper East Side to the Bronx. I was always embarrassed when I came as Dean, having my own car and driver. I soon realized that was necessary. I wasn't used to that. Richard Hodes and I would take the Metro down to the Senate hearings. Now I take the express bus most of the time, even though I have parking space.

There was a lot in this experience broadening my overall, and now when you're a Dean it's things like HIV, which I wasn't responsible for, suddenly responsible for everything. Very necessarily superficial, but I think it was very formative, very helpful.

KD: More learning. Well thank you. I've learned a lot. This has been a great experience.

AS: Thank you for your time and attention and thank you all for helping.