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JESSE ROTH, MD

Interview conducted by
Michael Chappelle
June 4, 2011

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INTRODUCTION

Jesse Roth, MD, Professor of Medicine, Albert Einstein College of Medicine, is best known for his pioneering work on cell surface receptors. The emergence of cell surface receptors from total obscurity to total equality with hormones and other cell signaling ligands is in large measure a result of studies he conducted at the National Institutes of Health (NIH) during the 1960s and 1970s. This success of Dr. Roth and his colleagues required conceptual as well as technological innovations that were then adapted widely by investigators worldwide. Descriptions of the first cell G-linked receptor, the first kinase-linked receptor, and the first of the cytokine JAK-STAT linked receptors were part of this legacy, as were some of the very first descriptions of diseases linked to receptors. That receptor concentrations and affinities are not static but highly regulated under a wide range of conditions in vivo with the ligand itself included as a regulator, was another key contribution of Dr. Roth and his group. Today, Dr. Roth finds great satisfaction in the careers of the numerous fellows he has trained, many of whom have become leaders in medical research throughout the world.

BIOGRAPHICAL SKETCH

Dr. Jesse Roth was born and raised in New York City, receiving his BA from Columbia and MD from the Albert Einstein College of Medicine in its first graduating class in 1959. As an intern and resident in internal medicine at Barnes Hospital, Washington University in St. Louis (1959-1961), he had close contact with Dave Kipnis, Lillian Recant, Seymour Reichlin, and Bill Daughaday. Dr. Roth sojourned in New York (1961-1963) as an American Diabetes Association research fellow at the Bronx Veterans Hospital, joining co-fellow Shimon Glick under Solomon Berson and Nobel Laureate Rosalyn Yalow, the two co-inventors of radioimmunoassay. The quartet's work on the immunoassay for human growth hormone was among the earliest immunoassays ever created. In 1963, Dr. Roth began a twenty-eight-year career at the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) as a clinical associate with J. Edward Rall and Jacob Robbins and collaborator with Ira Pastan. It was the pioneering work he conducted with Dr. Pastan in this period that opened up the field of cell surface receptors. From 1991 to 1998, Dr. Roth served at The Johns Hopkins University School of Medicine as the Raymond and Anna Lublin Professor of Medicine, Director of the Division of Geriatric Medicine and Gerontology and Head of the Johns Hopkins Center on Aging, where he studied endocrine disorders that relate to aging and mentored young investigators, especially in the genetic basis of obesity and type 2 diabetes. Dr. Roth moved back to New York where he served as President of The Picower Institute for Medical Research from 1998 to 1999. Since 2000, he has been Professor of Medicine at the Albert Einstein College of Medicine. Dr. Roth's more than four hundred publications include landmark studies of acromegaly; pioneer work on proinsulin in blood and the heterogeneity of circulating hormones; and solving the long standing riddle of hypoglycemia associated with non-islet cell tumors--demonstrating the central role of IGF-2-related peptides. Dr. Roth's achievements have been recognized by numerous prizes and awards including: the Banting Medal and the Eli Lilly Award from the American Diabetes Association; and the Koch Award, Robert H. Williams Distinguished Leadership Award, and the Ernst Oppenheimer Award from The Endocrine Society. Dr. Roth's accomplishments as both mentor and teacher were specifically recognized by the American Diabetes Association's Albert Renold Award.

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I. DISCOVERING CELL SURFACE RECEPTORS

Chappelle: Dr. Roth, as you look back over your career, what do you consider its most important aspects?

Roth: The thing that I feel is the most important--and I think that we're known for--are receptors. And it's hard to imagine now that somebody had to discover receptors, but we really did. And in the olden days--nowadays, if you say I discovered a new hormone, the first question that our graduate students turn to is(??), What's the receptor. So given that hormone and receptors are such a *pair*, it's hard to image that not so long ago there were no receptors. And you say, Well, what were they thinking? They used to think that the hormones went right into the cell. If you put a cell--or a tissue--in with hormone, some enzymes would get turned on or turned off. So they assumed that the hormones were like vitamins; they would go into the cell; they would find the enzymes, and then the combination of the hormone with the enzyme would do what it's supposed to do. So we were kind of lucky. We were a little unhappy with that. My buddy and I, Ira Pastan--it was 1963--we had just gotten to the NIH, and our boss there [Ed Rall]--we had both been doing some nice work on other things--and my boss said to me, he said, "You know Jesse, you could keep doing that; that's a good way to go, but you know this is a special time, special place, why don't you think of the *best* thing you could *possibly* work on." And so that's when we started to work on the receptors. And the question we were asking is, Well, let's say insulin gets to a muscle cell, and the muscle cell starts to take up glucose, how does the muscle cell know that insulin is there? The muscle is being bathed with ten million different molecules, and only one of them is insulin, how does it know the insulin is there? And that was what got us to say, There must be something there that's really recognizing insulin from everything else, and we thought, Well, that must be--going to be the receptor. Initially, we thought it might be inside the cell, but, in fact, we started to play around with it, and it's clear that it was out on the cell surface. That was a surprise to everybody. Everybody had assumed that the hormones just went right in, and once we were able to convince ourselves--when you do research, the first thing you have to do is convince yourself that you are right, and then you have to figure out how you can convince the world that you are right. We started in 1963, by 1965 or 1966, we *knew* we were right, but it took us another three or four years to get the system to work well, so that we could prove it to the world. We were also very lucky that once we did, they accepted it. So by 1969 or 1970, we could actually label hormones with radioactivity; we could get preparations of receptors from cells; we could put the two of them together and show that they really were receptors. We did it first with ACTH--adrenocorticotrophic hormone--on adrenal cells. We did that one because, again, we're guessing that this was the simplest system to work with. In those days, you could hardly ever get any pure hormones, and that's why we had to pick systems where you could get them. Nowadays, every hormone--you get as

much as you want if you have, you know, a little bit of money. In those days they were hard to find: you could get insulin--that was available--and ACTH was one of the others. Also, they didn't know the structures of a lot of the hormones. So we were lucky. We took ACTH because you could buy a lot of it relatively cheap, and you could--you knew if you put radioactive iodine onto the molecule, you knew exactly where it was going to go, and you knew how to purify it. So we knew a lot about ACTH. And then we picked the adrenal because most hormones, once you broke the cells, you didn't know what happened. But [Earl] Sutherland--a few years before--had discovered that a lot of the hormones, when you put them in with cells, would activate adenylate cyclase. So with the adrenal, you could break the cell, get cell membranes that still had adenylate cyclase. So when you put in ACTH, it would turn on the adenylate cyclase--you knew there had to be the receptor there. And it was that combination that allowed us to really do the first one. Once we did that one, then the rest were a cakewalk. We did the insulin receptor almost immediately after that. Our neighbors next door, upstairs, all got excited, and they did their own pet hormones. So within a few years *everybody* was doing receptors to hormones, using basically the concept and the techniques that we showed for ACTH and then insulin.

Chappelle: When you say cell *surface* receptors, how do they work?

Roth: Okay. Now the cell surface receptors, they're proteins; they are manufactured in the cell, and then they're brought to the cell surface, and they sit there waiting--a recognition site that sits out there. Then when the hormone binds to the receptor, some activity in the receptor is activated. In the case of adenylate cyclase--some of them have adenylate cyclase attached to them, so when hormone binds to the receptor, adenylate cyclase turns on: that's what happened with the ACTH receptor. Indications of the insulin receptor: there are tyrosine kinases--these are proteins that phosphorylate other proteins on tyrosine--so when insulin binds to that receptor, the tyrosine kinase gets turned on. Now, *that* wasn't known for another ten years after that, but at least we could show that the binding of insulin to the insulin receptor fulfilled all the expectations you had of how an insulin should work, and then we had that.

Chappelle: What were the scientific ramifications of all this?

Roth: It turned out they were much more than we ever dreamed they would be. First of all, there were diseases that we could find that were associated with disorders in the receptors. We found that, for example, some patients who could hardly respond to insulin at all, and you have to give them massive doses of insulin to control their sugars, and it turned out that one group of them had a congenital defect--they were born with insulin receptors that were imperfect. There was another group of them that had antibodies against the receptor, and antibodies were binding to the receptor and interfering with the binding of the insulin. We got six patients in a very quick time, three of them with antibodies, three of

them with congenital defects. In the clinics--where they would work--the doctors were just mystified: why they were unable to respond to insulin? We were able to show [why this was so]. And once we did that, other people found a lot of disorders of receptors, Nowadays, if you discover a receptor, there is no reason you won't expect to find a receptor that's overactive or under-active, or [that there are] diseases associated with it. The other thing that we found that was, again, retrospectively not a surprise, but prospectively a surprise: the receptors are *regulated* to an enormous amount. Everybody knows that hormones go up and go down as the biological system needs it, but a hormone will go up tenfold, twenty-fold, but the receptors can go up and down one-hundred fold, one-thousand-fold in number and make all the difference in how the system works. I remember what happened--even my own lab, it was tough convincing the guys that we were right. We did many more experiments than we ordinarily had to do because we could convince ourselves early, but we had to convince our--[if] we couldn't convince our buddies; how are we going to convince the world? So that was a very big surprise, again, that regulators were so highly receptive. The affinity of the receptor changes, but much more so, the *number* of receptors--it could be one-thousand-fold, ten-thousand-fold--up and down--makes all the difference in how the system works.

Chappelle: What about--excuse me go ahead.

Roth: One of the other surprises that, again, caught us off guard, and I can remember the minute we thought, God! You know what that means! Everybody assumed that the hormone binds to the receptor--by this time, that was the [dogma]--and that the hormone [and] receptor together would turn on whatever [it] turned on. But it turns out that's not the case. The hormone binds to the receptor, and the receptor is *activated* and doesn't need the hormone anymore. So it's really the receptor that has the full activity of what we called--so when I say, "This hormone has that action"--it *doesn't*. The action the hormone has is to turn on the receptor; it's the receptor that has the action.

Chappelle: But that's still not presented that way.

Roth: It's still not presented that way, but if you ask people, they really all know that. I remember when we first published it: insulin and its receptor, Is the receptor more important than the hormone? And I started to get hate mail from the endocrinologists because they thought I was trying to undermine the whole Endocrine Society because I'm downgrading the hormones. But what it really means actually is that you could turn on that receptor with things other than the hormone. Because the receptor is big, there's a lot of room on it. So, for example, there are antibodies that bind to the receptor and turn on the receptor without the hormone being there. In fact, shortly after we did our early pioneer work on the receptor, the guys who worked in hyperthyroidism realized that was the answer to a very long-standing problem. One of the most common forms of *hyperthyroidism* is called Graves' disease. In Graves' disease the

thyroid gland is big and overactive and pours out a lot of thyroxine and the patients are hyperthyroid from too much thyroid hormone. It turns out there are antibodies against the receptor for TSH. So it's not too much TSH that's driving the thyroid, in fact the TSH levels are very low, so the normal stimulator is out of the picture. It's these antibodies binding to the receptor, and then the receptor has all the information, gets turned on, and is driving the over-activity. And so that came along just a few years after we did our work and kind of extended the idea that really the activity is in the receptor, not in the hormone.

On mentoring

Chappelle: Besides your receptor work, what other aspect of your career means a lot to you--when you look back on it?

Roth: One of the things that came out of the receptor work that was nice is we became a "hot" lab. So we got the very best of young people from around the world coming to work with us, and so we had an opportunity to mentor a very large number of good young people starting out early in their careers. It was a hot topic and each of them took a piece of it and developed it and then went on to become very successful on their own. There were guys all over the United States, all over North America, all over Europe, all over the far East, who came out of this cooking pot--this chowder that I was cooking on our stove--and then went off to do great things. Now every place I go--there is a guy getting an award tomorrow, Derek LeRoith, he came--a guy got a big medal here a few years ago. So the young people that came to work with us then have grown up and become top guys, and I must confess that at my age and stage--some of the papers that we did, we were very proud of before--we still are--but I think we are even more proud of the people that have gone on to become outstanding people on their own. In a sense, it is funny because as a teacher you start out hoping that they'll learn, and learn whatever you're teaching them, and that maybe--if you're lucky--they'll become your equal. But in the sense, you don't really teach them specifics, you more teach them an exciting way to approach things. And they then take off on their own, and before you know it, you're learning more from them than you taught them, and pretty soon they are better than you are. And you're not hurt, insulted--it's nothing. You're just proud and thrilled. So when you get up to see them do it, you just say, Wow! So I would say that one of the great joys in this field is that it's such a friendly field, so mentorially committed. And then to watch your offspring--there is another guy who has gotten an award who is the offspring of one of *my* offspring. So they are grandchildren--effectively--intellectual grandchildren, intellectual great-grandchildren in this tree that we're all very pleased with--and like each other and get along well.

II. FAMILY BACKGROUND AND EARLY YEARS

Chappelle: Could I ask you a little bit about your family background, starting with your grandparents?

Roth: Sure. Grandparents: My four grandparents were born in Europe, Eastern Europe. They came to the States like millions of others; they started a life just before--just after World War I. They were energetic and hardworking. None of them went to college, not my grandparents, not my parents. My dad was unlucky. His father died when he was twelve. He was the oldest, so he went out to work at age twelve to support the family. In those days, the social net was very unpredictable. He was lucky there was greater family who helped out as he went along, but he basically was the family supporter from age twelve to age eighty--whatever it is. I was very lucky that my parents were born with optimism. They got married in 1932 at the very bottom of the Great Depression. My sister was born thirteen months later. They not only had one kid, they had me sixteen months later. They were optimistic people. That was one of the nice things that everywhere we--business things went up and down, but we were kind of buffered from it, so we didn't feel the ups and downs. They were very supportive of us going to school. My father actually had even greater difficulty than most because the family was orthodox Jewish and wouldn't work on Saturday. In those days, everybody worked six days a week. So to get a job--he said, he'd get a new job every Monday, and he would lose the job the following Monday because he wouldn't show up on Saturday. [laughs] He finally found an industry which was--they were wholesalers that sold to mom and pop stores. The mom and pop stores were open on Saturday, closed on Sunday, and their big day was to sell to the mom and pop stores on Sunday. So actually that was an industry that he could be Sabbath observant. So he was amazing [in] that he was able to keep the family together. My parents really liked each other. My older sister and younger brother, we like each other, so we were very lucky. All the things that are destructive of families and stuff, we were cushioned from. We didn't have to call the weather bureau to find out whose mood was where. Everybody stayed around home; it was a very nurturing and very positive environment.

Chappelle: What kind of education did you have?

Roth: My opening education was actually a very good one. I went to a Jewish day school, in the days when these were pioneered. So we spent all morning from eight to twelve doing bible and Talmud and advanced studies; then we'd do the English studies from one to five. So we used to go to school five, actually, almost seven days--part of that time I was going seven days a week, and you get pretty--I was having a good time; I wasn't feeling oppressed. The other guys felt the same way, and we were just having a good time. Then I went to a public high school from there. But we were lucky: both in elementary school and in high school, we had the gifts of the deprivations of the teachers. The

women could almost do nothing else but teach or be librarians or things like that in those days. So we had *very* talented people as teachers. Also, the restrictions against Italians [and] Jews kept them out of a lot of other jobs so a lot of them became teachers--people who [in] the next generation would become “chairman of institutes” and things like that. So these were a bunch of very devoted, very talented teachers. So I look back on all the teachers I had through grade school and high school--and they saw us as the “future,” and they really treated us, again, not quite, but almost like Pharaoh’s children. I mean they were very devoted teachers.

Columbia University (1951-1955)

Chappelle: Why did you choose to attend Columbia?

Roth: You really want to know the true story? I’ll tell you.

Chappelle: Yes.

Roth: Okay. I was all set to go to University of Pennsylvania. The Wharton School was a business school, and since all of our families were in business, I was kind of thinking, well, maybe I should [go there]. But New York State in those days used to give out scholarships called New York State Scholarships. You sat for an exam--an all-day exam--and if you got a good score on the exam, they gave you fourteen-hundred dollars a year towards tuition, which now seems like a pittance, but that was more than half of tuitions in those days. But you had to use it in a school in New York. So when that came through, I got an acceptance from Columbia and Cornell. Cornell was way upstate New York. My parents were afraid to send me so far away, so I wound up going to Columbia because there was a nice scholarship and it was close to home. But that was just fabulous for me; Columbia was really an eye-opener. It really was. Columbia, unlike a lot of schools, had very small classes, very intimate relations with the faculty. So we learned literature and music and art and science, and we just were--we couldn’t shovel it in fast enough. I still look back on those days with--actually, it was actually interesting. The public high school I went to was a very ordinary high school, and a large number of the kids were not going anywhere. We were very smart--my group that had really [the top ranking]--so in high school, we were the [upper percentile]. I got to Columbia, and they were kicking sand in my face--the kids that had gone to private school, the kids that had gone to Stuyvesant or Bronx Science, we were just nowhere anyway like those guys. So we really had--that first year was *a* struggle. But by the second year, we were picking up speed, and by the fourth year we were really doing it. But that transition from being the smartest kids in the class to being the weakest was a shock.

III. ALBERT EINSTEIN COLLEGE OF MEDICINE (1955-1959)

Chappelle: What drew you to medicine?

Roth: Medicine was always fascinating to me, and I was actually lucky. Among my relatives, I had a couple of cousins, who were younger than me--[on] my mother[']s side of the family]--and they went into medicine. They were very instrumental in warming me to how exciting it was. I even remember that one of the doctors--he had a full skeleton in his room when he was studying anatomy. I remember as a nine or ten-year old going in there and just couldn't get over the skull and the bones and the excitement of it. We always did science. Science was very exciting in those days, and I remember having scientific experiments going on, even as a kid in the basement. We were always putting dry ice into water, or we were putting baking soda with vinegar and making minor explosions. You know, the kinds of things that kids would do. The fascination with science in those days was total. So I think the fascination of science, the influence of relatives who were physicians and liked it, was the stimulus.

Chappelle: How about Albert Einstein College of Medicine, how did you end up there?

Roth: That's a good question. I was very lucky. And that's the other thing--I didn't say, but I'll say it later--is [that] my life has been very, very, very lucky, and even things that look like they weren't so good turned out to be very lucky. My grades were good, but not outstanding. In those days, the prejudices of medical schools against Jews, Italians, African-Americans, women--very, very strong. And if you wanted to go into medicine you had to be very, very good. My pre-med advisor at Columbia was very good to me and really helped me a lot. But I didn't get into any of the great medical schools. I got into--I don't want to call them second-line schools, but schools that nobody would--so I had a handful of acceptances, but none of the schools were out of this world. They were good, reputable, nearby. Albert Einstein was just starting to begin, and my cousin--one of the physicians--was very excited about this school because he saw all the great faculty they were recruiting. He was the one that convinced me that there was such a spectacular faculty, "Go." Had I had a really hotshot school in my hand as an acceptance, I probably wouldn't have gone. But given that the other schools were--you know, "What the hell." So we really took a chance. My parents encouraged me also to take the risk, and it turned out to be a very important break because the faculty was very young, exciting, and they devoted such attention to us and they so stimulated us. We did all kinds of experiments with them, just all kinds of things that never would have happened anymore in a--I'm sure doesn't even happen at Einstein anymore because now it's a regular school. [When] it was a brand new school, it was just one of those extraordinary experiences. And it's funny, too, Hofstra--the medical center I'm at now is now partnered with Hofstra [and is] opening up a new medical school. I was telling them, I said, "You know I had such a fabulous time." I

talked to another guy who was in a first class of another medical school; he had that same experience. A third guy--so a guy from University of Texas Southwestern--outstanding place, now--he was there in the first [class]. This guy of the medical college in Hershey--same thing--he was there first. Being in the first class of a medical school has its--it makes you nervous, and it's not so neat. Things are a little bit not exactly tucked in, but the enthusiasm and energy of the faculty and of the students, the esprit is just a--covers all the little shortcomings. I've remained very close friends with these people I graduated with over fifty years ago. It was like being a buddy in wartime. It's a kinship: same with the faculty.

IV. BARNES HOSPITAL, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE: INTERNSHIP AND RESIDENCY (1959-1961)

Chappelle: After you finished up at Albert Einstein, how did you envision your career?

Roth: We were lucky. In those days research had a very high profile, highly respected by everybody. So to go into research, or think of doing research, was not such a big barrier. Nowadays, the students tend to shy away from research, and there are only a small number that then catch the bug. For us, there were many more small research opportunities, but the general sense of research in medicine in those days was a very high priority and very much revered. Academic medicine was the same way; in the sense of going into academic medicine was a career that people favored. I think the young people feel much less attracted to it--for whatever reasons, it's not important. So I was--if I wanted to go into academic medicine or going into research, I wasn't an exception. We were also very lucky that from Einstein we got excellent guidance. When I was trying to pick an internship and a residency, they sat us down and asked us which ones--where we would go--helped us find the proper places to go. They used their influence and connections to try and match us to the right places. We felt like we were *placed*; we weren't just applying. And I got into a fabulous--one of the best ones in the country at Washington University--Barnes. My roommate wanted to go to Yale; he went to the Yale one. So again, a new faculty, they felt their fulfillment had to be in getting us placed in all the good places, and they did it.

Chappelle: You said you went to Barnes?

Roth: Yes.

Chappelle: Why is that?

Roth: Again, I wouldn't have known to go to there. But, in fact, in those days, [Barnes] was probably one of the four or five best places in the country. You can't image--in the old days, there was no medicine west of the--I don't mean no medicine--but the outstanding academic medicine stopped at the

Mississippi. The California schools were going to regional schools; University of Washington was just getting started. San Diego didn't exist; Denver didn't exist. So this place--I picked it because when I went to visit it, it was clearly--can you image it was an internship class of ten people? The faculty were outstanding. You know it was a great break. They had fabulous endocrinologists there. First of all, there was a Nobel Laureate pair there called Carl Cori and Gerty Cori, and they attracted fabulous people. Dave Kipnis was one of the young endocrinologists, he had just come out of Cori's lab--Bill Daughaday--these people are outstanding endocrinologists in the annals of endocrinology, and they were among the faculty. And in those days when you were taking care of patients, the consultants would come around every day, and it wasn't a big army of consultants, it was a small group. So you met all these people all the time.

Chappelle: Is that why you went there, for those people?

Roth: I realized that they had excellent endocrinology, but in fact that helped establish endocrinology in my ethos because of such a strong teaching program, and you saw these people all the time. Lillian Recant was another endocrinologist there--a guy by the name of Reese(??) So the department was small in those days, and yet they had four--actually there was another one named Frances Alexander--five first-rate endocrinologists in the department was unthinkable in those days. That had a big impact on me.

Chappelle: You were just getting into endocrinology then?

Roth: Yes.

Chappelle: What was the big picture in terms of hormone action at *that* time?

Roth: In those days, the idea was, absolutely, that hormones got into cells, would find any number of enzymes inside the cell to pair with, and then they would basically just help the enzyme to do what the enzyme was destined to do. It was a way to switch on the enzymes. And that was the whole--and, in fact, we went to an Endocrine [Society] meeting, in fact I went back and looked at it in the library at the Sawin Library and got out some of the old programs. You could find those papers. When I went to my first Endocrine [Society] meeting in the early sixties, hormones turning on enzymes was the major theme that went through the meeting. So hormone action was really in its infancy in those days.

Chappelle: Now when you were learning about hormone action, were you questioning it at that time?

Roth: No, we weren't thinking that then. In fact, in those days you couldn't measure any of the hormones. You could measure an approximation of thyroid

hormone, a less good approximation of steroid hormone, and none of the other hormones could you measure. So you had to make a diagnosis of too much or too little, or are we giving the right amount, just on the basis of clinical medicine. You had to--it was a *guess*. And that was where my next mentors came along, [Solomon] Berson and [Rosalyn] Yalow. They were the ones who invented radioimmunoassay and that was the major method for measuring hormones. That was nineteen--so I was an intern from '59 to '61; they did their grand paper in 1960, and I went there in '61.

**V. WITH BERSON AND YALOW AT THE BRONX VA HOSPITAL
(1961-1963)**

Chappelle: Now how did you get there?

Roth: By good luck: I had bad luck/good luck. I mentioned before that my roommate from medical school went to Yale as an intern. He stayed on in endocrinology at Yale. There was one other slot open, and they tentatively said, "Okay, Jesse, you could come, but we are not going to be sure until we see if the other guys who are here might want to go." At the last minute, a Yale guy wanted to stay, and they called me up and said, "Jesse, we're terribly sorry, we can't take you." So here it was November; I need a job in July, and they just bumped me. My professor of medicine at Einstein [Irving London] happened to come to St. Louis to give a talk at Barnes, and he says, "Where are you going next year, Jesse?" [I said,] "I don't know." [He said,] "Well, it's a little late." [laughs] He said, "Meet me at the Chase Hotel after the talk." I met him at the Chase Hotel; that was the fancy hotel in St. Louis; it was like you go to the Waldorf. In fact, it is so funny at how naïve and young we were. He ordered a drink and he *signed* the bill. I never saw anybody *sign* the check. [laughs] I told him I was interested in endocrinology and ___(??) the thyroid.

Chappelle: Thyroid did you say?

Roth: Thyroid. I was very interested in the thyroid. In medical school, I had done a project on the thyroid and did a couple of other things on the thyroid. And there was a guy in the Bronx named Berson--worked with Yalow--and they did thyroid work, and I knew their thyroid papers. So he said, "You know, I know Berson, I'll give him [a call]." He said, "Write to Berson and tell him you want to come." So I wrote to Berson saying I'd like to come. And he wrote me back quickly a letter, "Well, I'm not sure we can." He gave me all kinds of excuses, clearly hesitating. Then a couple of days later, before I had a chance to answer all these long questions [that Berson had asked. Berson contacted me again, saying], "I just got a letter from Dr. London; he says that I should take you. You're on." So again, I was sent by person to person. And it was just at that time they [Berson and Yalow] were leaving the thyroid field going into diabetes. They had just developed a radioimmunoassay for insulin, and all the thyroid work, which they had done--which was very well respected, but not

revolutionary--was shifted aside. So I matched with them because of the thyroid, but we never really did any of the thyroid work.

Chappelle: Could you say a little bit about the stature of Berson and Yalow and the ethos of their lab?

Roth: It was clear to the cognoscenti that that 1960 paper was going to ignite the whole field--the whole world--and it did. So they were the first ones to measure insulin in blood at the levels that it really was. When we [Shimon Glick and I] came to the lab, they helped us, and we helped them. We did growth hormone, and somebody else did--*suddenly* every hormone could be measured. But it turned out that a lot of biology is hormone-like, where cells are talking to each other using messengers like hormones, and *those* could be measured. So pretty soon almost every messenger by which one cell talked to another could be measured using this technique, the radioimmunoassay. It even worked for viruses. So hepatitis B virus could be picked up that way. When AIDS came out, it could be picked up. So it was just totally revolutionary. Within a couple of years, the people who knew what was going on said, These guys are headed for a Nobel Prize. And nobody disputed that.

Chappelle: Did you know of that before your initial inquiry?

Roth: No, no, no. When I went there, they were unknowns. They were “miracle people” in the sense they worked at the Veterans hospital in the Bronx, which was not any mainstream place. They didn’t train in an excellent laboratory. Most of us who trained--we’ve come through first-rate laboratories who taught us and tutored us, and so on. They were really almost self-taught. They taught themselves research. And they worked in a place that was a good *hospital*, but not a research center, and they had no connections. But by dint of their brilliance, really quickly made those kinds of connections and were recognized. Then Berson died, unexpectedly, at age fifty-four in 1972. And in fact, Sutherland got a Nobel Prize for the cyclic AMP (cAMP) work in ’71. And you almost wish--there were two empty chairs on that Nobel--they [Berson and Yalow] should have been in that one. But that wasn’t to be. And in fact, they gave it to Sutherland then because Sutherland was sick; he was known to be ill, and you know, “not gonna make it(??)” But Berson was young and not known to be [ill]. So he died. In those days, if a member of a team died, they often pushed them aside, and they didn’t give them the Nobel. So in fact, she was very grief stricken because this lifelong research partner of hers dies suddenly, and, in addition, she probably was harboring her Nobel dreams, and they were shattered, maybe forever. Gene Straus, who was a fellow in the lab, really helped her recoup herself. They did a whole burst of new things from the radioimmunoassay on hormones, from the GI tract, in the brain--and that convinced the Nobel committee and gave her the prize in ’77. And it was interesting too because [prior to this oral history interview] you mentioned [Roger] Guillemin and [Andrew] Schally, who had the prize, they suffered the

same problem because a guy by the name of Geoffrey Harris was the dominant leader of the hypothalamic idea. When I was growing up, the pituitary was the master gland--"didn't take orders from anybody." Just then it became clear that the pituitary gland was not the master gland, that the lower part of the brain--the hypothalamus--was actually controlling the pituitary. That was work where Geoffrey Harris was the dominant man, and Guillemin and Schally were the brilliant biochemists who actually isolated these hypothalamic hormones, so that was a perfect threesome for them. And Geoffrey Harris went ahead and died the year before--and they again [were in a similar position as Rosalyn Yalow]. But the wisdom was the Karolinska [Institute] took these two groups, Roz Yalow and Guillemin and Schally--both of them who in the old school might not have gotten it--but in fact [the Karolinska Intitute] broke that dumb barrier [and therefore established] that you could give it to the remaining members of the team. So it was an exciting Nobel Prize. It was exciting to be in Stockholm with Roz Yalow--part of the party--and with Guillemin and Schally. It was really a splendid time for endocrinology.

Chappelle: What were you working on with Berson and Yalow?

Roth: I was again very lucky when I got to work there. Until that time, they took very few fellows into that lab, and I was lucky. In the same way they did a favor to Dr. London to take me, they did a favor to a Dr. Goldman, and they took one of his fellows, a guy by the name of--in those days he was Seymour Glick--he has since immigrated to Israel, and his name is Shimon Glick. But he came there, also as a fellow. They said to us--they meaning Yalow and Berson--said to us, "You know we have been very successful, much more successful as partners than we could have been as two individuals, so we encourage you to try and form a partnership.

Chappelle: That explicit?

Roth: Yes. And we were also lucky because they were just suddenly becoming big shots, and the Yalow family and the Berson family decided to go to Europe for the summer. So they told me to take off July. By then I was an intern, but I was broke. So I couldn't even go on vacation; I got a job as a doctor in a camp. So I had a vacation in the Berkshires--paid for. But what it allowed me to do was, I read every one of their papers before then. So by the time I came to the lab, I had really read everything. Meanwhile, Glick was working there. And when I came there he was working on one--Berson and Yalow had left us with two problems: one was to develop a radioimmunoassay for growth hormone, and the other one was to learn how insulin makes glucose go into cells. He started on the growth hormone problem, and I thought I'd start on [the glucose transport problem]. He said, "Let's do a partnership. Let's both work on the immunoassay for growth hormone." And that turned out to be very lucky because that problem we solved in two years. The insulin-glucose problem didn't get solved for twenty years. [laughs] Now, we struggled; we had a lot of

help from them. They treated us, literally, like Pharaoh's children. We were tutored day and night. We were given all the help you could image. They worked at the bench themselves and were very busy, as well. We'd have to elbow them and they'd elbow us because, you know, [for space] to get your experiments done. I remember one morning we came in at 5:30 in the morning to get started, and they were planning to come in at 6:30. They came in and the whole place was filled with our stuff. And they were--it was the gentle anger of parents, you know, Who ate the turkey? [laughs] But it was that kind of a lab, and they were totally devoted to our success. We were very lucky that the thing worked out.

It then turned out there was a whole physiology of growth hormones not known at all in those days, and we stumbled into it. It was thought that growth hormone would just change as people grew from puberty, or adolescent growth spurts, but it turned out that growth hormone was a very dynamic metabolic hormone. And we stumbled--ninety percent of what's known now about growth hormone, we learned in about four months in the spring of 1963. And we were also lucky in a way--they had hit the parathyroid assay at that time, which was again another blank that needed filling and was exciting. So they were distracted, and we had a chance to develop it pretty much without being micromanaged. The other thing that happened--we then presented at a meeting. The big meetings in those days used to be in Atlantic City in April or early May, and we had the prime spot, Friday morning. It was the best spot to be on: Friday morning, ten o'clock. My friend Glick presented the paper--brought the house down. So we were stars--young stars--overnight. Berson and Yalow were, again, very good to us because everyone was [assuming it was Berson and Yalow who had done the work, saying], Oh, Sol, that's great work you have done. [But Berson insisted,] "No, no. The boys did that." And it wasn't in a demeaning way; it was in a--so they shunted all the credit to us. Now it turned out that the growth hormone assay helped validate the general concept of radioimmunoassay, because they were in the insulin field, and the insulin field was mired in conflict about the bioassays, and so even though the insulin assay came out there was still intellectual civil war going on. But the growth hormone assay, the glucagon assay that Roger Unger did, the vitamin B12 that Sheldon Rothenberg did in their lab, these were undisputed. So it validated the radioimmunoassay away from the civil war that was raging on the insulin side. But we also became stars, literally, overnight. And those papers became citation classics. Again, we were lucky that I didn't take the glucose transport problem, and I'm glad that I got kicked out of Yale. [laughs]

VI. NATIONAL INSTITUTES OF HEALTH (1963-1991)

Roth: Let me go back to the spring of 1963. So, suddenly, here are these two kids, me and Shimon Glick, and we were stars. What happened was, in those days, the draft--America was at war--and in those days they had a doctor draft. Now, ever since the age of eighteen, I was trying to stay out of the Army. And how I

managed to dodge it, I don't know, because they tell you to sign up, do this, do that, and I didn't do anything [different] that the other guys were doing, and I kept not getting drafted. So the first year of my research, the advice was to go to NIH. If you got a job at NIH or Walter Reed or some of these, that would serve instead of having to go to Vietnam or wherever you were going to be sent. I went down to get a job at the NIH, and I got very good advice from one of the guys. He said, "Jesse, I know you want to stay out of the draft, and they are going to offer you a job, but it's not going to be a good job, and don't take a not good job here; only take a good job." So in fact I turned down a job, and I spent a year in terror that I was going to get drafted. But that turned out to be a lucky break because it was in that second year when the work all came together. It then turned out also that the job I had wanted and didn't get the year before was [in the lab of] a good colleague [of Berson's, by the name of Ed Rall] from the thyroid field--[which was] previously Berson's [field]. Berson called [Ed Rall] up and told [him about] us and about the exciting work [I was doing]. So again, I got a job because I got sent from Berson to Ed Rall. And when I came to NIH, I was already a young hot shot. I wasn't just--Ed Rall became a mentor.

Chappelle: Ed Rall?

Roth: Ed Rall. R-a-l-l. And he was, again, a prominent member of the Endocrine Society. He was the guy when I came, he said, "What do you want to do, Jesse?" "I said," "Oh, we'll do the growth hormone. You know, and we'll run the--He said, "That's a great idea; it's okay. But you know, this is a special time, a special place!" And that's when I started the receptor work. We were, also though, lucky that even though we got excited about the receptor work, we didn't drop the other work. So my advice to the young guys is, "You have a great, great idea: do it about a third of your time [laughs], because you've got to pay for the lunch, today; you have got to pay the rent this month. You need to do research that is bringing home results that you can present and go to meetings with." So, in fact, I continued to do radioimmunoassay work all during those early years at the NIH while we were doing the receptor work because the receptor work--when we presented that early receptor work nobody listened--but we were doing radioimmunoassay work; we did vasopressin; we did gonadotropins, and that really kept the shop open. So Rall was right: take on doing something new, but I think we were also lucky that both Ira Pastan, my partner, and I, myself, continued to do other stuff that was productive. That's my wisdom to the young people: make sure you got your lunch and rent money covered, even if it's a great idea. The other thing that happens is that even if the idea works out, the scientific public may not be ready for it, so you could really bring it home and have no audience. So you really need the other stuff to keep you alive. And I've seen it where kids get very good ideas, drop everything, bring it home, and they starve out of the field because the timing was off.

Chappelle: What was Ed Rall like as a teacher, personality, and scientist?

Roth: He was very smart, very encouraging. He was very nice in a sense you would always see him immediately. If you gave him a call, Hey, can I come by and show you--within the day you got to see him. He always kept up with your work. If you sent him a paper to correct, he would get it back the next day, and it would have a couple of always good points. You never went to him not getting some good thoughts. Money was tight; space was tight--like everywhere else--but you never went away feeling you were shortchanged. You felt uplifted. You felt rewarded, even if you got nothing. So he had the best way to send you away empty-handed but full-hearted. It's a very good style for a leader or for a parent, you know, that you have very few pennies to give out and don't make the success of the meeting dependent on spending those few pennies.

Chappelle: What about Ira Pastan? What was his scientific background and how did you come to team up with him?

Roth: Yes, he and I remained, again, good colleagues and we're still in touch--Shimon Glick, also. These guys are all lifelong buddies. Pastan came from a relatively modest background in the Boston area, went to Tufts Medical School, and came under the sway of Ted Astwood--the leading endocrinologist. When I first came as a young fledging researcher to the meetings, Ted Astwood was one of the elite. He came over to talk about my work, and I was--in fact, the Astwood lecturer was sitting at my table last night at the awards dinner, and I had to tell him who Astwood was. But Astwood really influenced Ira Pastan, in terms of research. He started on thyroid research because that was what Astwood worked on. Gerald Aurbach is another namesake; there is another award. One of my descendents is getting the Aurbach Award, and again it was another Astwood ____ (??). So the family-ness of this thing is very real and, again, handpicked, sent, nurtured, and tutored. Pastan came to the NIH earlier than I did. He then went and worked in an outstanding lab there and was just coming back to the endocrine group at NIH--to Rall's group--as I was coming in. Again, Rall encouraged us to, "Think big, guys!" So it was then that we sat down--and it was really, really in July 1963, we posed the question, How *does* the cell know insulin is there? How does a thyroid cell know that TSH is there? And he--working on the thyroid--and me--working on insulin--were limping along together, creating the concepts, and creating the tools.

More on the discovery of cell surface receptors

Chappelle: You mentioned earlier that the dominant model of hormone action was enzyme based, and you just mentioned that you started asking, how does a cell know the hormone is there? What got you onto that question?

Roth: It's interesting; we were very lucky. We actually went around and looked at all of the modest attempts--

Chappelle: Excuse me. People were happy with the enzyme paradigm, is that correct?

Roth: People were happy, and they were happy with the--adenylate cyclase was now capturing it--maybe that was the intermediate before it got to the other enzyme. So everybody thought by then that when adenylyl cyclase and cyclic AMP were discovered that answered the whole question. We were convinced that cyclic AMP was being made inside the cell--how did the hormone get there--couldn't get across. How could so many hormones turn on adenylyl cyclase and have any specificity? Insulin didn't turn on cyclic AMP. So we were dissatisfied. We were--just in looking at the data--we just weren't happy that it made sense. And then we were lucky in that we went back and looked at all the other experiments that had done previously--thinking about and attempting to do it--and just went through the experiments, you know, where did they go wrong--what mistakes they made. So we actually went ahead and found some old experiments that were trying to get at measuring how insulin would bind. In fact, Berson was actually a major critic of those experiments. So we just took those experiments and looked at them more carefully and redid them with much more sophistication, much more precision. We were also lucky--Berson and Yalow--in a run up to their insulin assay--studied very carefully how antibodies against insulin, bind insulin; their introduction into the radioimmunoassay was through naturally occurring antibodies that patients with diabetes who got insulin developed. They quantitatively studied that interaction in a very serious way--a much more sophisticated way than anybody else did. We said, Well, why can't we--just like they recreated in a test tube, how the antibody sees insulin--why can't we recreate, how the cell sees insulin. So they were giving us a good idea of how to go about it without knowing it. That was a good break for us because that model--that was really our goal: recreating in a test tube what the cell was seeing.

Chappelle: What hormone materials and target tissues did you use?

Roth: We started with insulin, on muscle; and TSH, on thyroid. It turned out that those tissues were just--the hormones and the tissues were not--they were good, we could get our experiments done, we could develop the concept, we could dip the hormone, I'm sorry, we could dip the tissue into a bath of hormone, wash it away, and then show that the hormone effect continued. But that left a question, Was it continuing because it started something that doesn't need the hormone anymore, or did the hormone need to be there? So the advantage we did then was--we then took the tissue and dipped it into antibody or into a destructive enzyme to destroy the hormone. We showed that, in fact, you got rid of the persistent effect--meaning that the hormone was still there right on the cell surface. We were also lucky that we worked at low temperatures. Everybody who had done this before had worked at 37 degrees

because that was the physiological temperature, but by dropping the temperature, we could get the key first reaction in our hands without getting the second step or the third step interfering with it. So we were able to actually figure out that they were binding--each hormone was binding to a moderate number--a fixed number--of receptors, those receptors were on the cell surface, and we could get at them.

Chappelle: And which hormone was this?

Roth: Insulin on muscle and TSH on thyroid were the first two that we did.

Chappelle: You were doing both at the same time?

Roth: Yes. He was interested in thyroid; I was interested in insulin. And it was good because we did one, one-way, one the other, and they supported each other. So each experiment worked--but that the two together were so supportive really made it much more convincing--to us and to our coterie of people that believed us.

Chappelle: And then you switched?

Roth: We switched. And we switched to ACTH and to the adrenal because we could buy ACTH in fair amounts, the structure was known, we figured out where we were going to put the radioactive iodine tags and still keep the biological activity. It was known what the structure-function relationship of ACTH was. You could chop here, not there; you could fool here, not there. So ACTH was a marker that was well mapped. Insulin was more complicated; they hadn't really mapped out insulin anywhere near as well. We couldn't iodinate it as cleverly. The other thing was, you could break the adrenal cell and still have hormone action activating adenylate cyclase. You broke the muscle cell; insulin action was gone. TSH--you couldn't get pure TSH in those days. So we were piecing--we took the system where the idea could be best worked out--based on the idea that all the others would work the same. Now it is interesting that at that time--that was another thing I didn't mention--people really thought that each hormone had its own way to work. In other words, if there were twenty hormones, each hormone was going to have--just like each vitamin had its own way--each hormone had its own way. We were already thinking that the rules were going to be simple, and so switching from TSH to insulin to ACTH didn't bother us. We were overconfident that that wasn't going to be a barrier.

Chappelle: Then you did your paper on ACTH?

Roth: We did. We did the first paper on ACTH, [that was during] 1969-1970, a preliminary and an actual. Then we came "bang," "bang," "bang," three more on ACTH--different aspects of it. By taking calcium out of the system, we

could really show binding without any activation of adenylate cyclase-- showing they were separate. We could do a radioreceptor assay showing we could use the receptor to measure hormone. We did a couple of others. But anyway, we were able to--not just measure it--but really do a few things with it.

Chappelle: Was that your first breakthrough paper--in 1970?

Roth: Yes. The first receptor paper we published, which was a moderately primitive system, was 1966.

Chappelle: And that was the insulin?

Roth: Yes, TSH and insulin with a relatively crude system. It was well received by a smaller number of cognoscenti; it got published in an absolutely class "A" journal, but didn't have a big impact, and was hard to grow it from there. But it was the basis that we then worked to do--'69/'70 was the culmination of the technique. The insulin followed within less than a year. We were already working on--while we were finishing up the ACTH, we now made an elegant insulin system. We then made other systems; other people made other systems. So that ACTH in 1970 was the wellspring for all the cell surface receptors--for ourselves and for our neighbors and everybody else.

Chappelle: What happened to your career and your career goals at that point?

Roth: We were very lucky. The receptor stuff became fabulous. We started to close down any of the immunoassay stuff and other stuff because we were--the receptors were just pouring good things. Diseases were showing up and regulation was showing up, all kinds of ancillary issues. Other people were doing work, so we were getting invited to meetings everywhere to talk about receptors. And at that time, the receptor--as it sprung up in a new field--saw the kinship with the other receptors. So we were meeting people in ten, twelve other fields who wanted to know about receptors. Now the fields tend to be in silos, again, you know, the insulin guys work with the insulin people, but in those days there was a great fluidity, like the Renaissance--Ah! The boundaries didn't hold; the ideas spread!

Chappelle: Would you talk a little bit about rising through the ranks of the NIH and what made it so attractive that you stayed there for nearly three decades?

Roth: One of the most important things was Ed Rall. Ed Rall was a spectacularly good man, too, and he stayed in his job. And I teased him, "As long as you stay in your job--you've got to give your boss a month's notice, and you have got to give me a half a year notice." Quickly, I became--I was a senior investigator, which was the first rank of full-time, permanent. Then I became a section chief very early, and then they made me a diabetes branch very early. And I had wonderful colleagues: Phil Gorden was recruited to help do some of the clinical

work. Ron Kahn, who is now the head of the Joslin [Diabetes Center], came there. So we had a substantial science group. We liked each other--a very egalitarian group. The ideas just flowed. The space was tight, which was very good in a way because you saw everyone--we worked in a very large building, and you saw everybody. You know the Bauhaus in Germany in 1919 to 1933, artists and designers came from all over the world, doors were wide open, ideas were everywhere: that was the NIH in those days. And because--unlike universities or hospitals--they didn't--the departments didn't have a service function that made them separate units. In other words, they didn't have the biochemistry department or a physiology department; they were just kind of organizational. It's not like in a hospital, where you had to have something. So there was this fluidity of structure, fluidity of ideas that was terrific. You also didn't have to ask anybody [for permission] to do it. I used to joke about it: if your grandmother came to you in a dream at night, you could do the experiment the next morning. The equipment was there; the funding was there; you could just do it. I even joked if you were really ambitious you could go in that night and just do the experiment. Science was simple in those days, too; you could do world-class science. With much less training and much less background.

VII. JOHNS HOPKINS UNIVERSITY (1990-2000)

Chappelle: It must have been a hard to leave and go to Johns Hopkins.

Roth: It was a hard decision to leave. A couple of things came into the decision. One was I was just getting into my mid-fifties, which was around the age when--I was getting good offers all the time--but then somewhere around the mid-fifties, they stopped giving you as many good offers. So the decision I was going to move--this was a good time to move. My kids were, I think, going ahead to college. If I moved I could take my pension, whereas if I didn't move, I couldn't. But even more so it was--I went to one of my former bosses, and I saw that his books were lying exactly on the bookshelf, in exactly the same place from ten years ago. So I said, Oh, maybe I should move; maybe I'm getting that way, too. So a bunch of things collaborated to do it. And it was fun.

Chappelle: What were your responsibilities, what areas were you going to work in at Johns Hopkins?

Roth: Johns Hopkins--[when] I took over, the endocrine job was open and the geriatrics job was open. The geriatrics job was a much richer job and had a bunch of very good people, so I took the geriatrics job. I started to do endocrinology in aging as sort of the connections there, and that worked out to be very good. Diabetes was really growing and getting the spotlight [and so was] obesity. Also, it's recognized that endocrine disorders in aging are different then they are in younger people--and had been neglected. Also [I] got excellent people, so you could still do a lot of tutoring, a lot of mentoring. In

fact, one of the guys that came to me as a rookie in Baltimore, my first year at Hopkins--he was just installed in a professorship. We went down there for the dinner in his honor, and he was the third incumbent of the professorial chair that I had occupied when I first came to Hopkins.

Chappelle: What chair was that?

Roth: It was the Lublin, L-u-b-l-i-n, professorship. A family--a physician alumnus of Hopkins endowed the chair.

Chappelle: What was the significance of the move in terms of the amount of time you could put in research and funding--

Roth: It wasn't bad; it wasn't a bad change for me. It was very invigorating intellectually because it was an area that I didn't know well. There were about twenty-two docs in the group, very smart, very nice. Geriatricians are among the nicest doctors you ever want to--a little nicer than pediatricians even. They were very nice and very smart. There were branches of the National Institute of Aging--on the other side of the campus--that we collaborated with. So we still had a lot of research going on, but more time teaching, a broader range of teachers--but again, a vigorous program of mentoring and research.

VIII. NORTH SHORE LONG ISLAND JEWISH HEALTH SYSTEM (2000-present)

Chappelle: How did you come to be at the North Shore Long Island Jewish Health System?

Roth: Again, I had good luck in my bad luck.

Chappelle: This was 2000 now?

Roth: Yes. I'd spent almost now eight or ten years at Hopkins. I was getting to be--there was an excellent lab, small research lab up in New York, called the Picower Institute. A very distinguished guy and a friend of mine, Tony Cerami, was the founding director, and his wife--and then ex-wife--was also a friend of mine and she was there. I met some of the other young people--there were two very good geriatric fellows that had jobs there that I'd met through the geriatrics community. Cerami left and went to set up his own place elsewhere. The Picower Institute had a search committee, and they recruited me. It looked like a perfect job for me, in the sense that what they wanted me to do was to head up this Institute and do the kinds of things I did at NIH and even more so. I was there, and I worked hard there. I thought I did an excellent job. At the end of the year, they decided they didn't want me to continue. I had a five-year contract, and I was still on leave from Hopkins, so I was going to go back to Hopkins. But [as] good luck had it--Picower was fighting with the North Shore

Long Island Jewish Hospital System; the Picower was housed in research space at the North Shore Hospital. I got to know the North Shore people because I was trying to keep peace between the Picower bosses and the North Shore bosses, and they got to like me. I would never have known these guys, and they never would have known me, but then when the Picower bosses and I parted ways--that night I got a call from the North Shore guys. They said, You know, Jesse, I know you're supposed to go back to Baltimore, how about you staying here? So in fact, they turned around and gave me an offer. I became the geriatrician at the North Shore Health System and then became a member of their research institute. After a year of Picower--without me--Picower decided they didn't want the Institute anymore; they decided to pack in the Institute, and then people were scattered. But the North Shore was trying to build up research programs, so the Picower Institute actually was largely taken over by North Shore. So a lot of the people that I had met in my year at Picower moved over to North Shore with me. In fact, we had about eighty-five percent Picower alumni now as part of North Shore. And it was much easier because the North Shore guys were much easier to live with than the Picower guys. The Picower guys were very smart and very nice, but they were micromanaging the program in a way that was done better by North Shore--kind of left us to our own--and they built--one of the guys who left Picower is now the chair, the CEO, and the president of this research institute. They've doubled the size of the space, brought in a lot of excellent young people, and now--with the establishment of the medical school--this is now the heart of the medical school's basic science program. The medical school is very proud of it, and they've set up a graduate school that had been a Picower graduate school, and has now stayed on as the North Shore--the Elmezzi Graduate School [of Molecular Medicine]. They attract very good young physicians to get PhD degrees. I'm on the faculty; I meet with them, work with them. So my bad luck of not completing my term with Picower was a stroke of good luck--just like not getting the job at Yale, not getting a job at NIH--I was lucky when I was unlucky.

IX. CURRENT RESEARCH

Chappelle: What research areas are you interested in now?

Roth: Obesity and diabetes is one of the hottest topics in endocrinology and in all of medicine. It causes devastation, all kinds of diseases. And we're learning that obesity affects all the organs of the body; diabetes--we used to think--affected the eyes and nerves, the kidney, but now affects every cell of the body. We used to think it starts when the sugar got high, and we now know that it even starts before the sugar is very high. They really are very serious illnesses, very widespread--North America, all over the world--it's just the fastest growing disorder. Let me go back to Berson and Yalow, the early days. One of their biggest discoveries they had when they measured insulin was they found that type I diabetics didn't have enough insulin, and they showed that. But patients with type II diabetes had plenty of insulin, if anything had more than enough

insulin. It was clear that the patients were not responding to the insulin and, in fact, that they were insulin resistant. That idea was a theme developing in the 1960s. That theme really came to full fruition probably in the late-eighties with the concept of the metabolic syndrome, and the metabolic syndrome was a concatenation of several things, but one of the key features is insulin resistance. So the metabolic syndrome has insulin resistance in there as the cornerstone, and then high blood pressure, abnormal lipids, and other things that come with it. We think that the metabolic syndrome is being turned on by the obesity, and the metabolic syndrome is driving a lot of the damage all over the body. If we could regulate--exercise turns off the metabolic syndrome, dieting turns off the metabolic syndrome. See it's the struggle of the body turning on and turning off the metabolic syndrome. We have been working very much on it, trying to analyze its features, its components, and coming up with aspects of it. We developed mice that made too much insulin, and we could show that these mice--just by making too much insulin--could develop the features of the metabolic syndrome. We think that actually it may be--at some early point--the insulin level goes up and that then drives the rest of the metabolic syndrome. That's one of the things that we're working on now. And that brings together a lot of the old work that I had been exposed to at Berson and Yalow's lab [and] work we did at NIH with the receptors. One of the earliest mechanisms of *how* insulin resistance develops--we're showing that high insulin levels knock the insulin receptor levels down; it knocks down the post-receptor activation. We actually--early on in the insulin resistance field--could show each of the *pieces* that were associated. Our younger colleagues, again, developed more of that. So there has been a continuity of this idea of insulin resistance starting really in 1960, through the receptors, through metabolic syndrome, and now the disease states that are really reaping the whirlwind because of the epidemic of obesity and diabetes.

X. THE ENDOCRINE SOCIETY

Chappelle: Could you weave the Endocrine Society into that story a little bit?

Roth: It's funny because in those early--Berson and Yalow were both very active members of the Endocrine Society. The second presentation--the one that really brought it together on the growth hormone back in 1963--was a symposium here at the [annual meeting]--Berson presented work and paraded us as the stars of that work. Year after year, we would come back and present our work at this meeting. I was on the council of the Endocrine Society. All this work that I've done has been richly rooted in the Endocrine Society. We come to the meetings every year; we participated in the workshops, and so I would say this is really one of our major homes--here at the Endocrine Society.

Chappelle: Are you looking forward to anything in particular at this year's meeting?

Roth: This has been an exciting meeting: first of all, to be interviewed by you via

history--going to the awards dinner. I've been to the awards dinner on multiple occasions--I have three awards from the Endocrine Society, the junior, the middle and the senior awards--so, I've been to those award dinners before. I have nominated colleagues and friends who have worked with me who have gotten [awards]. Many of my young colleagues have now gone on to get major awards from the Endocrine Society. I was there last night when, again, one of my colleagues just got the Aurbach Lectureship. As I said, one of the mentees of a mentee got an award. So, we've really been part of it. We did that last night. He is going to give a major address tomorrow, and I will be there to cheer him on. We're very much at home here, and the kinships are--one of the great things about endocrinology is it's a very friendly field; the people like each other, and even when we're competing, it's a friendly competition. It's a sportsman like competition. I think the mentoring is--one of the things that's done--most of us--Berson and Yalow came on, you know, they sprang from Zeus's head--most of us were mentored and tutored. I just had unselfish, devoted, talented tutors. I hope--I think I've inculcated that in the people who worked in my group, and they continue. It's a pleasure for me to go to their groups and see them mentoring their young people in that same kind of enthusiastic, unselfish commitment to their success.

XI. CURRENT VIEWS OF ENDOCRINOLOGY

- Chappelle: I would like to ask about your current views of the field in terms of your own general views, but also would you mention something about the complexity and the levels of complexity that you have encountered since you first started with the simpler theories--
- Roth: The complexity is daunting in a couple of ways. It's hard for people to--it's easy to get into a silo, that is, a limited area where you just talk to each other about the complexities of your system, and the generalizations seem to get lost. Also, I think the fields stimulate each other a little bit less because they don't--in the olden days we could go to meetings and understand all the papers and talk to each other--the complexities have made it a little more of a Babel, where the languages don't cross easily. It's also hard for the young people. In my day, smart, young hardworking guys could be doing world-level science in two years; it's hard to do that now. The apprenticeship is longer. The same thing that has happened, also, is that the medical school has gotten more complicated. They don't have as much research training or time because the teaching has been more intensive. The debts that the young doctors accumulate pushes them to go into higher paying areas. In my day, we just did what we wanted to do; somehow there was just enough money to manage everything. So it's a much tougher time, and they--but we had the draft; that was [laughs]--again the kids can't imagine those kinds [of things]. The other nice thing to see, though, is that the prejudicial barriers in medicine have largely disappeared--even for the women. The women had it worst of all, worse than the other minorities. At least for the men, at least their families and friends

were on their team, even if the medical schools were against the Italians and the Jews and the African-Americans. But with the women, even their families were against them: Go become a secretary. Go to work and help your brother go to medical school. So it's nice to see now that, in fact, the women are given full opportunities. And foreigners--it's a pleasure to see so many people from abroad getting full opportunities. It's a very impressive change that's happened in fifty years; fifty years has made all the difference--the rainbow that you see at the Endocrine meeting, and the number of outstanding women. Yalow was a pioneer, almost unique, when she was doing her work. She had all those barriers. They wouldn't take her into graduate school; she couldn't get jobs; her family didn't want--so it's amazing now to see the total change, and the young people can't imagine it was that way.

It's funny. I remember there was a guy next to me in college; he was a premed; he was African-American, track star, and everyone knew he was either going to go to Meharry (Medical College) or to Howard, because African-Americans only went there. I used to attend down at Howard when I was at the NIH, and you talked to the attendings at Howard, and they couldn't take graduate work, and they had to go--it was just amazing. Now you go to medical schools or hospitals and, again, [you find] women, African-Americans, Jews, Italians, foreigners. We've had a rebirth of freedom in America.

Chappelle: Thank you.

[End of Interview]

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Interview History—Jesse Roth, MD

Dr. Roth was interviewed by Michael Chappelle on June 4, 2011, during the Endocrine Society's Annual Meeting held at the Boston Convention and Exhibition Center in Boston, Massachusetts. The interview took place in a conference room at the Westin Hotel and lasted seventy-three minutes. The transcript was audit-edited by Mr. Chappelle and reviewed by Dr. Roth prior to its accession by the Oral History of Endocrinology Collection. The videotape and transcript are in the public domain, by agreement with the oral author. *The original recording, consisting of two (2) 45-minute mini DV cam tapes, is in the Library holdings and is available under the regulations governing the use of permanent noncurrent records.* Records relating to the interview are located in the offices of the Clark Sawin Library's Oral History of Endocrinology Project.