A conversation with Jesse Roth

We take it for granted today that all hormones and other intercellular messenger have their own specific receptors. But this was not the case until the groundbreaking work of Jesse Roth and his colleagues. Indeed, Roth (Figure 1), currently at the Feinstein Institutes for Medical Research of Northwell Health Zucker School of Medicine, is best known for his research on cell surface membrane receptors. His studies on the receptors for insulin, growth hormone, and adrenocorticotropic hormone (ACTH) in the early 1970s became the model for many others. See the *JCI* website for the full interview (https://jci.org/videos/cgms) to get a sense of whether Dr. Roth could have instead been satisfied as a clinician with a black bag doing house calls.

JCI: Can you start by telling us a little bit about your parents and your upbringing?

Roth: I have a New York accent notched into my tongue. I was born in 1934 in the depths of the Great Depression. I grew up in a happy middle-class family. My mother was an immigrant from Romania. My father's parents emigrated from Austria. His father died when he was 12; my father left school to support his family. Despite the truncation of his school years, he was very well read.

At the time I was growing up, science was just the hottest thing. Three or four of us in each class in elementary through middle school were turned on by science from the beginning. We did those silly experiments — adding vinegar to bicarbonate soda and detonating small explosions. The school I went to was such a small school that they had to hire a science teacher to come from the outside for an hour a week. That let them pick from among the best public school teachers. These were enthusiastic and energetic people who in other times might have been active scientists themselves instead of teachers.

JCI: How did you end up at Columbia for your undergraduate studies?

Roth: It will surprise parents nowadays that tuition back then was $600 per year. In those days, you could compete in a six-hour exam for a New York State Scholarship. Based on the score, the state paid $350 out of the $600. The same thing happened when I went to medical school with a New York State Medical Scholarship. You sat for a multiple-choice exam and if you came out above the cut line, you got $750 for each of the four years. At that time, medical school tuition was $1,000 per year.

Figure 1. Jesse Roth in New York City on October 16, 2019. Photo credit: Alexey Levchenko.

JCI: You were in the first medical school class at Einstein; why take a chance on a completely new medical school?

Roth: In those days, the prejudices in medical schools were tough. If you were Jewish and you were from New York, you had a tough time getting into medical school. I didn't get into a fancy medical school, and Einstein was just beginning to admit its first class. My cousin, a physician, was very impressed with the faculty that Einstein was putting together. When I went to the interview, the only building they had was a small one-family house in the Bronx. I needed imagination and courage, but I trusted my cousin's opinion.

The other positive force came from my parents. We were a committed Jewish family. My parents said, "If the Jewish community is opening its first medical school, of all people that should take a chance on them, I guess we ought to." It was such a good choice.

JCI: After a life in New York City, how did you decide on St. Louis and Washington University for your residency?

Roth: In those days, the best of academic medicine in the US was largely north of the Mason-Dixon line and east of the Mississippi River. My professors of medicine convinced us to shop more broadly, so my classmates and I actually went out and looked; they were the ones who pointed out that Washington University was really in the top echelon. They called ahead for me. It was much like horse trading, along the lines of, "Hey Jesse, where do you wish to go?" "Oh, I thought St. Louis was terrific." My chief got on the phone, and the arrangements were made.

JCI: What put you on a track towards doing research?

Roth: The group I worked with in St. Louis were both very good clinicians and very good researchers. I started to see myself doing both. Near the end of my residency, I was on a waiting list for a fellowship when Irving London, my professor of medicine from Einstein, introduced me to Solomon Berson and Rosalyn Yalow. London knew they were doing very exciting, cutting-edge research, but the greater world of science didn't yet realize it. I had written to Berson and Yalow before that, and Berson had sent me back a very hesitating letter until he got the letter from London. Berson then wrote back, "Forget the first letter. Come!" And that's how I got started in research.

Yalow and Berson had just published their landmark paper on insulin, the first radioimmunoassay [RIA]. International recognition was just starting for them. Berson and Yalow ran a small group, and they were often at the lab bench. From the point of view of the people who understood how science and teaching were done, we saw that hands-on dedication right there.

My project was working on an RIA for growth hormone with Shimon Glick. Growth hormone was slow in emerging as

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an important factor among the hormones. It turned out that the animal growth hormones were different from human growth hormone, unlike almost all the other peptide hormones. It was a big puzzle.

JCI: Given this exciting research, how did you end up as a clinical associate at the NIH?

Roth: In those days, the Vietnam War was going on, and young MDs were being drafted. I didn't want to go to war, so I went down to NIH to try to look for a job, because if you went to NIH or CDC or FDA, that was considered a full government job and you would not be deployed. I looked at the endocrine jobs, and I didn't get one. I risked that year not having a deferment, and I was lucky I didn't get drafted; the next year, the plum job that I wanted was open and it came to me because Berson called the guy at the NIH and said, "I got this kid for you."

The group leaders at NIH were terrific. Another terrific thing about the NIH was there seemed to be no walls. It was not like universities where they had lots of different groups, but not much talking between groups. NIH was just one big, wide, open house. We lived all in one giant red brick monster of a building, Building 10. We all ate in the same cafeteria, had our hair cut in the same barber shop, covered night calls in the same places. Science was also much easier in those days. You could get the help you needed, complete a competitive piece of work in a year or two, and have it published and recognized. The time was right and the environment was right, and we were in heaven.

JCI: You rose from being clinical associate all the way to being the scientific director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), with the rank of assistant surgeon general. And this coincided with the time when you came up with your extremely controversial idea that hormones could have receptors.

Roth: That was really fun. Ira Pastan was my scientific partner at the time. He was just finishing up a research project in a major biochemistry lab at NIH. I was coming from the Berson and Yalow lab. There was a tendency in those days that whatever success you had, you continued in that line for the rest your career. When I came to the NIH, my new boss (Ed Rall) told me I could continue researching growth hormone for the rest of my life. I recall him adding, "But this is an exciting place. Why don't you see what else you might want to do?" While I continued working on growth hormone to pay for lunch and the month's rent, Pastan and I decided to focus on one question: how does the cell know when insulin is present? We started in 1963 and succeeded, but it took us much longer than we expected to define that first step in insulin action.

JCI: How difficult was it for the field to accept the fact that insulin could have a receptor?

Roth: I remember presenting some of the receptor work at several excellent academic centers and the audience just looking at me, wondering why I would be doing this. We persisted; the concept of cell-surface receptors eventually started to gain wide acceptance.

JCI: Why did you leave NIH to go to Johns Hopkins? And why did you pivot towards geriatric medicine?

Roth: I was at NIH for 26 years. By that time, I was entitled to a pension and my three children were approaching college age. If I had stayed at NIH, I was worried that my kids would wind up with big college debts and I thought that was such a burden; I had gone through college with no debt. That prompted me to look around, and Hopkins had a job open in geriatric medicine. The big advantage of that position was that the National Institute on Aging (NIA) had a very good research program in Baltimore (adjacent to Hopkins) which included a very rich endocrine group. On paper, the move looks big, but in reality, it was not a great leap.

JCI: After nine years at Hopkins, you moved again to become the president and CEO of the Picower Institute in New York. Was that driven by a desire to return to New York or the opportunity for a leadership position?

Roth: It was really an opportunity for a leadership position. I was just turning 65. A lot of the universities want to move you along at that point. The Picower Institute had good young people. I had a long-standing record of helping young researchers develop, so I was a good fit for their job. I was there for about a year when the Picower sponsors started to consider a change in direction. I was considering going back to Hopkins, when the Picower's neighbor, North Shore–LIJ Health System [now Northwell Health] asked me to stay. They offered me the position as geriatrician-in-chief of the medical system. It was at that time they decided that they were going go major league, start a medical school and invest in cutting-edge research. It was yet another exciting opportunity. And so far, Northwell has been very prophetic in which way to go. They are now the largest health system in New York State.

JCI: Your trainees over time have included Nobel Prize winners, National Academy members, a who's who of the metabolism field with Bob Lefkowitz, Barbara Kahn, Ron Kahn, Jeff Flier, among others.

Roth: I think that we were lucky. I always thought that my job was to convince my trainees that if they worked hard, they would have every chance to succeed. Many of the MDs came with relatively little research background compared to the PhDs. We worked very hard with them, and our job was to encourage them and help them do the right experiments.

JCI: Turning from mentoring to being mentored: Yalow was notoriously fiery. What was that relationship like?

Roth: For much of my research career, Yalow treated me as a favorite, including me and my wife Susan in Yalow family events, including the party in Stockholm at the time of her Nobel Prize. On the other hand, she often went out of her way to challenge (in public) work from my lab. In my early years at NIH, it took me months to convince her that the immunoassayable insulin in blood also included proinsulin and other insulin precursor molecules. In later years, she challenged our findings that bacteria have bioactive peptides that are very similar to mammalian hormones. Regrettably, she did not live to see our recent publication of the 33–amino acid peptide released by *E. coli* that resembles α-MSH and ACTH in structure, but especially in bioactivity in vitro and in vivo.

JCI: What other career could have kept you engaged over your life?

Roth: I'm increasingly convinced that this was the right path for me. I'm not sure I would have been as happy and fulfilled doing anything else. What else could I have done? I could see teaching. I like teaching.

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