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PHILLIP GORDEN, MD

Interview conducted by
Adolph Friedman, MD
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FAMILY BACKGROUND

Dr. Friedman: Phil, am I doing this with your permission?

Dr. Gorden: Yes.

Dr. Friedman: According to your CV, you were born in Baldwyn, Mississippi, December 22, 1934. Where is Baldwyn, Mississippi?

Dr. Gorden: It's in Northeast Mississippi. It's about thirty miles from the Alabama line, thirty miles from the Tennessee line, right where Elvis Presley was born, so that makes it very distinct.

Dr. Friedman: How did your family get there?

Dr. Gorden: My father was an immigrant from the Ukraine, and after the revolution and after World War I--with his family--was able to get out of the Ukraine and into Poland. After a lot of difficulties, they were able to immigrate to the United States with the help of an older brother, who actually had left the Ukraine before my father was born. This brother somehow had managed to get a job, which at that time was a premium, no matter where it was. It so happened that it was in Mississippi. The brother then was able finally to open up a little business of his own, and then he finally was able to bring the rest of the family over.

Dr. Friedman: How much older was your uncle than your father?

Dr. Gorden: My father will be ninety on February third, and we're all planning to go celebrate his birthday in Baldwyn where he still lives--quite independently. The brother was probably about twenty years older.

Dr. Friedman: How much education did your father and your mother have?

Dr. Gorden: My father went to a chader, a Jewish school in the Ukraine, when he was a small child, but once he came to the United States at age eleven, he was really too old to go to public school in Mississippi, and so he had no formal education at all. Later in his life, when he was around twenty, he went to what was called a business college for about six months, which was really a place where you learn elementary accounting and a few things like that, in St. Louis. But basically, he had no formal education. My mother was born in the United States in a place called Morehead, Mississippi, which is a small town in the Mississippi River Delta. She was essentially abandoned by her father, and her mother then was really unable to raise her. She was raised by a grandmother in Cleveland, Ohio. She went to about the eighth grade, and that was the only formal education she had.

Dr. Friedman: How about siblings?

Dr. Gorden: I have no siblings. I'm an only child.

EARLY EDUCATION

Dr. Friedman: You went to high school in Baldwin. Did you do anything unusual in high school? Were you an athlete? Were you interested in music or art? Did you play an instrument? Did you do anything? Did you excel in science?

Dr. Gorden: You have to remember that the high school that I attended only had twenty-nine people in my graduating class, and the school was totally geared to the ambient population, most of whom were farmers and people who were really not going further in education. There were only three people, in fact, in my whole high school class who went to a senior college. So it really wasn't geared to any particular thing such as science. Fortunately, in a situation like that, you don't have to be very talented in athletics to play. So I played everything. I was a basketball player, a football player, everything, because the reality of it was they always had to field a team and they needed me.

Dr. Friedman: You were tall. You were ripe for basketball.

Dr. Gorden: I had the typical talent for athletics.

CHOOSING VANDERBILT UNIVERSITY

Dr. Friedman: Did your family stimulate you when you went to medicine, or did that come later? My second question is how did you come to go to Vanderbilt?

Dr. Gorden: I really knew little about one college versus another. Most of my exposure was very local. I really had traveled very little--not really been any particular place except an occasional isolated trip, so I had very little exposure. My family had no real exposure either, and really there was very little in the way of intellectual activity that really went on. My father worked very hard in his little business, his dry goods store. My mother worked in the store, and I was very involved in all the usual things that people do in small towns, so I was always very busy but not in an intellectual sense. I knew one person from a neighboring town named Tupelo--which is a little bit bigger--who had gone to Vanderbilt.

Dr. Friedman: Excuse me. Would you please spell the name of that town?

Dr. Gorden: T-u-p-e-l-o.

Dr. Friedman: Thank you. Please, continue.

Dr. Gorden: Because he had gone to Vanderbilt, I talked to him about it; and I decided to apply. It really was about the extent of my horizon. I really had no idea of any sort of college opportunities, or anything like that really, beyond the South.

Difficulties in pre-med

Vanderbilt Medical School

Dr. Friedmn: I take it you did well in college?

Dr. Gorden: Actually, going to college for the first two years was probably the most difficult time of my life. I had a very difficult time. At that time, I knew I was pre-med--I wanted to be pre-med--but it seemed like a hopeless situation. I simply couldn't manage academically. I was fine in every other way, but I found everything really difficult. Between the second and third year, I began to equilibrate and catch up. And actually, at that time, Vanderbilt had only fifty medical students. There were fifty students in the class, and I fortunately was the last student selected for the Vanderbilt Medical School class, which was a very good fortune for me. Once I got into medical school, there was really no problem; and I graduated AOA from medical school, but the trip to medical school was difficult.

RESIDENCY AT YALE

Dr. Friedman: How did you happen to be able to go to Yale for your subsequent training?

Dr. Gorden: I think it was probably related to the fact that I had done well in medical school. I don't know what all the criteria were at the time for Yale. It was a very competitive residency at the time. Perhaps they were interested in a broader representation. Maybe there weren't as many people from the South. Perhaps that was helpful. I don't know, but I had a good track record in medical school and came from the South, and those were all probably elements that led to my selection. Paul Beeson was chairman of medicine at that time, and he has a very interesting interview himself in the January 2000 issue of the *Annals of Internal Medicine* talking about his tenure as a chairman. It's a very interesting piece to read--about his own experience as a chairman and the evolution of medicine. It has evolved into something very different from what it was when he entered medicine.

CHOOSING ENDOCRINOLOGY

Grant Liddle as role model

Dr. Friedman: Did you excel in any particular field in medical school that sort of triggered your choice of future work?

Dr. Gorden: I suspect that it was the role models that I ran into that sort of led me in a particular direction; and, of course, one of the really key role models for me was Grant Liddle. One or two years before I entered medical school, he was recruited from the NIH to Vanderbilt. He was in the Heart Institute here at NIH, and he was recruited to Vanderbilt as chief of endocrinology. He was an extraordinary clinical investigator and an extraordinary teacher. I am quite sure--as I think back--that he probably was one of the strongest appeals of the endocrine

area for me.

MARRIAGE AND WIFE'S BACKGROUND

Dr. Friedman: I noticed from your CV, you got married while you were in medical school. How did you meet your wife? Did she do any professional work? Tell me a little bit about her.

Dr. Gorden: My wife, Vivian, and I met in Nashville. Her parents were immigrants from Russia, as was my father. We had a rather similar background in terms of how her parents got to Nashville, and she was a student at Vanderbilt, where we met. We were married as soon as she graduated from Vanderbilt College--between my second and third years of medical school. Of course, we then did everything together. We celebrated our 40th wedding anniversary this past summer. We've been a team ever since.

Children's education and careers

Dr. Friedman: Congratulations. I know that you have two children. Would you be kind enough to tell me about their occupations, interests, and so forth?

Dr. Gorden: Our oldest son, Lee, was born while I was a resident in New Haven, and the youngest, Jed, was born here at the Bethesda Navy Hospital when we were already here at the NIH. They both went to Whitman--to high school--here in Bethesda. Lee went to Brown University and then to Vanderbilt Medical School, graduating in the Class of '90. He then went to the University of Minnesota for surgical residency. He spent a couple of years in Geneva doing research and finished his residency and at the moment is doing a fellowship in hepatobiliary surgery in Toronto. He is a board certified surgeon--in the process of looking for a job at the moment. Jed, the youngest, graduated--as I said--from Whitman--went to Middlebury College. He also went to Vanderbilt Medical School, graduated in the Class of '97, took a medical residency at the University of Washington, Seattle where he is now a senior third year resident, and will do a pulmonary ICU fellowship over the next year.

Dr. Friedman: That's very interesting because I have a niece who is one of the chief medical residents in Seattle beginning July first. Her name is Liss.

Dr. Gorden: Okay. I'll write that down.

Dr. Friedman: Her father is an ophthalmologist in Baltimore.

Dr. Gorden: I'll have to write that down.

Dr. Friedman: Hillary Liss.

Dr. Gorden: Hillary?

Dr. Friedman: Hillary. She's from Baltimore. She went to Princeton and then the University of Maryland. She didn't want to get into Hopkins on her father's bootstraps.

Dr. Gorden: I understand these things.

Dr. Friedman: Her younger brother didn't care. He went to Hopkins.

Dr. Gorden: I understand.

METABOLISM FELLOWSHIP WITH JOHN PETERS

Beginning a career in research

Dr. Friedman: After Yale, what did you do next?

Dr. Gorden: I did the full three years of residency at Yale, and I spent two years in what was called a Metabolism Fellowship, which was begun by John Peters. He was a distinguished professor at Yale who had done a lot of work in diabetes and fluid and electrolyte metabolism and endocrinology, and this was a program that was clinically based. We had the opportunity to see a wide spectrum of diabetes, endocrinology, fluid electrolyte problems, and so forth. That started me in the investigative track with a young investigator by the name of Tom Ferris. Tom subsequently became chairman of the Department of Medicine at the University of Minnesota, where he retired about three or four years ago. He is a very distinguished nephrologist and was on the National Advisory Council at NIDDK (National Institute of Diabetes, Digestive, and Kidney Diseases) and was president of the American Society of Nephrology and a superb chairman of the Department of Medicine at Minnesota. So that's really where I began doing research.

Facing the military draft; deciding on the NIH

At the time that I completed this at Yale, I really was essentially faced with the draft--as were many of us who came to NIH at that time. In fact, I was supposed to go to England with Tom Ferris, who was going to join Paul Beeson who by that time had become the Nuffield Professor of Medicine at Oxford. I was really planning to do that, but it was very clear that the draft board wasn't going to permit that.

NATIONAL INSTITUTES OF HEALTH: DEVELOPING A CLINICAL DIABETES PROGRAM WITH JESSE ROTH

Then I had the good fortune of meeting Jesse Roth, a mutual friend. Jesse had already been at the NIH for about three years at that time. He had worked with Sol Berson and Roz Yalow and had been very involved in developing the whole concept of radioimmunoassay, in particular the growth hormone assay. He had been at NIH for three years as a clinical associate, but he had been offered, by Ed Rall and Jack Robbins, chief of a section, which was called Diabetes and Intermediary Metabolism in the Clinical Endocrinology Branch, and he was looking for someone who might want to develop a clinical program in diabetes. A mutual friend suggested that I might be an appropriate person, so we met and had a very nice get-together at a seder at his father's house in New York. By the time his father finished the seder, we had had a chance to discuss a lot of things. He literally took almost the same time that the Exodus took itself to complete the seder. It was really great, so we ended up coming to Bethesda to set up a clinical program where I joined an extraordinary group of people in the Clinical Endocrinology Branch.

Becoming a clinical director at the National Institutes of Health

NIH leave of absence: joining Lelio Orci in Geneva to work on insulin receptors

Dr. Friedman: I don't know when it was, but how did you happen to get to spend two years in Geneva?

Dr. Gorden: I started as a senior investigator, and several years later--along about 1972 or so--Ed Rall asked me to become the clinical director of the Institute, which I did. And somewhere around the middle of the 1970s--1976--I was interested in going into a cell biology laboratory to exploit some of the things that we had learned clinically about the insulin receptor. I had the good fortune of joining Lelio Orci in the Institute of Histology at the University of Geneva. So we went to Geneva, and the work turned out to be so successful and so interesting that I ended up staying for two years, which was a wonderful, scientific period for me. It was a wonderful period for the family. The kids and I went to a French speaking school, and it was just a wonderful experience for everybody. We were there until 1978, when I came back to the United States.

Dr. Friedman: Who financed this?

Dr. Gorden: I was basically on leave of absence from the Institute, so I was on what was referred to as a foreign assignment. In a university it would be called a sabbatical, but in the government system, there isn't really a sabbatical, but it's possible to do an assignment away from the institution. In this case, it happened to be at the University of Geneva. What was unusual about it was to spend two years. Ed Rall and Jesse Roth were very supportive. That really made it possible at the time--because they thought the work was very productive. So it was a very good situation.

Dr. Friedman: NIH financed?

Dr. Gorden: Yes. NIH financed the program.

Filling a clinical niche at the NIH: developing the first medical therapy for ectopic ACTH syndrome

Early work on proinsulin; early work on insulin receptors

Dr. Friedman: I went over your bibliography, and your first six or eight papers were in some aspect of renal disease, and I obviously assume that was related to the work you did with John Peters. About 1967 you apparently got interested in acromegaly, growth hormone, thyrotropin and ectopic ACTH, et cetera. How about telling me about some of that work.

Dr. Gorden: The work at Yale was actually done with Tom Ferris. John Peters died several years before I actually arrived, but his legacy was really alive at Yale, and so it was really very much a part of the Peters' program that I entered into. When I came to NIH, there was an extremely rich scientific program with some extraordinary people--Jesse Roth, Ira Pasten, Marty Rodbell, Jack Robbins, Ed Rall--just an incredible group, but no one who really had any special clinical interest; so I was really kind of unique in the program in that sense. I was able to assimilate a large number of interesting patients. We did the first medical therapy for the ectopic ACTH syndrome. Much of that was stimulated by my previous exposure to Grant Liddle. I had been exposed by this time to people like Phil Bondy at Yale, Frank Epstein at Yale, Tom Ferris, Pat Morrow. Many of these people had an influence on a wide range of things from testosterone to adrenal steroids--to whatever. And so that's how I was able to really involve myself in a rather wide range of clinical activities, and then, most importantly, I was able to exploit two really fundamental observations from a clinical point of view. The first was the discovery of an unusual form of insulin by Don Steiner. In collaboration with Jesse Roth and Ira Pasten, we found that there was a high molecular weight insulin circulating in plasma. We then were able to study this in a wide variety of patients. As it turned out, Steiner then clarified the nature of this insulin, which turned out to be proinsulin. That is really history now, but we were able to do much of the clinical work on what we had originally called "big insulin" because it had a higher molecular weight than insulin, and we looked at it in a lot of clinical conditions. It turns out that--even today--one of the greatest utilities of this assay is in the study and the diagnosis of insulinoma. We're still using it on the service even today as we speak. The next and really very important thing was the development of the technology, which was spearheaded by Jesse Roth but had important contributions from people like Ira Pasten, Ron, Bob Lefkowitz to the development of technology to study the insulin receptor: first, the concept that the insulin receptor was--is--a cell-surface protein, and then the technology to study it. So once that was developed in the laboratory, we immediately were able to exploit this clinically. We had a wide variety of patients with insulin resistance, and we were able then to distinguish these unusual diseases of insulin resistance. This was really the marriage of technology to clinical science. Immunoassay had been the precursor and had led to a certain marriage with clinical medicine. Now, receptor biology became that marriage. We are able to study it at a deeper level, and it really was one of the first entrees into the concept of insulin resistance in the early phase of type 2 diabetes and obesity.

Research on hypoglycemia and insulinoma

First to treat islet cell carcinoma with streptozotocin; a collaborative adventure with the NCI

The clinical benefits to patients as participants in clinical research at the NIH

Dr. Friedman: When you got involved in islet cell tumors and insulinomas, you wrote on islet cell tumors in adults, malignant insulinomas, and carcinoids, was there any relation of the insulinomas to the carcinoids?

Dr. Gorden: We were interested originally in hypoglycemia, and insulinoma was an important part of that. We--in conjunction with the National Cancer Institute, and Vince DeVita was a collaborator at that time--were the first to give streptozotocin to patients with islet cell carcinoma. We admitted them once we had the availability of this new class of drugs. We had the extraordinary good fortune of having people like John Doppman and having an extraordinary group of surgeons in the NCI; like Murray Brennan, Sam Wells, Jeff Norton, and Rich Alexander, who collaborated over the years in the study of islet cell tumors. We had insulinomas; Kaiser and the Heart Institute had carcinoid tumors. We had, again, the parathyroid tumors from the Gerry Aurbach group. We had a host of gastrinomas. Our GI people were interested. So it was a wonderful collaborative adventure where we were able to study many of the clinical aspects and-- later now--the genetic aspects, like the MEN-1 syndrome. These patients were really being treated clinically, and one of the most interesting things about that was that we were one of the very few centers where patients could get this kind of care. Everyone who was participating in clinical research at that time was truly the immediate beneficiary. That's something that we must remember and keep finding ways for people who are involved in clinical research to appreciate: the fact that they are the important beneficiaries of that research. I know in your own experience you obviously had more difficulty in taking care of patients with very rare disease, and we had the opportunity to collect larger numbers. That's one of the unique things about the NIH. These patients truly benefited. It was a great time for clinical research in endocrinology.

DISCOVERY OF PROINSULIN ADVANCES THE FIELD; GROWTH HORMONE AND BINDING PROTEINS

Dr. Friedman: When I was in practice, I sent quite a few patients to Gerry Aurbach, but I didn't have any to send to other people here. In your notes, you mentioned big growth hormone. The "big insulin" was because proinsulin is a big molecule. Is that why growth hormone is called "big growth hormone"? What's the relationship?

Dr. Gorden: After the discovery of so-called big insulin, which turned out to be proinsulin, or proinsulin-like material, we began to look further; and because of our interest in growth hormone, we were able to carry out the same kind of experiment. We took plasma from acromegalics and normal patients and treated it in the same way that we had discovered the high molecular weight insulin. We found a higher molecular weight growth hormone. We referred to it as "big growth hormone" because that was the terminology that was being used. It turns out

that--once the biosynthesis of growth hormone was understood--there is no precursor. There is no *progrowth* hormone, so we realized that this couldn't be *progrowth* hormone. It turns out in the end that it's an unusual dimer of growth hormone.

Dr. Friedman: Spell dimer.

Dr. Gorden: D-i-m-e-r. And there were other higher molecular weight oligomers that we now realize are larger molecular weight aggregates and the more recently discovered soluble receptor for growth hormone, which bound growth hormone in plasma. This was one of the first times that we realized that a polypeptide hormone had a binding protein. This is, of course, common for steroid hormones, but it was not thought to be the case for polypeptide hormones. This was one of the first times that this phenomenon--that is, a binding protein for polypeptide hormone--was really noted.

THE RADIORECEPTOR ASSAY: A BIOLOGIC METHODOLOGY TO STUDY GROWTH HORMONE

Roth, Pasten, and Lefkowitz develop the first radioreceptor assay for ACTH

Dr. Friedman: What stimulated you to get involved in the radioreceptor assays for growth hormone.

Dr. Gorden: The technology for doing radioreceptor assay was developed by Jesse Roth, Ira Pasten, and Bob Lefkowitz--first for ACTH--that was just fortuitous that it just happened to be that the materials were available, and they were able to iodinate ACTH in a biologically active form. But basically the idea was to study each of the hormones for which we had an interest by receptor techniques. Growth hormone, as you know, was difficult to measure biologically. You could do radioimmunoassay, but the biological measurements were very crude and required high concentrations. The receptor assays were much more sensitive, and they tended to simulate the bioactivity that was measured in other ways, so that's why we wanted to begin to look at the biologic forms--the so-called big growth hormones. We wanted to determine whether they had the same biologic activity and what the relationship--whether they were isoforms of growth hormone. There is a 20-kilodalton growth hormone. There is a 22-kilodalton growth hormone. We wanted to know if all these forms of growth hormone had a similar biological activity or [if] there were differences. We know that for certain polypeptide hormones, particularly the glycoprotein hormones, there are differences in the bio- and immuno-ratios of these hormones. So this was an attempt to begin to understand this from a biological point of view.

NSILA; sulfation factor; MSA; the discovery of IGF-2

Dr. Friedman: What about the NSILA [and] proinsulin both being found in serum and hypoglycemic states. Is there a connection there?

Dr. Gorden: As you know, Bill Daughaday first discovered something that he referred to as

sulfation factor, which later proved to be IGF-1. This was the growth hormone responsive molecule in plasma. Froesch in Switzerland and others described another molecule, which was referred to as NSILA--they referred to later as IGF-2--they basically were insulin-like molecules but were different from insulin. The sulfation factor and so-called NSILA that Frosch described had certain similarities to insulin and certain differences. Now we began to see--and this was part of this very rich clinical program that we had of bringing patients in with unusual syndromes. We began to see a group of patients who had tumors. They clearly were not making insulin. Their plasma insulin levels were very low. You extract these tumors, and they had no discernable insulin, and yet these people had very severe hypoglycemia. Several people were working with tissue culture preparations of that time--Mat Rechler, Pete Nisley--and we were able to look at the question of whether or not some of the extracts in these tumors, or some of the plasma from these patients, cross-reacted with this so-called multiplication stimulating activity, so-called MSA, which turns out to be IGF-2. And--to make a very long story, short--we found that the concentrations of this MSA was elevated in these patients with this non-insulin type of hypoglycemia, and it turns out now that they seem to make a higher molecular weight form of IGF-2. In many ways it's analogous to insulinoma except [for] the biologically active principal: rather than proinsulin, which is the common situation in insulinoma, they make a high molecular weight form of IGF-2. Daughaday and others put this together and confirmed this. Well, we had originally shown that this appeared to be the case, and this was confirmed by a number of others.

Doing clinical research: time, patients, and technology

So, it was again this opportunity to study these patients, and to wonder, and have the time to be concerned about [what] could be related to this form of hypoglycemia that lead us to this discovery. This was a coincidence of having a technology going on in the laboratory, having patients who really provoked us to think about what was going on with them; and the marriage of these two things is what clinical research is all about.

Dr. Friedman: How did this MSA substance--or group of substances--cause hypoglycemia?

Dr. Gorden: It seems to work presumably through the insulin receptor, and we know that these substances cross-react with the insulin receptor, and it binds to the insulin receptor; and that's how it seems to cause hypoglycemia.

DISCUSSION OF INSULIN RECEPTORS, SIGNAL TRANSDUCTION PATHWAYS, AND INSULIN RESISTANCE

Dr. Friedman: I was about to ask you, what's the significance of an insulin receptor deficiency? Is it a form of diabetes? Does the high level circulating insulin result in hypoglycemia? What's the story about that?

Dr. Gorden: You mean with respect to receptor deficiency?

Down-regulation compared to receptor deficiency

Dr. Friedman: Yes. What regulates insulin receptors in normal human[s] in diseased states? Or are they just there?

Dr. Gorden: Well, they are part of the cell machinery. They are made in the usual way. The proteins are synthesized and get transported to the cell surface. One of the things that I had the opportunity to help explore in Geneva was the discovery that hormone receptors for insulin or growth factor receptors bind hormones; that's one of their functions. Once they bind hormone, they internalize that hormone by a process of receptor mediation and endocytosis, which is very similar to the process that LDL uses to get inside the cell. The difference between LDL and insulin and growth factors appears to be [that] the biological activity of LDL seems to require its internalization, whereas the insulin receptors and growth factor receptors are so-called tyrosine kinase molecules [that] transmit a cascade of signals inside the cells. [If] the receptors are mutated in one way or another, they may not get transported to the cell surface. If it doesn't get transported, then it wouldn't bind insulin, and the patient will be very insulin resistant. They might have huge levels of insulin in the circulation, but it can't act because there is no receptor. The receptor may be defective because a key biologic site may be affected by the mutation. The protein kinase area may be affected by the mutation. All these different potential mutations can cause insulin resistance--we see that in a variety of patients--that go under a variety of names. We even see autoantibodies that are made to these receptors--where the autoantibody essentially blocks the insulin binding site, and in some instance stimulates insulin-like activity causing hypoglycemia itself. In other instances, it seems to desensitize the receptor and cause insulin resistance. We also see a certain kind of regulation; that is, when the insulin receptors [are] expose[d] to high concentrations of insulin, as it is in obesity or in type 2 diabetes, the receptor tends to down-regulate. We now understand that that's driving more receptor inside the cell; that's the phenomenon that's referred to as down-regulation of the receptor. You can see this in vitro and by exposing it to high concentrations of hormone or in vivo when you take cells from patients. So these are things that we've learned by understanding these phenomenon in a laboratory setting, developing the technology to do it, and then taking the proper clinical material and exposing it to this technology.

Dr. Friedman: The down-leveling in receptor deficiency are rarely parallels? If it's down-regulated, they're not working; so it's the same as a receptor deficiency?

Dr. Gorden: Yes. It acts as if there is a deficiency. In other words, the deficiency may be real or apparent; there may be a reversible situation as it is in most obese type 2 diabetics where there is no mutation or anything that prevents the receptor from being inserted into the membrane. It does get down-regulated by the high concentrations of hormone, but once you lower insulin, it reverses. That was one of the things we were able to show experimentally a number of years ago once this technology was worked out. It helps us explain--it doesn't solve the problem how we get patients to do that, but it does help explain what the return of insulin responsiveness is all about.

ISLET CELL TUMORS; MANUFACTURE OF CHORIONIC GONADOTROPIN; DEREPRESSION

Dr. Friedman: I'm changing the subject a little bit. How do ectopic chorionic gonadotropin and its subunits come to be manufactured by islet cell tumors?

Dr. Gorden: I don't really know the answer to that. It would appear that tumors, because of a dysregulation of normally suppressed genetic machinery, are able to make proteins that normally would not be made by that tissue. It seems to be a form of de-repression that's being imposed on the tissue by the malignant state, and so you commonly see things like chorionic gonadotropin--or the subunits more commonly of gonadotropin--made in endocrine producing tumors, such as many of the islet cell tumors. Presumably, this is the phenomenon of derepression.

REFLECTING ON A CAREER IN CLINICAL RESEARCH

Dr. Friedman: Of the various fields of work that you've done, which of them did you enjoy the most, which fascinated you the most, which caused you to want to work on and continue to work the most? Is that a difficult question?

Dr. Gorden: It's difficult in the sense that what you're more successful at--or what you're more independent at--frequently is the thing that excites you the most. Certainly, I've had the good fortune of being at the right place at the right time. For instance, I was in Geneva and a wonderfully equipped laboratory, which was ready to exploit this whole notion of receptor mediated endocytosis of hormones. And, at the same time, the LDL phenomenon had been discovered, as well as EGF [epidermal growth factor]. I had the very good fortune to collaborate with people like Mike Brown and Joe Goldstein, who were working on LDL with Stanley Cohen, who had been one of my professors at Vanderbilt on EGF. It was a time that knowing these people--having worked with them at NIH, or having known them at Vanderbilt--allowed me an opportunity. That was very exciting, but I think that for me the most exciting times have been in the clinical arena when we've been able to work directly with patients, where the science and the interaction with patients go hand in hand. I've always enjoyed clinical medicine. I've always enjoyed being with patients, seeing patients; and those weird opportunities when you really have a chance to do something for somebody is an exhilarating feeling that can only be described when you've experienced it. When you can either tell someone about the course of their disease that is positive and beneficial or that you have elucidated a new mechanism that offers a therapeutic opportunity. When you can do that, then you sort of have vibration between you and the patient; that is a feeling that really, I think, can only happen to people who are involved in clinical medicine or clinical research. I think for me that has been clearly the highlight of everything that I've done.

Dr. Friedman: As the expression goes, it's gratification that money can't buy.

Dr. Gorden: Absolutely.

MAKING THE TRANSITION FROM ACTIVE CLINICAL RESEARCH TO A MORE ADMINISTRATIVE ROLE

Dr. Friedman: I have a question here that you've already answered. I was going to ask you, amongst the things I was going to say is, chief or director, how did you manage to get so many other things done? I mean your research. You give honorary lectures; you've traveled all over the world, and so many other places. One of the things I was going to ask is did you ever have time to make _____? Obviously, you have because you've enjoyed it so much. How did you manage all these things? Or didn't you have much in terms of administrative obligations?

Dr. Gorden: At the very beginning, I had very close connections with the laboratory and the clinical service, which lasts for a certain period of time even when you're physically removed from it. So that there is just a certain lasting quality and an interest that I had. I still had fellows working in the lab, and so I had ties to it intellectually that were very invigorating and very important for me. It's very important taking on an administrative job to be able to continue some form of that clinical laboratory experience that I'd done before, because that really was my interest. Different people handle it in different ways. For me, there was a waning in my ability to continue the activities that I had been involved in from a clinical point of view, so that I really am now ready to come back a bit full circle--back to some of those activities--because I think you begin to lose that edge that helps you maintain them in the beginning. I've worked with some very good people--the administrative people I have worked with and the clinical people.

RETURN TO CLINICAL ACTIVITIES

Learning the latest technology

Dr. Friedman: Before we get into these people--of course, I have a list here of people I want to ask you about. Are you going to be able to get back into research now? Are they going to let you?

Dr. Gorden: [laughter] I certainly have started to get back into some of the clinical activities. The sabbatical was an extraordinarily enriching experience for me and something that I've given some thought to the possibility of doing again--or at least another assignment. I'd like to relearn and retool in some of the technology that really is now cutting edge that is different from the technology that I had worked with, at least in the early states of my career. Genetics has now become front and center in terms of it's importance in both clinical and laboratory research. I think these are the things that I need to retool and sort of increase my store of general knowledge about. I have a chance to do that--to reflect on some of the things that I haven't been able to quite reflect on for sometime, so it's really an opportunity now. It's very hard to know how all this works out. I mean whether it works out to be anything that's terribly useful, but it is exciting to think about.

COLLABORATORS AND ASSOCIATES

Dr. Friedman: Look at what the other guys have done. Leslie DeGroot took off a year from the department in Chicago to study molecular biology--to learn enough to keep up with his staff. Paul Walfish took six months off to do the same thing up in Toronto. So you surely could do that. I was reading over your bibliography again, and there were names I never heard of. I mean a lot of names I knew, but you mentioned Orci from Switzerland. Who was Lesniak? Who were Freychet and Carpentier?

Dr. Gorden: Maxine Lesniak was actually a technician working with Jesse Roth when I first arrived. Maxine is still here in the Diabetes Branch --still very active participant in the Diabetes Branch--and has been involved in doing laboratory research over all this period of time. Pierre Freychek is a very interesting person who is a very close friend. He and his wife are very close friends of my wife and I. He came from Paris as a visiting scientist in 1969 and then went back to Paris after being here for about three years. He was really the person with Jesse Roth who developed the technology for studying the insulin receptor. He was the first to make biologically active iodinated insulin and then found an appropriate tissue to exploit the insulin receptor technology. So we worked on a variety of things together, and then he actually went to Nice to open a whole new laboratory, which was a very unusual thing in Europe at the time as much of academic medicine [was] centered in Paris. When I was in Geneva--because Nice was very close--we had a chance to get back together and to collaborate. Jean-Louis Carpentier was a young fellow in Orci's laboratory from Belgium. He had gone to the University of Liège, and he was the only MD in the lab--most people in the Orci laboratory were not MDs. It was a very basic laboratory--doing morphology and cell biology. He wanted to work with me. He had done some work on fat cells at the time. So we began to collaborate and, as they say, this whole process of endocytosis kind of unveiled itself before us, and he now has gone ahead to develop his own independence in Geneva. He is now professor at the University of Geneva and has just become the deputy dean at the University of Geneva. He was really one of the people that I had the very good fortune of working with and being part of--this very rich group of young scientists who I have had a chance to see develop over the years.

Dr. Friedman: Is there anything in the work you did or in your career you would like to talk to me about, that I didn't ask you?

Dr. Gorden: I think that I've really emphasized mostly the good fortunes that I've had by working with such an extraordinary group of people. One of the fond recollections that I have is a journal club--or a data club that we had when I first came here, in which we had an extraordinary group of clinical associates. In 1968, the clinical associates that we had were Bob Lefkowitz, Harold Varmus, Barry Sherman and Bruce Weintraub.

ON FILLING A CLINICAL NICHE AT THE NIH

I found myself in the midst of an extraordinary group of people that I learned a lot from. I found them to be totally dedicated, very generous. I was able to offer a particular niche, which I think everybody needs to have. Mine was the fact that I knew more clinical medicine than anybody else, and I could use that to bring out the kind of clinical research that we needed to do at that point in time.

AN INCUBATOR OF SCIENCE: THE NIH INTRAMURAL PROGRAM AND THE CO-EVOLUTION OF NETWORKS AND TECHNOLOGY

And so for me, the NIH intramural program was really an incredible incubator of science. It taught me the value of things that I truly didn't understand. I really didn't understand much of the technology that was being talked about. Rodbell was talking about transducers and so forth. Gerry Aurbach was doing the kinds of things that he was doing--having to do with cyclic AMP, and then exporting this to study hormone resistant states--and then to see how the technology then has evolved. Once the genetic technology opened up, it opened a new door. For instance, we had all these patients with insulin receptor defects, but we couldn't study the primary problem until the genetic technology opened up. That happened about 1985 and '86. So at each point in time, you began to appropriate the new technology to apply to your clinical problem. That really, I think, has been the exciting part of seeing that evolution take place. That's really what I've tried to convey in our conversation.

Dr. Friedman: Interesting point. I had dinner with Barry Sherman ten day ago.

Dr. Gorden: Really?

Dr. Friedman: I went out to San Francisco to a Bar Mitzvah, and the fellow whose son it was used to be with Genentech, and Barry Sherman had been his boss, so he invited Barry. We sat at the same table. It was interesting. I had a very enjoyable conversation there.

Dr. Gorden: We saw Barry and his wife, Esther, who we've known for years, in October; they were here visiting, so we had a chance to visit with them.

ENDOCRINE SOCIETY SERVICE AND SERVICE TO THE FIELD OF ENDOCRINOLOGY

Dr. Friedman: The Endocrine Society gave you two awards in the last two years, and, except for working on the editorial board of *JCEM* back in 1970 and '75, I couldn't find much of your contact with the Society. Am I missing something?

Dr. Gorden: No. I think that I have not really been an active member in terms of serving on

councils, but I've certainly participated. In a general sense, I've been an active reviewer for the endocrine journals and certainly an active participant in endocrine research--as the director then at NIDDK. I think that that is another dimension; because endocrine research is really one of the very important bridging types of research that brings together an awful lot of what we do. It's been really exciting to see the quality of research that's carried out in endocrinology. When we look at more diabetes specific things, we see a lot of things, but in terms of some of the best science--in terms of hormone action, the whole explosion of information about hormone receptors, both steroid hormone receptors, cofactors, costimulators, corepressors--all these things that come out of the endocrine science community. One of the things that I have had a chance to emphasize--while being director--to the Congress is that is the only form of treatment we have for advanced prostate cancer is endocrine therapy. It's the discovery of gonadotropin-releasing hormone (GnRH). It's these things that have led to this important clinical activity. Coming from an endocrine background gave me a special pride because as an Institute director I was constantly called upon to explain what we're doing and the value of this research. One of the things I could always fall back on was what was going on in endocrinology, because of the very high quality of investigators and investigations in the field.

FUTURE PLANS

Continuing to uncover etiology and search for therapeutic options

Generating support for research in Congress and the community

Encouraging emerging scientists

Dr. Friedman: So what are you going to do now?

Dr. Gorden: [What] I really need is just a little time to clear my throat and clear my head, but I really have very many of the same interests. Many of the problems and the challenges are not different. I mean we've moved a lot of things very far ahead, but still when you look out there you see that, except for a few diseases, we still don't understand the etiology of most diseases. Even if we do understand the etiology, the therapeutic armamentarium is still quite limited in terms of being specific for most diseases that relate to the general aspects of diabetes and endocrinology. Sure, we have wonderful replacement therapies. If you're hypothyroid, we have a wonderful treatment, but once you get away from that--the ideal treatment--we're really kind of wanting in many ways. So there are lots of things, I think, that are still left to be done. I hope to continue to be challenged and stimulated by some of the patients that I see on the ward. That's what the excitement of science is all about. None of us is ever at an end--in any way at all. We're just simply a conduit that keeps moving through the field--until we make things just a little bit better for people, and I hope to continue to participate in that process in one way or another. I've had the opportunity to try to support science through my actions, both in the Congress and the community, and in trying to stimulate the growth of science, and I have the very good fortune to see the extraordinary growth at NIH that has taken place over the last two or three years. The commitment that I see of the Congress and the administration to doubling the NIH budget is really exciting. Because now we can begin to talk to young people and people

who are interested in entering the field and say, Look there is a real opportunity here--rather than trying to stimulate them into a field where they actually did not believe there is any real opportunity for them. Now, we've got to explain that and get them to believe it and get them involved. I hope to stay a part of that system in one way or another. We've got an extraordinary institute here at NIDDK. We've got Allen Spiegel now, who is a person that I've known since he was a clinical associate, who I had a chance to appoint as scientific director, an extraordinary person. I want to continue to work with Allen and people like him in this Institute and throughout NIH to try to keep some of these things going that I have a vital interest in.

Dr. Friedman: That's great. Very idealistic. Phil, unless there is anything else you can tell me that I didn't have presence to ask you, I want to thank you for the time you've given me. I really enjoyed it. Unfortunately, I wish I could have gotten more out of you.

End of Interview

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