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GERHARD P. BAUMANN, MD

Interview conducted by
Michael Chappelle
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INTRODUCTION

Gerhard P. Baumann, MD, Professor of Medicine Emeritus at Northwestern University, is an internationally recognized endocrinologist and expert in growth hormone biology. Dr. Baumann's clinical research interests include pituitary disease leading to hypopituitarism or hormonal excess syndromes, while his basic research interests are focused on the growth hormone-IGF I axis. Dr. Baumann discovered and characterized the growth hormone-binding protein. His extensive work in the growth hormone field eventually allowed Dr. Baumann and his co-workers to find a mutation in the growth hormone-releasing hormone receptor, which in turn led to the recognition of a new syndrome of dwarfism that can be successfully treated with growth hormone.

BIOGRAPHICAL SKETCH

Dr. Baumann was born in 1941, in Basel, Switzerland. He attended Basel University and received his MD from the University of Basel Medical School in 1967. Upon completing his residency at the VA Hospital, SUNY Downstate, Brooklyn, New York, he completed his fellowship in endocrinology at Peter Bent Brigham Hospital (now Brigham and Women's Hospital), Harvard University, in Boston. He then returned to Switzerland to complete his training in internal medicine at the University of Basel Medical Center and the University of Lausanne Medical Center in 1974. He then went to the National Institutes of Health (NIH) to work with Andreas Chrambach in protein chemistry and the isolation of various molecular forms of growth hormone. In 1977, he joined the faculty at Northwestern University where he continued to do research on the molecular forms of growth hormone, determining which isoforms were artifacts and which were naturally occurring. His pioneering work on growth hormone-binding protein, which turned out to be a fragment of the growth hormone receptor, provided a new window on receptor biology and led to the development of an assay for growth hormone receptor abundance. Currently his ongoing studies include the characterization of genetic growth hormone-releasing hormone receptor deficiency and the evaluation of tissue-specific growth hormone actions. The author or co-author of over 200 scientific publications, Dr. Baumann has been elected to the Association of American Physicians and to the American Society for Clinical Investigation.

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I FAMILY BACKGROUND AND EARLY YEARS

Chappelle: Dr. Baumann, please tell me where your parents were born, and what kind of education did they have?

Baumann: My parents were born in Basel, Switzerland, and they had secondary school education. My mother was a homemaker, and my father was an executive in a firm. Their education was not university, but secondary school.

Chappelle: And when and where were you born?

Baumann: In Basel, Switzerland, in 1941.

Chappelle: Was education a priority in your family?

Baumann: It was a priority, yes. But I didn't have to be pushed; I was interested myself.

Chappelle: What kind of education did you have?

Baumann: Elementary school followed by what's called gymnasium, which is eight years of secondary school, preparatory for university education, and it was called classical gymnasium, which is a school that emphasizes the classics and was one of the best schools available in Basel at the time--still is.

Chappelle: Were you making any decisions at this point about what you might want to be doing later in life?

Baumann: It was at the early phase of my gymnasium time; I was too young to make any such decisions. Later on the decision certainly was to attend university, but exactly what field was not clear at the time, until the later years of my schooling.

II UNIVERSITY OF BASEL (1960-1967)

Chappelle: Why did you choose Basel University?

Baumann: Because it was in the same town, and it was a natural place to go to. This would be standard in the European system, at least in the Swiss system: you go to your home university.

Chappelle: And this was in the 1960s, 1960 to 1967?

Baumann: Correct.

Chappelle: What was life like socially in that period?

Baumann: I lived at home. I went to classes, as everybody else did; it's not a campus situation in Europe, for the most part. So you went to classes, you had a beer with your colleagues at night, and you came home late or early in the morning. It was not campus life, but similar, in a more dispersed fashion.

Choosing a career in medicine *and* science

Chappelle: How did you envision your life as a future physician at that point?

Baumann: Well, I decided to study medicine after entering university because I was interested in science, but I didn't want to necessarily do only science, but have some human contact, and medicine would provide both of these aspects.

III VA HOSPITAL, SUNY DOWNSTATE, BROOKLYN, NEW YORK (1968-1969)

Chappelle: And then you did your residency in the United States. How did you decide to do your residency in Brooklyn, New York?

Baumann: Well, I was interested in coming to the United States or at least go abroad and look at a different system of education. I was looking around for open positions in the United States. I picked the cities, and--not having any particular guidance on where to go or how to go about it--I simply wrote to various places that I thought might be interesting for me in terms of cultural environment and found an open position.

Chappelle: And you were looking at large cities?

Baumann: Looking at large cities, cities that provided enough excitement for me to do things other than medicine.

Chappelle: When you came to the United States, it was the late 1960s; how did that strike you in terms of excitement?

Baumann: Well, the social upheaval in the United States at the time really was not something that I was particularly concerned about, perhaps wrongly so. I just didn't know too much about it. I was basically working in the hospital full-time and really had no major contact with the upheaval that was going on at the time.

Chappelle: And what features stand out about this phase of your training?

Baumann: It was a busy time: learning a lot, taking care of patients day and night, and being in New York, and--when the time allowed--taking advantage of all the amenities that New York permits.

Chappelle: And how did you picture your life as a physician at this point?

Baumann: At that point, I had pretty much decided I wanted to pursue an academic career. I was already interested in endocrinology and most likely would become an endocrinologist.

IV PETER BENT BRIGHAM HOSPITAL, HARVARD MEDICAL SCHOOL (1969-1971)

Chappelle: Then you got a fellowship at Harvard Medical School?

Baumann: Right, Peter Bent Brigham Hospital.

Chappelle: What research were you doing there?

Baumann: I worked in the--George Thorn was the endocrinologist at the time and also chief of medicine, and he was a major mentor and role model in my life. There were several labs under his overall guidance. I worked in Joe Dingman's lab, and that lab worked on vasopressin, or antidiuretic hormone, and I learned my first laboratory techniques in that lab.

V UNIVERSITY OF BASEL MEDICAL CENTER (1971-1973) UNIVERSITY OF LAUSANNE MEDICAL CENTER (1973-1974)

Chappelle: You got a position at the NIH in 1974?

Baumann: Yes. But I went back to Switzerland for two years to finish my clinical training, my general internal medicine training. I went back to Basel and a year at the University of Lausanne to finish that for two reasons. Number one, I wasn't sure whether I wanted to stay in the United States at the time--still sitting on the fence whether that was a good idea or not. I wanted to go home, and also I had a J-1 visa, which--I had to go home because of that.

VI NATIONAL INSTITUTES OF HEALTH (1974-1977)

Chappelle: So when you were at the NIH --

Baumann: After that I decided it would be better for me--for an academic career and for the type of work I wanted to do, namely, a major laboratory career--the environment in the United States would be better. That's when I decided to

come back and do some additional training in the sciences. I became a visiting scientist at the NIH at the time.

Chappelle: Is that when you decided to relocate to the United States?

Baumann: Yes.

Chappelle: Was that a difficult decision to make?

Baumann: It's not easy to leave your home permanently, but what was dominant was the desire to pursue my interests professionally.

Chappelle: Could you say a little more about what the advantages were in the United States at that time?

Baumann: There was more time for academic endeavors, as opposed to patient care. At the time in Europe, it was very difficult as a physician to have enough time to do laboratory research because of the system that didn't allow that.

Working on growth hormone with Andreas Chrambach

Chappelle: What was going on in your field at the time you were at the NIH?

Baumann: Well, in the pituitary field--I was in a lab run by Andreas Chrambach, who was working on growth hormone and different growth hormone forms, molecular forms, at that time. One of the things that he found is that growth hormone comes in more than one form, and in particular that there's a cleaved form that was more bioactive than what we knew as growth hormone at the time. I happened to be in that lab and pursued that line of work during my time at the NIH, and also afterwards.

Chappelle: So Dr. Chrambach--you would call him a mentor for you?

Baumann: Yes.

Chappelle: And what did he teach you?

Baumann: He taught me protein chemistry, a lot of electrophoretic techniques that allowed the separation of these various forms of growth hormone, and just biochemistry in general and techniques applied to biochemistry.

Chappelle: What was he like as a personality?

Baumann: He was a very independent sort and had his own way of doing things but was basically a very freewheeling spirit. He allowed me to do what I wanted to do.

Chappelle: And what research were you doing?

Baumann: Well, I was involved in trying to isolate these various molecular forms of growth hormone, including these more bioactive forms, which in retrospect turned out to be extraction artifacts, but they were interesting extraction artifacts in the sense that they had higher biological activity. So we tried to isolate those. Once it became clear that perhaps they were not naturally occurring forms, it became important to pursue what are the naturally occurring forms. And that led to the identification of these various native, or naturally occurring, isoforms of growth hormone during my subsequent time at Northwestern.

VII NORTHWESTERN UNIVERSITY MEDICAL SCHOOL (1977-PRESENT)

Chappelle: And then you went to Northwestern Medical School?

Baumann: Correct.

Chappelle: What made that position so attractive to you?

Baumann: Well, I was looking around for a university position at the time, and again I wanted to be in a major city. It was a very good environment, a very nice place to be, a very nice campus, great city, and a good position. So that's where I went.

Chappelle: Did you continue with your research on the pituitary?

Baumann: Yes. I continued along the same lines.

Questions, findings, and advancing the field

Chappelle: And what questions were you asking?

Baumann: The main question at the time was: which among these various molecular forms of growth hormone--are artifact from extraction from pituitary, and which are naturally occurring? So we went about--in my lab--extracting large amounts of serum, trying to isolate these various circulating forms, and finding out what is actually not--what has not seen an extraction process, but rather what is natively circulating in blood.

Chappelle: What were your findings?

Baumann: And the finding--one of the main findings, and disappointing finding to some degree, was that this highly bioactive cleaved form did actually not circulate in blood.

Chappelle: Why was that so disappointing?

Baumann: Well, it's always nice to have a more active molecule than a less active molecule. And I think--the thinking at the time was that perhaps growth hormone as we know it--coming from the pituitary--needs to be activated by a process--a proteolytic process in the periphery or in the pituitary during the secretory process in making it more active--similar to, for instance, proinsulin going to insulin. However, that was not the case, it turns out.

Chappelle: How did this advance the field?

Baumann: It advanced the field in actually making clear that growth hormone is more than one substance, that it comes in these various molecular forms, and that there are these native forms that occur naturally. And it sorted out fact from artifact, basically.

Chappelle: Who supported you in this research?

Baumann: This was NIH supported.

Implications of complexity and heterogeneity

Chappelle: Are there further implications of this work and its complexity.?

Baumann: The implications of this work were really--two major implications. One has to do with the measurement of growth hormone in serum--as a diagnostic test. Different labs and different assays give you different numbers. And one of the main reasons for that is the heterogeneity of growth hormone as it circulates in blood and not every antibody or every assay seeing these various forms in the same way. So that's one major implication: the difficulty of coming up with a solid number of what a growth hormone level should be.
The other implication is for abuse of growth hormone among athletes or body builders. The molecular heterogeneity that is naturally occurring is not occurring in injected growth hormone, which is a pure, single substance. So the implication of this heterogeneity for detecting exogenous--or for differentiating exogenous growth hormone from endogenous growth hormone has been used by the anti-doping agencies or is being used in developing assays to detect growth hormone abuse in athletes, and that's currently on-going.

Chappelle: Are you involved in that?

Baumann: I've been involved with the agencies in consulting, yes.

VIII DISCOVERING GROWTH HORMONE-BINDING PROTEIN (GHBP)

Chappelle: Where did these questions you were asking about the complexity of growth hormone lead you next?

Baumann: Well, one of the side products of this whole research was in one or two unexplained components in blood, which turned out to be the growth hormone-binding proteins. The main one was, basically, an unexplained form of growth hormone in blood that was always hidden away in what at the time was called "big growth hormone." Now, big growth hormone is a combination of things--polymers, aggregates of growth hormone--but there also was this complex between the growth hormone-binding protein and growth hormone, which is one component of the so-called big growth hormone. When we looked at big growth hormone there was always this component or this peak on columns that we couldn't explain. One of the thoughts was maybe--after all--this is a growth hormone form that is bound to another circulating protein. And to make a long story short, that's what it turned out to be. Hence, the discovery of the growth hormone-binding protein.

Challenging a dominant dogma

Chappelle: Your discovery [of growth hormone-binding protein] came up against the dominant dogma of the time.

Baumann: That's correct, yes. Peptide hormones were supposed to be circulating in the unbound form, and that was a pretty strongly held dogma by the endocrine community in general and particularly promulgated by Nobel laureate Rosalyn Yalow who--earlier on--had very clearly stated, on relatively weak evidence at the time, that growth hormone bound to a serum protein was almost certainly *not* the case. So this was the prevailing dogma at the time.

Chappelle: What allowed you to see growth hormone-binding protein where others had not?

Baumann: Well, it takes a prepared mind, perhaps, and also the techniques that allow you to separate things. So I had the latter and perhaps the former, too. This unexplained phenomenon was a peak that I couldn't explain--and pursued it, as to its nature, and that's what came out.

Chappelle: Could you outline the critical experiments?

Baumann: Well, one of the critical experiments was to postulate that maybe there is such a binding phenomenon, and let's show whether you can bind growth hormone to serum proteins. It's actually a relatively simple experiment, which had been done before in a more crude way by others: radio-labeled growth hormone incubated with serum, and then you separate it on a column and see whether it

has the same size as before. What happened is that the smaller size of growth hormone was converted to a bigger size after incubation with serum. Now this could be a number of different things, including aggregation, which everybody had thought, That's what it must be. But then we went on and actually purified this component and showed that it's composed of both growth hormone and the growth hormone-binding protein. And there's actually yet another species of growth hormone-binding proteins that are even bigger, so there's more than one growth hormone-binding protein.

Chappelle: How difficult was it for you to get your findings published, and what was the reaction in the endocrine community at large?

Baumann: Well, the publication wasn't that difficult; I think one reviewer rejected it, just based on the dogma. The other two reviewers couldn't really ignore the evidence completely, so it was published. But there was a lot of skepticism for a number of years--whether it was actually a true finding. What helped is that other workers or colleagues, namely, Adrian Herington in Australia had found the same thing and also described the same binding protein in his lab. And there's yet a third one who was involved in the field, Mike Waters, who also had evidence to the same effect. So I wasn't alone in fighting this battle.

Chappelle: Did the reaction that you got surprise you at all?

Baumann: Not necessarily. I knew I was up against a strong dogma. I wasn't surprised.

Chappelle: How did you feel confronting a strong dogma?

Baumann: Well, it's somewhat intimidating perhaps, but it's also fun to debunk existing dogmas. I think the evidence was so strong I couldn't ignore it. It certainly helped me to be recognized for somebody who doesn't back down from a fight.

Advancing the field

Chappelle: How did growth hormone-binding protein eventually advance the field?

Baumann: Well, the growth hormone-binding protein turned out to be a fragment of the growth hormone receptor, namely, the extra-cellular domain that's shed from cells and floats off into the circulation and circulates as a soluble receptor fragment, which contains the binding site for the hormone. This circulating receptor was relatively easy to sample and measure, as opposed to the full receptor, which is on cells and you can't really sample it--certainly in humans--very easily. It gave us a window on receptor biology, or growth hormone receptor biology and growth hormone receptor physiology--how it's regulated and how it functions in various physiological and pathophysiological states. It provided an assay or measurement of growth hormone receptor abundance

perhaps--and perhaps function that would otherwise not have been possible as easily.

Chappelle: What are the diagnostic implications of that?

Baumann: The only really established diagnostic use is in a disease called Laron dwarfism, which is a mutation in the growth hormone receptor. Most of those patients can be diagnosed--other than clinically--the critical diagnostic step would be the absence of the binding protein in blood because the receptor is absent; therefore, the binding protein is also absent or dysfunctional. It's not true for all patients, but for the vast majority.

That's one implication. The other implication is: the binding protein complicates, once again, the measurement of growth hormone. You have to basically--in the assay--take into account the presence of the binding protein and its abundance, or its concentration, and its possible interference in the assay.

A paradox and further implications of GHBP

Chappelle: Does growth hormone-binding protein enhance growth hormone activity?

Baumann: It can. It does two things. In vitro, it's clearly inhibitory; it competes with the growth hormone receptor for binding of the hormone, so it's therefore inhibitory. It also probably acts as what's called a dominant negative player; in the sense that it forms heterodimers with the receptor, and the receptor can only signal as a homodimer, and if there is exchange of the one receptor versus a binding protein in this dimer, that would be a dysfunctional receptor, or a dysfunctional complex that cannot signal. So it would be inhibitory along those lines, also. However, it also prolongs the half-life of growth hormone in serum. There are some experiments showing that if you give enough binding protein you can actually enhance in vivo--in a rat--the effect of growth hormone, probably by a prolongation of its half-life. So it's a complicated situation with both local inhibitory or negative regulatory effects and more global enhancing effects. Exactly where that balance lies in physiology is still not known.

Chappelle: Who were your collaborators in this?

Baumann: There were fellows in the lab--we were pretty much alone at the time--Adrian Herington's and Mike Waters' labs were also working on this. But we were pretty much working independently. So the collaboration was local, not outside.

Chappelle: Are there any implications for growth hormone-binding protein beyond endocrinology?

Baumann: Well, it was the first example of a circulating--I believe it was the first example of a circulating ectodomain of a membrane receptor of the cytokine receptor family. And since, it's been shown that most of the cytokine receptor members have similar cleaved or circulating ectodomains. So it was an example of a much bigger phenomenon.

GHBP and the African pygmy

Chappelle: This new tool you had with growth hormone related binding protein--this was in the mid-1980s?

Baumann: Correct.

Chappelle: Why did you study the levels of growth hormone-binding protein in the African pygmy?

Baumann: We were looking for a number of physiological states where there might be abnormalities in growth hormone receptor biology or function. The Laron dwarf, or the Laron syndrome patient, would be a classical example of somebody who doesn't have a binding protein--there's a genetic defect in the receptor, and therefore a genetic defect in the binding protein. This was the first example. But we were looking at all kinds of short stature and tall stature syndromes, looking for either impaired or enhanced growth hormone action via the receptor. The pygmy was just one of those unexplained short stature phenomena that we pursued in collaboration with Dr. Merimee, who had sera stored from pygmies in Africa. That was a collaboration with him in terms of finding out whether the pygmies actually had perhaps growth hormone resistance based on impaired growth hormone receptor biology. And they do have low growth hormone-binding protein, so they may have abnormal growth hormone receptor expression. However, there are other things in pygmies that also occur and are not explained by this finding. So it's still not clear exactly why the pygmies are short--nutritional effects, growth hormone resistance effects, maybe IGF-I resistance effects--so it may be multifactorial.

The Dwarfs of Sindh

Chappelle: How did you find yourself on a desert expedition to Pakistan in the late 1990s?

Baumann: That's an interesting story--a fun story to tell, actually. One day I received a letter from Karachi, Pakistan by one Hiralal Maheshwari, MD, PhD, who enclosed in the letter a newspaper article entitled "The Dwarfs of Sindh." Now, Sindh is the southern-most province of Pakistan. The article described a village--or two villages, actually--where there was a cluster of very short people. They were all related, and they were all men. It sounded like it was either a genetic problem, or a local problem in the water, or whatever. And he asked me, "Would you like to study this?" It sounded interesting to me. He

included a crude pedigree, and it looked like there might be some recessive genetic trait involved here. So I wrote back and said, “Go to the village and see if it’s true. And if you’re there, see if you can get some blood and send it here,” which he did. He confirmed it. And he actually came himself with the blood samples. And that’s how the long story started--trying to find out why are these people so short, and what’s the genetic underpinning.

We found out from the blood samples he brought back they probably had growth hormone deficiency, so we knew that much. We knew it was probably a pituitary problem, but we didn’t know which one. So we had to go back and get DNA and RNA and study them properly with dynamic tests and so on. We organized an expedition to go to the village, or the two villages, to do all that.

Chappelle: Who funded this expedition?

Baumann: Who funded it? The expedition itself was funded by a Northwestern intramural grant.

Chappelle: What questions were you asking?

Baumann: The question then was--it looked clearly genetic. And it became very clear that this was a recessively inherited disease, and they’re short because there are consanguineous marriages, and only those from consanguineous marriages were actually short. It turns out most of the marriages in those villages are consanguineous at some level--a high degree of inbreeding. So we went there and we did pituitary function tests; we measured their height and BMI and everything, looked at their clinical phenotype in detail. We got DNA, we got RNA, we got cells, and we brought all this back to my lab. And again, to make a long story short, we found a mutation in the growth hormone-releasing hormone receptor, actually the first such mutation in humans--a mouse analogue had already been published. It was a new syndrome that had not been previously described, except a few months before our paper another paper came out from New York describing the same mutation in two patients who were short and of Pakistani descent in New York. So we weren’t quite the first, but almost.

Chappelle: When you were doing your work there, how did the local population react to you?

Baumann: Well, at first they were very skeptical. We don’t want to come as a colonialist and use these people. But thanks to my colleague Hiralal Maheshwari, who was a local, we overcame this very quickly, and they became very cooperative and very friendly. So it wasn’t really difficult on the human level. I think the society, and the mullahs, and the religious leaders were still a bit skeptical, but that was overcome.

Chappelle: What solutions, either therapeutic or social, resulted?

Baumann: Well, these patients, of course, [inaudible] so they have a null mutation in the growth hormone-releasing hormone receptor, which means the brain cannot signal to the pituitary to either make growth hormone, to make enough cells that produce growth hormone, or to release growth hormone from the cells that store it. Therefore, they should respond to growth hormone, and indeed they do: you give them exogenous hormone and they respond perfectly normally. And we tried that. It's not easy to do in Pakistan; at least we were unable to import growth hormone to Pakistan and have a local physician actually take care of these patients and do it properly. The sad story is they're still not being treated in Pakistan. However, since then there have been many other such mutations described in different parts of the world. A very big cluster is in northeastern Brazil, in a town named Itabaianinha--with a similar mutation in the same gene--also inactivating--and the same phenotype, and they're being treated. So first of all, we put this new syndrome on the map so that people could start looking for it. So, many more patients have been found since, and the majority is being treated with growth hormone.

Chappelle: Are there any social solutions being tried in Brazil? Can they be applied there?

Baumann: I'm not sure whether that's happening--they certainly could. What you want to avoid is consanguinity. It's easily said and not always so easily done in certain societies, and we found that out in Pakistan. They understood perfectly what the problem was after we explained it, but the society was not ready to accept a different mode of marriages and so on. I don't know what the future will bring.

IX THE ENDOCRINE SOCIETY

Chappelle: I'd like to ask you a little bit about the Endocrine Society. What are some of the boards or committees that you've served on?

Baumann: I've been on the membership committee. I've been on the JCEM Pfizer jury. I'm currently the chair of that. I've been on the editorial boards of *Endocrinology* and *JCEM* for a total of eight years, [for] each. And I do many ad hoc reviews for journals of the Endocrine Society.

Chappelle: Why have you chosen service on those particular boards?

Baumann: I was asked to join those various boards, so that's why I do it.

Chappelle: In what way has the Endocrine Society supported your professional development?

Baumann: The Endocrine Society has been my home scientifically and also clinically as a place where you can present your work, where you meet your colleagues, and

there is a high standard of science and also a high standard of patient care. So it's been the main scientific home for me.

X CURRENT VIEWS OF THE FIELD

Chappelle: And what are your current views of the field?

Baumann: Of endocrinology, in general? Well, it's still an exciting field. It's a very interesting, cerebral specialty that's very poorly paid for; we're not paid well for thinking, for the most part. So there's some concern about the endocrinologist, at least the clinical endocrinologist, being a vanishing species because reimbursement is very poor. And now funding for scientific work is also very difficult. So there's some pressure on endocrinology currently, but hopefully we'll overcome that.

Chappelle: Okay. Did you want to say more about those issues?

Baumann: No, I think we pretty much covered everything you wanted to hear.

Chappelle: Well, thank you.

Baumann: Thank you, very much.

End of Interview

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Interview History—Gerhard Baumann

Dr. Baumann was interviewed by Michael Chappelle on June 16, 2008, during the Endocrine Society's Annual Meeting held at the Moscone Center in San Francisco. The interview took place in a small auditorium at the Moscone Center and lasted 36 minutes. The transcript was audit-edited by Mr. Chappelle and reviewed by Dr. Baumann 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 one (1) videotape, 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.