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SEYMOUR REICHLIN, MD, PhD

Interview conducted by  
Adolph Friedman, MD  
June 13, 1999

It is recommended that this oral history be cited as follows:

Seymour Reichlin, MD, PhD, an oral history conducted on  
June 13, 1999 by Adolph Freidman, MD,  
The Endocrine Society, The Clark Sawin Library,  
Chevy Chase, Maryland, 2009.

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## **FAMILY BACKGROUND AND EARLY YEARS**

**Dr. Friedman:** This is Dr. Adolph Friedman interviewing Dr. Seymour Reichlin on June 13, 1999. Dr. Reichlin, am I doing this with your permission?

**Dr. Reichlin:** Yes.

**Dr. Friedman:** Suppose we start with when and where you were born, whether you had any siblings, who your parents were, and what your siblings are doing.

**Dr. Reichlin:** I was born in New York City on May 2, 1924, went to Stuyvesant High School, started college at City College of New York. My father and mother both came from a small town in Russia, and my father became an American citizen through serving in World War I. Neither had more than a sixth grade education, but they were, like all the immigrants at that time, very eager to have their children become more educated. I have a brother and had a sister. My sister died of an endocrine secreting tumor of the pancreas, a VIPoma, and my brother is still living and well. He is a World War II veteran and had a number of injuries during the war.

## **MEDICAL TRAINING AND CAREER OVERVIEW**

**Dr. Friedman:** Would you mind telling me about your medical training?

**Dr. Reichlin:** I did my pre-medical training at Antioch College, went in the Army in 1943, and left after a year to attend medical school at Washington University. I served as an intern and resident at the New York Hospital, and resident and chief resident in medicine at Barnes Hospital in St. Louis. In 1952, I went to London to work for two years as a fellow with Dr. Geoffrey Harris, who was then professor of physiology at the University of London at the Maudsley Hospital. While there, I got a PhD from the University of London in neuroendocrinology. Fortunately, I was able to get a Commonwealth Fund fellowship through the influence of Dr. Barry Wood, then chairman of medicine at Washington University.

**Dr. Friedman:** When did you get married?

**Dr. Reichlin:** In 1951.

**Dr. Friedman:** Where is that in reference to when you finished clinical training?

**Dr. Reichlin:** I got married during the last year of medical training and after completing my residency went with my wife to work in London. We had a little kid who was six months old at the time.

## NEUROENDOCRINE RESEARCH AND TEACHING AT WASHINGTON UNIVERSITY

**Dr. Friedman:** When you came back from London, where did you go for work here in the States?

**Dr. Reichlin:** It was very hard to get a job in neuroendocrine research in those days. I wanted to continue working in neuroendocrinology, and that was not a well-defined area of special interest anywhere. The only people who were willing to take me on were Dr. C. N. H. Long, who was at Yale University at the time, and Dr. Edwin Gildea, Professor of Psychiatry at Washington University, who offered me an instructorship at six thousand dollars a year, which one could hardly live on. I got a senior type of fellowship in the Department of Psychiatry at Washington University, which allowed me to continue doing neuroendocrine research. Dr. Gildea recognized that there might be some importance of neuroendocrinology in understanding psychiatric illness.

**Dr. Friedman:** What years were you there?

**Dr. Reichlin:** I was at Washington University on the faculty from 1954 to 1961.

## CAREER OVERVIEW

**Dr. Friedman:** And then what did you do?

**Dr. Reichlin:** I left to become head of endocrinology at the University of Rochester. I was at Rochester until 1969, when I left to become head of the Department of Medical and Pediatric Specialties in the new medical school at the University of Connecticut. I was there for only three years. In 1972, I resigned as head of the Department of Medical and Pediatric Specialties and became the head of the Department of Physiology. I then decided to go back into clinical investigation when Dr. Edwin B. Astwood, who was the chief of endocrinology at the New England Medical Center, resigned, and I took his job in 1972.

## EARLY INTEREST IN NEUROENDOCRINOLOGY

**Dr. Friedman:** Let's back track a little bit, and tell me about your research and the scientific work that you did in each of these periods when you went from one place to the other.

**Dr. Reichlin:** Well, I first became interested in neuroendocrinology when I was still a medical student. During the second year of medical school, I heard a lecture by a professor of neurology, Dr. Irwin Levy at Washington University, who told us about the work of Hans Selye on stress. This would have been 1945. I was so excited about that work that I decided I really wanted to work on it, and in 1946 and 1947, as a medical student, I began to see whether I could find the center in the brain which regulated ACTH. One of my classmates, Dr. Frank Norbury, suggested that this could be done by making various lesions in the hypothalamus. I did that work in the laboratory of George

Bishop and James O'Leary at Washington University, who were at that time extremely well known neuroscientists. But it was a very difficult time for such studies because, for example, there was not even a rat stereotaxic instrument in the department, and the animal care conditions were terrible. There was no air conditioning, and I was doing my work in St. Louis in the summer time. So that any work on stress was markedly overshadowed by the laboratory environment and environmental stress. Nevertheless, I just started doing hypothalamic lesions freehand and looking at adrenal test responses.

**Dr. Friedman:** I think at that time, the only stereotaxic instrument was at Yale. I think they had one at Yale at that time.

## **NEUROENDOCRINOLOGY: STATE OF THE ART, 1948**

### **Krieg-Johnson stereotaxic instrument**

### **Studying adrenergic control**

### **Internship and residency at New York Hospital**

**Dr. Reichlin:** Yes, there was the Krieg-Johnson instrument, which was the one that everyone used at that time. I do not think that was even available when I started that work. I started doing research in neuroendocrinology in the summer of 1946, I believe, and I ended up doing a study of adrenergic control using blocking agents. It was easier than hypothalamic lesions. That was very exciting, and I decided that was the area I wanted to work in. So even though I was in clinical training, I kept following the literature, and the year I graduated, Geoffrey Harris wrote a review in *Physiological Reviews* summarizing all of the evidence that linked control of the pituitary to the hypothalamus. It was then, and it still is, the best review of the state of the art in 1948. Also in 1946, two years previously, George Sayers and Marion Sayers, his wife, had published a paper in *Recent Progress in Hormone Research*--I think it was in the second volume--in which they described the adrenal stress response and the feedback control of that. Very close to that time, Dr. Charles Sawyer and Dr. J. E. Markee reported the effect of pentobarbital on ovulation in the rat, showing that if you anesthetize the rat at a critical stage, you would block ovulation. So that fascinated me. I decided I wanted to get training in endocrinology, and after I finished medical school, I took my internship and later a residency at New York Hospital in New York. By coincidence, Dr. Harris was giving a lecture at the old Downstate Medical School, then called the Long Island Medical College. I went over and heard him speak, and I was very impressed by his presentation. He was talking about the effect of electrical stimulation of the brain on adrenal function inferred from lymphocyte counts. This is an idea of where we were at, at the time. I talked to him about going over to England as a fellow. I was very flattered because he had actually read my paper. Dr. Harris was the man to work with because of the quality of his presentation. It was quite a wonderful experience to have someone present the material in such a thrilling way and to turn you on.

**Dr. Friedman:** And to inspire you.

**Dr. Reichlin:** Yes, and to actually know the time that it took place, really very exciting.

**FELLOWSHIP WITH DR. GEOFFREY HARRIS**

**Measuring thyroid function and stress in rabbits**

**Monte Greer's experiments in Astwood's lab**

**Dr. Friedman:** Where did you go from there?

**Dr. Reichlin:** I went to London, worked for two years, and worked with another two or three people besides Dr. Harris. Their group--Keith Brown-Grant, particularly, who was a graduate student and Dr. Harris--had already developed a device for measuring thyroid function in rabbits by doing serial counts of the thyroid gland after injecting radioactive iodine. The method was to inject rabbits with radioactive iodine and then measure the uptake and clearance of radioactivity from the neck. Radioactive iodine is incorporated into thyroid hormone and leaves the thyroid gland at a constant rate. You could plot a semilogarithmic curve and predict the rate of release of labeled hormone from the gland. Changes in the curve, either an increase in rate or a slowing of release, could be interpreted as changes in thyroid function. We showed that emotional stress markedly inhibited thyroid function, that cold exposure stimulated thyroid function. Harris prepared rabbits with a section of the pituitary stalk, using his very fancy approach, including putting a piece of waxed paper between the hypothalamus and pituitary to prevent regeneration of the portal vessels. And we showed that stalk section inhibited the thyroid and blocked stress responses. Now, I believe that the stress response we were studying was actually due to somatostatin, but, of course, that is another story. But at the time, we inferred that it established the fact that there was a neural control of the pituitary and led to the postulation that there was a thyrotropin-releasing factor [today called thyrotropin-releasing hormone (TRH)]. I should mention that at almost the same time while I was in London, Dr. Monte Greer did essentially a similar experiment, working as a postdoctoral fellow in Astwood's laboratory. He was using rats that had hypothalamic lesions placed with a stereotaxic instrument that was manufactured for them. He showed that lesions of the hypothalamus in rats inhibited the development of goiter when the rats were fed with goitrogen. I think that work was published in the same year or within a year of the time that we were doing the work in Harris laboratory.

**Dr. Friedman:** I left Astwood in June 1949, and at that time Monte was going down to Yale to learn how to use the stereotaxic instrument.

**Dr. Reichlin:** So that fits very well. That was 1949?

**Dr. Friedman:** Yes, June 1949. That is how I knew that they had one there.

**Dr. Reichlin:** I still have that very instrument. I took it with me when I left Boston and kept it as a souvenir of the time. I should give it to Monte. It really belongs to him. There was no one at the New England Medical Center who had any interest in this except Monte. He developed the whole thing himself. However, there had been a number of papers before that suggesting that the brain controlled the thyroid. I reviewed all of that

literature at one time and found that Dr. J. Howard Means had come to the conclusion that the brain controlled pituitary TSH secretion. In the first edition of his textbook, he outlined the evidence to support the idea that the brain controlled the pituitary and controlled the thyroid. Of course, they had it totally wrong at the time because he thought it was important for pathogenesis of Grave's disease, but now we know that has nothing to do with Grave's disease. Anyway, that is an interesting separate story. So Monte's work was very original, and he deserves a lot of credit for that because he started that work all by himself.

**Dr. Friedman:** Monte worked alone.

**Dr. Reichlin:** Yes, he worked all by himself, and what he got from Astwood was the model of propylthiouracil-induced goiter. Monte was not a trained neuroendocrinologist; he was a trained thyroidologist. In my case, I went to London to work with an established group, so there was a difference.

### **JOINT APPOINTMENTS AT WASHINGTON UNIVERSITY: DEPARTMENT OF PSYCHIATRY, THE ENDOCRINE CLINIC, AND PREVENTATIVE MEDICINE**

#### **Demonstrating hypothalamic control of the pituitary**

**Dr. Friedman:** Continue on from there, chronologically.

**Dr. Reichlin:** Okay.

**Dr. Friedman:** Unless you want to stop and rest.

**Dr. Reichlin:** No, it is easy. In Harris's lab, we showed that the brain controlled pituitary secretion. I went back to Barnes [Hospital]; as I told you, I could not get a job as a conventional anything, so I went as a senior post-doctoral fellow at the Department of Psychiatry at Washington University. The chairman then was Dr. Ed Gildea, who was an organically minded psychiatrist. He himself was well known because he worked with Dr. Evelyn Mann and Dr. John Peters to do the first thyroid hormone test at Yale. And he thought that working on hypothalamic control of the pituitary had something to do with psychiatry. He was willing to bet on that. At the same time, I had a joint appointment in Medicine, and I ran the Endocrine Clinic, and I also had a joint appointment in Preventive Medicine. So I was teaching in three departments [and] doing research in neuroendocrinology. In those early years, I tried to show in rats--in a more definitive way--a mechanism of control. I did hypothalamic lesions--repeated Dr. Monte Greer's experiments--and then went on to show that fundamentally the effect of the hypothalamus was to alter the set point for feedback control and--in that period of about four years--attempted to isolate thyrotropin-releasing factor, develop an assay for thyrotropin-releasing factor but only got so far as to have an active preparation from hypothalamic tissue.



**Dr. Friedman:** Did you actually isolate it?

**Dr. Reichlin:** No, no. I did not isolate it.

## **THYROTROPIN-RELEASING HORMONE AND THE EMERGENCE OF MODERN NEUROENDOCRINOLOGY**

### **The work of Roger Guillemin and Andrew Schally**

**Dr. Friedman:** Who isolated it?

**Dr. Reichlin:** Taking into account the physiology and the biological activity of hypothalamic extracts, Dr. Roger Guillemin, who had initially questioned the idea that the brain controlled thyroid function, thought there was enough information to really go after TRH, thyrotropin-releasing factor. He had been unsuccessful in isolating corticotropin-releasing factor. He and Dr. Andrew Schally had worked on that for a long time. And so--sometime I guess in 1964, 1965--Dr. Andrew Schally and Dr. Roger Guillemin both began in earnest to try to isolate the thyrotropin-releasing hormone. There were other claims. There was a claim from Japan by a man named Dr. Shibusawa--I repeated his work and could not confirm it--and from Czechoslovakia by a scientist named Dr. [Vratislav] Schreiber, who also claimed to have some biological activity. But none of that was as important as the work of Drs. Guillemin and Schally, both of whom succeeded in getting an active, highly concentrated compound, probably in late 1966, early 1967. That is part of the story that is written up in Nicholas Wade's book, *The Nobel Duel*. I also have reviewed the history of that time in the *Annals of the New York Academy of Science* as the introduction to a symposium on TRH.

**Dr. Friedman:** Would you be interested in donating any of these pieces of literature to The Endocrine Society?

**Dr. Reichlin:** Yes. I have a lot of my correspondence with Dr. Roger Guillemin at the time.

**Dr. Friedman:** You are safe; I did not record the fact that you said you were going to give it to us.

### **Establishing that the brain controls the pituitary and secretion of GH**

**Dr. Reichlin:** Okay, I will give it to you, but the journal is here. I was doing physiology that established firmly that the brain controls the pituitary and that the brain controls growth hormone secretion. Dr. Joe Martin, who was one of my fellows, stimulated the hypothalamus. A great deal of information had been obtained which made it a certainty that the brain controlled pituitary-thyroid function. These included studies of hypothalamic lesions, electrical stimulation of the hypothalamus and pituitary stalk section. To nail it down, however, and convince the skeptics, it was necessary to isolate and characterize the actual chemical mediator. And that is what was accomplished in the laboratories of Guillemin and Schally.

**Dr. Friedman:** Well, I talked to Dr. [Elwood] Jensen this morning about receptors. We can work back to the first if necessary.

### **Dissension and controversy surrounding the work of Guillemin and Schally 1968 TRH Conference, Tucson, Arizona**

**Dr. Reichlin:** This is a very long and fascinating story. It took a whole book by Nicholas Wade to delineate it. But by 1967, despite the effort of Andrew Schally and Roger Guillemin and expenditure of large amounts of money--in those days, very large amounts of money--there was no evidence of a chemical entity that could be called a releasing factor. The personal antagonism between Roger Guillemin and Andrew Schally had created a great deal of dissension in the endocrine community. A lot of people thought that they were disgraceful, and they did not believe their work. At that time I was in the Endocrinology Study Section with a number of other people, Sam McCann, Irving Geschwind and Joe Meites, who represented--you could say--the neuroendocrine community. The other members of the study section thought it was unproved and possibly nonsense. Roger came with a request for an additional, I think, hundred thousand dollars to pay for hypothalamic tissue that had been lost on a column. So a number of the members on the study section were in favor of pulling the plug on the research and not giving him the money. But the neuroendocrinologists of the group made a successful plea that we have a conference at which Roger and Andrew Schally would be obliged to present their best proof that they had something and for me to write the grant request to the NIH to support the conference. I had the additional task of getting Andrew and Roger to come to the meeting at the same time. They had a personal animosity at the time, and they also did not want to reveal where they were in their research. They did not want to give the other side an advantage. We also decided to invite some established peptide chemists who would critique the peptide work of Dr. Guillemin and Dr. Schally. The only person who I remember who was specifically assigned that task was Dr. John Potts, who had recently sequenced parathyroid hormone. John was called in as the external chemical observer, and Andrew and Roger gave the presentation. All of this was presented at a conference in 1968 at the Tucson Inn, Tucson, Arizona. Dr. Geoffrey Harris came and discussed the physiological evidence, and at that time both Drs. Guillemin and Schally revealed their knowledge that TRH was made up of three amino acids. At one point, they thought that this was only a partial fragment of TRH. Both agreed that the three amino acids were glutamic acid, proline and histidine. Dr. Schally had already--in the year previously--made all peptides in all three combinations, histidine, proline and glutamic acid, none of which were active. In 1968, it was very clear that TRH had only three amino acids. Dr. John Potts made the suggestion that it might have an amidated terminus, which is the case for a number of other physiological peptides.

### **Synthesizing TRH and confirming structure by iteration**

Dr. Potts suggested that if they would amidate their tripeptide, they would produce an active compound. Both Guillemin's group, including Roger Burgus, and Schally's group, including Karl Folkers and [Franz] Enzmann, went at trying to make an active TRH compound by treating a tripeptide with an acetic anhydride, which amidated the

terminus but also cyclised the glutamic acid, so they ended up with pyroglutamic acid, histidine and proline. But they did not know that they created that. They did not know the chemistry. They got an active spectrometry, which enabled them to confirm its structure.

TRH is unique amongst all other peptides that were ever isolated; in that, the structure was not obtained from the material but was obtained by a process of iteration.

**Dr. Friedman:** I-t-e-r--

**Dr. Reichlin:** I-t-e-r-a-t-i-o-n. They synthesized a number of model compounds. After that, they had an active compound made by iteration; they then were able to go back and show that the compound was the physiological material. So it is an absolutely unique situation for peptide chemistry. Meanwhile, Folkers's group had done much of the same. They got the structure of TRH, also. As outlined in Nicholas Wade's book, Folkers patented the compound without Dr. Andrew Schally knowing, which is absolutely fascinating. So the patent for TRH went to people who came in very, very late in the process, and who only had an indirect interest in the physiology of the compound.

**Dr. Friedman:** How do you know?

**Dr. Reichlin:** This is written up in Nicholas Wade's book.

### **Advancing the field and clinical applications**

**Dr. Reichlin:** What happened with this discovery is that every one of the releasing hormones was identified chemically, synthesized, a receptor isolated, and structure identified. Every one of these compounds has been put into clinical practice, one way or another. A series of analogs have been studied and the use of the hypothalamic hormones has become an essential part of endocrine diagnosis and endocrine care. Most important is the LHRH, which has been used extensively now to control gonadotropic secretions in infertility. These are all outgrowth of the tremendous studies that were initiated by proof of TRH structure.

## **REICHLIN'S CONTRIBUTIONS TO NEUROENDOCRINOLOGY**

### **Pioneering physiological studies of hypothalamic compounds**

#### **Proving the presence of a growth hormone-releasing factor in the hypothalamus**

#### **First to demonstrate prolactin-releasing factor**

#### **Clinical investigations**

My own work has been largely, over the years, to do physiological studies with hypothalamic compounds. We were among the first to prove that there was a growth hormone-releasing factor in the hypothalamus and first to show a prolactin-releasing factor. We did a lot of clinical investigation introducing the various compounds into clinical practice. If you want to see what the status of the field was in 1963, I wrote a review in the *New England Journal of Medicine* in 1963.

**Dr. Friedman:** That is about thirty years old, then.

**Dr. Reichlin:** I was invited by Les DeGroot, who at that time was an associate editor of the *New England Journal of Medicine*.

**Dr. Friedman:** Yes.

**Dr. Reichlin:** Thirty-six years ago. I think, if you want to go back and look at that, you will see a very clear statement of what was known and not known. None of the hypothalamic hormones had been identified.

### **WIFE'S PROFESSION**

#### **DR. WILLIAM DAMESHEK, FATHER-IN-LAW: ORIGINATOR OF THE CONCEPT OF AUTOIMMUNE DISEASE; PIONEER IN THE USE OF IMMUNOSUPPRESSANTS IN ORGAN TRANSPLANTATION**

**Dr. Friedman:** We have a little bit more room on the tape. One of the things I did not ask you about is, does your wife have any professional activity?

**Dr. Reichlin:** My wife is a professional archivist. She is the daughter of a very famous clinical investigator. Her father was Dr. William Dameshek, a hematologist, and he was a very marvelous man, a very wonderful father-in-law. He wanted very desperately for me to go into hematology.

**Dr. Friedman:** Of course.

**Dr. Reichlin:** He had many, many original contributions.

**Dr. Friedman:** I remember when I was with Astwood; he was next door.

**Dr. Reichlin:** Dr. Dameshek originated the concept of autoimmune disease. He was the first person to treat autoimmune disease with 6-mercaptopurine, an immunosuppressant, which led directly, in work he did with Dr. Bob Schwartz, to organ transplantation. In the Nobel address that was given by Dr. [Joseph] Murray, who was the first to do a successful kidney transplant, he acknowledged that a kidney transplant of nonrelated donors was only possible through the development of immunosuppressants by Dr. Schwartz and Dr. Dameshek. This was really a major step. Dr. Dameshek was an excellent scientist and medical politician, who founded the journal *Blood* and edited it for twenty-six years. He founded the American Society for Hematology. My wife has never been interested in medicine.

## **CHILDREN'S CAREERS**

**Dr. Friedman:** I knew that. What about your children?

**Dr. Reichlin:** None of them are interested in medicine. One of them is an artist who teaches at a university. One of my sons got a PhD in sociology, but works as a marketing director for a large publishing company, and I have another son who is in the export-import business. So none of them went into medicine or endocrinology.

**Dr. Friedman:** Thank you very, very much. I appreciate you giving me the time, and I hope you will still send me some of these critical reviews if you have copies of them and also your CV.

End of interview

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