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ROGER GUILLEMIN, MD, PHD

Interview conducted by
Michael Chappelle
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INTRODUCTION

Roger Guillemin, MD, PhD, is Distinguished Professor at the Salk Institute for Biological Studies. His pioneering research proved the hypothesis of Geoffrey W. Harris that the hypothalamus releases hormones to regulate the pituitary gland, thereby, laying the foundation for the field of neuroendocrinology. Among the hypothalamic hormones that he and his colleagues discovered, isolated, analyzed, or synthesized were thyrotropin-releasing hormone, growth hormone-releasing hormone, and somatostatin. He was first to isolate the endogenous, opiate-like peptides in the brain, which he named endorphins. His studies of cellular growth factors, inhibin, and activins led to the recognition of multiple physiological functions and developmental mechanisms. The impact of Dr. Guillemin's research has been profound for a variety of diseases and disorders, including thyroid diseases, growth deficiencies in children, problems of infertility, eye disorders, diabetes, and several types of tumors.

BIOGRAPHICAL SKETCH

Dr. Guillemin was born in France in 1924. He began his medical studies in German-occupied France during World War II, studies which were interrupted when he became active in the French Resistance. Following liberation and the war's end, he received an MD degree from the Faculty of Medicine at Lyons. Dr. Guillemin briefly practiced medicine before joining Hans Selye as a research assistant at the University of Montreal in 1949. With Dr. Selye, he conducted studies of mineralocorticoids on hypertension in rats, efforts that led to a PhD degree in physiology in 1953. At Montreal, he became interested in the physiological mechanisms involved in the hypothalamic control of adenohypophysial secretions, making his first contribution to the field of neuroendocrinology by demonstrating that the ultimate mechanism triggering the release of adrenocorticotropic hormone (ACTH) was not histamine. In 1953, Dr. Guillemin was recruited to the Baylor College of Medicine in Houston, where he taught physiology and continued studying the release of ACTH. At Baylor, he began working with biochemist Walter Hearn in the search for the hypothalamic hypophysiotropic substances. When Walter Hearn departed for Iowa State University in 1957, Andrew Schally replaced him in Dr. Guillemin's group, and they collaborated over the next five years in pursuit of the ACTH-releasing substance. In 1960, Robert Courrier recruited Dr. Guillemin to the Collége de France in Paris. While in France, Dr. Guillemin maintained his Baylor laboratory, commuting between Paris and Houston. In the Paris laboratory, he began working with Marian Jutisz, and together they produced solid evidence for the presence of a luteinizing hormone-releasing factor (LRF) in hypothalamic extracts and reported its early purification by gel filtration and ion-exchange chromatography. In addition, they produced the first incontrovertible evidence of a thyrotropin-releasing factor (TRF) in hypothalamic extract. Dr. Guillemin left the College de France in 1963 and returned to Baylor on a fulltime basis. During the early-1960s, his group continued their efforts to purify both LRF and TRF. In 1965, Roger Burgus joined the group, and Dr. Guillemin decided to concentrate his team's efforts solely on isolation of TRF. In 1968, he at last achieved the isolation and characterization of the first hypothalamic hormone, TRF. Dr. Guillemin moved his laboratory to the Salk Institute in La Jolla, California, in 1970. At the Salk Institute, he reopened the LRF project, and succeeded in isolating and sequencing ovine LRF in 1971. The following year, his group isolated a third hypothalamic hormone, which he named somatostatin. Among Dr. Guillemin's numerous other achievements were the isolation of the first endorphin and his pioneering studies with fibroblast growth factors (FGFs), inhibin, and activins. In 1989, Dr. Guillemin retired from the Salk Institute to become Distinguished Scientist at The Whittier Institute for Diabetes and Endocrinology in La Jolla, California, becoming its director in 1993. Dr. Guillemin retired from the Whittier Institute in 1994. After three years as an adjunct professor at the University of California, San Diego, Dr. Guillemin rejoined the Salk Institute as Distinguished Research Professor. Dr. Guillemin is a member of the National Academy of Sciences, the Association for the Advancement of Sciences, and is a past president of the Endocrine Society. In 1977, Dr. Guillemin received the Nobel Prize for physiology or medicine, which he shared with Andrew Schally and Rosalyn Yalow.

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I. FAMILY BACKGROUND AND EARLY YEARS

Chappelle: Dr. Guillemin, would you please tell me a little bit about your family background.

Guillemin: Well, sure. My parents were very simple people, to put it simply. They were not intellectuals. My father actually had gone to a school for technical handling of mechanical equipment and so on, and he remained in that field all of his life. His father, my paternal grandfather, was a rather unusual man who had invented the very first machines to automatically install rivets. He actually had gotten several patents for those machines, and he created a small company, which started manufacturing all this equipment. My father was involved with all of this practically all of his life. The grandfather in question was a rather handsome man as I remember him. I also remember that he was deaf as a table, supposedly having been slapped on the head by one of the ulans in the War of 1870, which the Germans won over France at that time. He was very active in sports and, unbelievable to me, he was world champion of boxing, what was called the *savate*, the French boxing with not only the fist but also the back of the foot. And he was really handsome and a very pleasant person. My mother--from her side--came from the northern part of Burgundy where they--what's the best word--had some fields.

Chappelle: Wine?

Guillemin: No, there were not vineyards, even though my paternal grandfather was for many years of his life in the wine business. He was selling wines throughout the country place. I do remember as a child going with him, and the horse--they were in a carriage with one horse--and very often it was the horse who came home, who knew the way to bring everybody back home. [laughs] But my father--actually on his own--read quite a few books and had a couple of nice bookcases, and that's where I started reading the French literature as a child until I went, of course, to the local schools--elementary school and high school--the structure of early education in France was somewhat different from what we have had in this country. But we had more or less the equivalent of K-16, if you wish. Then I got my baccalaureate degree out of that; actually, I got two successive baccalaureates: one in general education, and the other in so-called science, B-S-C (Bsc). Then, having gotten that far--I would have been seventeen or so--I hesitated between going to medical school--because I was interested in medicine--or going to engineering school because I always was interested in doing something with my fingers; in fact, I built early radios and this sort of thing like all the other kids. I had a small microscope; I collected plants. At that time the tragedy was that--we are now in 1940, 1941, or so--the war, which had started in 1939, 1940--the French had lost; the Germans were occupying France. Dijon was part of the severely occupied part of France, out of which we couldn't travel: it was against the law--which the Germans were

running--to go anywhere. [If] you were in Dijon, you had to stay in Dijon. You needed a special pass to go out, and the German commandant would [have to approve]. In fact, some of these earlier radio [sets] that I had made--I had a small transmitting station, which I had actually been setting on the frequency that the German planes were using--Dijon had a major air field, which the German army air force, Luftwaffe, was using. I managed to use my small station to actually disturb their radio communication. A friend and neighbor of mine, who was also doing it, got arrested by the Gestapo; I had to be careful about that. I stopped it at that time.

Participation in the French Resistance

Chappelle: Would you discuss your participation in the French Resistance?

Guillemin: Well, yes. At that time the French government of Vichy, in collaborating with the Germans, had decided that all young people between eighteen and twenty would receive an order from the German side, forcing us to go to do some labor in Germany on some ammunition plant. And sure enough, one day all the young people--the few of us in medical school and I--we did receive our marching orders to go to the station with a couple of days of eating and food and mattress or comforts for a two-day trip. We were supposed to go to somewhere in Southern Germany. So we, the young people, we talked about it and most of us decided just to tear up the thing and disappear in the underground, which is what I did, and against all the rules. But I should say that, in those days, I spoke German absolutely fluently, which I had learned in the French school. You had to--besides Latin and Greek--you had to learn a foreign language, and my mother had decided that I should learn German rather than English, so I did. I repeat; I spoke German absolutely fluently; in fact, with some sort of a southern accent of Germany--because there is such a thing as northern spoken and southern spoken--because the teacher I had came from Bavaria. And I decided, after having torn up my marching orders, that I would go to a place in the Jura mountains, near the town of Besançon, where I suspected--I did not know for sure--but I suspected that some friends of mine where involved in the underground, and that I would, of course, participate.

So I took my bicycle and went on for about one hundred and fifty miles--to go there up in the mountains. I was stopped by the German patrols on two occasions, was thrown in jail on those two occasions, *but* since I spoke German I was able to tell them some sort of a story and I got out. Eventually, I arrived in this place near Besançon where there was the beginning of an underground camp. The face of it [cover] was that this was a Red Cross station to receive children which were evacuated from the suburbs around Paris because of the bombardments of the [industrial] plants over there. We had about one hundred children whom we were taking care of, *but* this was *actually* a major passage point of the underground: whereby, we would get people whom we managed to pass through into Switzerland, which was quite cooperating. We had American

and British pilots, or airplane people, who had been shot down, who somehow had survived the whole thing, and were trying to get back to the side of the Allies. We also had people--I remember we had this one member of the Vichy government who had decided that he wanted none of this anymore and that he wanted to reach [Charles] de Gaulle in London. We had him--took care of him, and put him on his way to Switzerland. That very same day, a couple of hours after we had sent him to his [destination], the whole camp was surrounded by a couple of hundred German soldiers with tanks and everything; they had gotten wind that there was something going on there. And here again, the fact that I spoke German allowed things to go relatively smoothly.

Later on there was some sort of a skirmish between the American Fifth Army, which was beginning to come up north and that came around and the Germans were still there, and I was wounded actually. One shell exploded too close to me, and I still have--to this day--a scar in the back of my skull. I was completely out for several days, and then I recovered out of it. The worst part of it is that ever since that day I still have a tinnitus--I have a hearing--I have a noise in my head, which is probably due to some minor scar of the meninges or something.

Resumption of medical studies after the liberation of France

After that I came back to Dijon--after the liberation--and started again my medical studies, my medical school, eventually to get my degree. The medical education was five years from after the baccalaureate, as I remember. The French system was such that once you had done all the internship and so on and passed the examination of your fifth year, you could practice medicine in France, with some minor restrictions. But to get the MD degree you still had to defend a dissertation, a thesis. So short of that, I decided that I would start practicing medicine. And sure enough, I was the physician of a small town in Burgundy called Saint-Seine-l'Abbaye, north of Dijon, and I was a physician there for over a year. It was wonderful in many ways--in terms of the responsivity of the people. In those days, the two most important people in a small town were the priest and the doctor--and I never had much of anything to do with the local priest. But being in charge of all these people was actually very touching. I was a GP: I did everything, delivering babies and so on. But really it takes a great deal of generosity to be a good practicing physician, and maybe I was not generous enough. But also in the back of my mind, I always wanted to do some laboratory research because I always liked to look into new things.

Meeting Hans Selye and beginning a career in research

One day, totally by chance--I have forgotten the details of it--since we had been completely cut off from the outside world during the war and during the occupation with the Germans--one day, somehow, I learned that this man

called Hans Selye, whose name I recognized because in my medical studies some of my early teachers were interested in the beginning of endocrinology and his name had come up. Well, I heard that Selye was coming to Paris to give two or three lectures on his new discoveries regarding what he called stress: the stress of life, the stress of disease, and what he called the general adaptation syndrome. So I went to Paris for a couple of days. I listened to Selye and I couldn't *believe* what I was hearing; it was so extraordinary! He even had some colored slides on the screen, which I had never even heard of. It was really very interesting. He described how, in response to stress, the organism always stimulates the adrenal cortex-secreting steroids and that somehow the pituitary gland was involved, but he still didn't know the mechanism, and that was something to be investigated in the future. So after his second lecture, I went to talk to Selye and I told him I was a young practicing physician, but I would like to do research in a laboratory and that my easiest approach would be to ask if I could somehow spend a year in his laboratory and at least write something for a dissertation. He was himself an MD from Europe, so he knew what I was talking about, and he had just moved from McGill to the French-speaking University of Montreal, and since I didn't know a word of English in those days, it was an ideal way for me to go where I would also learn English. Sure enough, Selye said, "Okay, do come by; we will organize something and out of my private money from the American research"--it was the NIH--"I will give you a monthly allowance of one hundred and twenty dollars a month," which I thought was superb--which it was in many ways.

II. UNIVERSITY OF MONTREAL (1948-1953)

Guillemin: So I went to Montreal--to Selye's laboratory at the University of Montreal--and I started doing some research in the laboratory in the field on a subject that he had given me, which was essentially to keep animals--rats--keep them alive after removing their kidneys to see--and give them a steroid which had become recently available, which was desoxycorticosterone acetate, a mineralocorticoid--to see if it would generate hypertension or not, since Selye had a theory, whereby, these mineralocorticoids would so modify the kidney that it would produce more and more of this molecule, which was to be isolated a few years later which is called angiotensin, which contracts the small vessel and elevates blood pressure. So I did those studies. I learned in the laboratory how to do all of this--surgery in the small animals and so on. Eventually, out of this, I got a dissertation, which I presented. I went back to France and presented the results of this research to the university in Lyon--because Dijon was still what, in those days, was called a medical school versus a medical *faculté* in Lyon, which was a much larger town and a higher academic standing, so to speak. So eventually I presented those results and I did obtain my MD degree, *formally*, from the University of Lyon: that was 1949. But, meanwhile, I had been so attracted to what was going on in the laboratory with Selye--and I had starting learning enough English to also take courses at McGill University--that I went back to Montreal--I dropped the practice of

medicine in Burgundy--and I went back to Montreal and registered for a PhD degree in physiology--it was called Experimental Medicine and Surgery--under Hans Selye at the University of Montreal, with combined courses between McGill and the University of Montreal. And sure enough, in 1952--four years later--I did receive a PhD degree in experimental physiology from the University of Montreal.

That would have been a relatively simple way of life except that something very dramatic happened in 1951 or so. Three of the young people in Selye's group--who were coming from young people from all over the world wanting to study and learn under this man--three of us became acutely ill with tuberculosis, TB. We never knew exactly what was the origin of that. There were some monkeys in the animal quarters whom we found out later had been sick, and it is quite possible that there was some contamination somehow involved; I repeat, we never knew exactly how the three of us got this acute infection. One of us died relatively shortly, another one had to have a lobectomy, and in my case--good God! I was diagnosed with TB meningitis, lung infection. When I saw the X-rays, I said, "Well, I'm in bad shape." But the meningitis was the worst part of it, because I remember very well in my younger days during my internship in the medical school that all the children that I had seen with TB meningitis had all died; there was no treatment, except that when that happened to me in 1949, it was about a year to two years after [Selman] Waksman had come out with streptomycin and dihydrostreptomycin. So I was immediately put in contact with some of the best physicians in Montreal, all French speaking. And I went to the Notre Dame Hospital, where I stayed, maybe three months, in the hands of good, superb physicians: neurologists and general GPs. I was given streptomycin and dihydrostreptomycin by spinal tap every day for one month, and then every week for the next three months. Somehow the treatment must have been rather successful--was well handled--to the point that I even married the nurse who had been taking care of my problems. My wife, Lucienne, and I were married in Montreal. That was in 1951. So I had actually been out of the laboratory for about six months and then came back to Selye's laboratory--I must say that Selye himself was very much involved in the supervision of all this treatment of mine; it was actually quite generous of him--I went back to the laboratory and completed what led to my dissertation.

Selye and I got along very well; in fact, the last year I was there--since he was deeply involved in the writing of a series of books including his famous textbook of endocrinology, which was the first one written as such, as I remember--he had asked me to be in charge of all the administration of the laboratory, which I did to learn how it was to be done and so on. But, intellectually, Selye and I started disagreeing on lots of things. He was more interested in general views of medicine than in doing specific experiments to know exactly what the answer of a specific question was. And at that time the main question that was in the mind of all of us younger people in that

laboratory came from listening to a series of outside lectures--all high quality--which we had every month in Selye's institute, which he called the Claude Bernard Lectureships. One of them was by an Englishman called Geoffrey Harris.

On the pioneering work of Geoffrey Harris

Geoffrey Harris was known in the literature as being the proponent of a new theory; whereby, the role of the pituitary gland would actually be subservient to some function of a part of the brain called the hypothalamus. Harris had conducted a series of experiments in his laboratory in London, where he was actually producing lesions--localized lesion--all stimulated with electrical stimulator coil causing the lesions. And he could *at will* stimulate or inhibit the secretion of one or another of the pituitary hormones, as observed by the physiological response in growing of the adrenals, or changing or inhibiting the sexual cycle in--mostly--rabbits that he was using, and also other animals. There was no question that this concept of a hypothalamic control of the pituitary function was real, except that there was an additional problem. It was by that time well known, going back to the days of [Santiago Ramon y] Cajal, that there were nerve fibers going from the brain, the hypothalamus, to the posterior lobe of the pituitary, which was shown to secrete vasopressin and oxytocin, but there were no nerves going to the anterior lobe of the pituitary. So the big question in Harris's life--and in the book that he wrote in 1949 or 1951, or so--was, What are the mechanisms for this unquestioned control from brain to anterior pituitary? And at that time, there were a couple of visiting scientists in England--I don't remember whether it was in London or in Cambridge--they were anatomopathologists. They had shown that in all the species they had studied, while there were no nerve fibers going from hypothalamus to the anterior pituitary, that they consistently could see in the pituitary stalk very unusual types of capillaries, which were going from the floor of the third ventricle to the anterior lobe of the pituitary. Harris postulated that with the blood flow being shown to go from brain towards the pituitary--by various people, including somebody whom I had met in Selye's laboratory, Bernardo Houssay, who received a Nobel Prize later for his work on pituitary and diabetes--that the direction of the blood flow was actually from brain to the pituitary. So the new concept was that the neurons and the neurofibers coming out of those neurons in the hypothalamus--there were two specific locations: in the paraventricular and supraoptic nucleus--would actually merge with these small capillaries in the upper parts, so to speak, and deliver their unknown messages to the pituitary through these portal vessels. That was 1952--about that time. That's also the date when I decided to leave the laboratory of Selye because if I really wanted to be in research in physiology, I really had to be on my own.

III. BAYLOR COLLEGE OF MEDICINE (1953-1960)

Guillemin: Through various interesting combinations of people, I was asked to join the Department of Physiology at Baylor College of Medicine in Houston in 1953 or 1952, and I agreed to that. Actually, I went from Montreal to visit these people. I had never heard of Baylor College of Medicine, and I asked where was it located. I was told in Texas, at least I knew about Texas. So it was in Houston. I took the plane--I remember it was in the deep winter in 1952 or 1953, and we were still in meters of snow in Montreal--I took the plane to go to Houston to see what these people had really to offer. And when I landed in Houston--gee, the weather was warm, there were azaleas blooming all over the place. The people at Baylor College of Medicine were very open. There was plenty of money; there was plenty of space. Mike DeBakey, the surgeon, had just joined the faculty. The chairman of the department was this wonderful man by the name of Hebbel Hoff, who actually had come from McGill a couple of years earlier. So the contact was immediately very pleasant, very constructive. So I decided to take their offer. And my wife and I--our first daughter was born, actually, in Montreal--so with the baby we moved to Houston, Texas, where we stayed for almost twenty years. I was teaching physiology, and it was my job to teach endocrinology in the Department of Physiology. Besides my teaching duties, I immediately started a small laboratory where I would start my own experiments to look into this concept of the brain control of pituitary function. It was obvious--at least to me--that the next important contribution in that chapter of physiology would be to find out and recognize the substances involved in going from hypothalamus to pituitary and conveying the mechanism to stimulate pituitary secretion. In the lectures we had heard at McGill--as part of the courses which I had taken before--the main teacher had said that all endocrine tissues coming from the ectoderm would always make peptides or proteins as part of their secretion, and those from mesoderm would make steroids--the structures of all these steroids were just beginning to be recognized, and Selye had actually written the first volumes of all the nomenclature of steroids--but this concept that these molecules from the brain, which I was looking for, would be peptide, was my basis to start. This was, of course, in keeping with the extraordinary work coming from [Vincent] du Vigneaud in New York, who had eventually--either a couple of years earlier or about that time--had isolated vasopressin and oxytocin and shown that they were peptides--small peptides, nine amino acids, both of them closely related. Indeed, he was able with his group to synthesize *de novo* the molecule of oxytocin with full biologic activity. That was a great achievement for which, by the way, he received a Nobel Prize in 1957, if I am not mistaken.

Let me relate a short anecdote. Du Vigneaud was asked to come and give lectures all over the country, including one in Houston at MD Anderson Hospital, which became the medical center. I, of course, had been following all what du Vigneaud had published, and I got to know him, and I invited him for dinner at my house, which he accepted. Du Vigneaud was actually a very

interesting man in many ways. He was tall, very handsome man, a little gruff in his ways; he was a superb horseback rider and, in fact, in the Army he had been with the cavalry, and he was always very proud of that. I wanted to talk to him, not about horses, but about what he had done in the isolation of these two new peptides of the pituitary. I remember in my naiveté asking him what was the best separation system, which in those days by the way, were essentially paper chromatography, early column chromatography, and simple substrate countercurrent distribution. I asked him what was the most efficient separation system in his isolation of oxytocin, and I will *never* forget du Vigneaud looking at me and saying, "Well, I'll tell you, the most efficient separation method in the isolation of those pituitary hormones was removing the pituitary from the cow, you cannot beat that, that resolution." [laughs] So I still remember that. We went on in the laboratory trying to isolate these molecules.

The tissue cultures of Charles Pomerat

Then one day I heard that in Galveston--which was just fifty miles south of Houston, where we used to go with the children to the beach--the University of Texas had actually opened, several years earlier, its first medical school; there was a medical school in Galveston, part of the University of Texas--and I heard, I have no recollection how, that in that school was somebody called Charles Pomerat, who had studied with Alexis Carrel at the Rockefeller, years earlier--Carrel, by the way, being the first to receive a Nobel Prize in medicine in the United States--and that Pomerat had a big laboratory doing tissue cultures, including tissue cultures of the brain. So I went to Galveston to Pomerat's laboratory, introduced myself, and said that I would like be shown what he was doing. And I again remember, very well, Pomerat, who insisted on speaking to me in French--the most perfect, slow, academic French, always looking for *le mot juste*, the right word to say. He showed me throughout the laboratory and showed me some of his time-lapse movie photography--which I had never even heard of--of cells, including neurons. So we went through the laboratory and--again I'll never forget--when we came to this part of the laboratory [where] there was this young fellow who was at his microscope, and he said, "This is Barry Rosenberg, one of our graduate students; he is doing cultures of the pituitary, the anterior lobe." And he said, "You know those tissue cultures, they grow for days, for weeks, for *months*, and he is doing a good job; they are in good shape." He said, "But by the way, we have been looking for secretion of hormones by those cells in tissue cultures, and they start secreting when we put them in culture, [but] while they keep growing for weeks and months, they stop making hormones." And I said, "What are you talking about? What hormones?" "Well," he said, "you know we take the fluid from the culture and we inject it in rabbits," or whatever, "to use in a pregnancy test, which would tell us whether they make gonadotropins." And I said, "Sir, I think I know why your pituitaries are not working a few days after you put them in culture; they are missing something coming from the hypothalamus." And Pomerat was not particularly impressed, and

nothing positive came out of that. So I left and went back to Houston. But I was so intrigued with the idea of doing cultures of the pituitary, which didn't look to me like it was that complex--that difficult--and that perhaps we should use something like this to eventually isolate these molecules of the hypothalamus, which we were looking for.

About a week later, I went back to Galveston, talked to Pomerat, told him my story again, and he was not impressed any more [this time], but he said, "Well, Barry Rosenberg wants to go to medical school; why don't you take him to Baylor?" And sure enough, about a week later, Barry Rosenberg came to Baylor, working in my laboratory. We recorded him as a candidate to go to medical school with us, and he showed me how to do the tissue culture of the pituitary. Then he was offered [an opportunity] to go to, I think, Cornell--in the medical school--so he went there. But at least I knew how to do the tissue cultures of the pituitary, which I did.

Devising a method to pursue the adrenocorticotropic hormone-releasing factor

I will never forget when I added those crude extracts of the hypothalamus, or a small fragment of hypothalamus, in the culture tube and was doing the testing in the fluid for secretion--in fact, looking for ACTH, not gonadotropins, because there was a relatively simple bioassay for ACTH, called the Sayers test, which was [a means for] measuring ascorbic acid in the adrenal glands, which was very rapid; you could get an answer in one day, instead of a couple of days or weeks with the gonadotropins--and sure enough, I showed, to my satisfaction, by following the secretion of ACTH from the moment of putting in the culture for the next few days, including the time of putting either the hypothalamic extract or the fragment of tissue, that, as Pomerat had said, the secretion of ACTH, or pituitary hormone, would disappear after about four days, but if I put in the fragment of hypothalamus or the crude extract, then I would immediately restart secretion of, in this case, ACTH. And I said, "Now that is the way to proceed and eventually look for what these molecules are."

Purifying hypothalamic extracts

So we now had a method, which we could use to follow the purification of these extracts of the hypothalamus with whatever simple systems we had at that time, which were essentially paper chromatography, later on purification on the ionic exchange column. And sure enough, by following essentially the release of ACTH--because the test, as I said earlier, was so much faster than for the gonadotropins--very rapidly--in collaboration with a young fellow who was my age and in the department of biochemistry at Baylor, Walter Hearn was his name--we very rapidly showed with our simple separation method that we could separate this part of the extract that would stimulate secretion of ACTH away from where oxytocin and vasopressin were, because we knew by

that time that the hypothalamic neurons were the origin of vasopressin and oxytocin, not the posterior pituitary itself. So that's how it started. We knew that there were some substances, which--the way we were making the early extraction--were or could indeed be polypeptides. We went on by collecting a few hundred of these hypothalamic fragments in the slaughterhouse locally in Houston. Very early it became obvious that these molecules which we were looking for--which are *extremely* active; we could show activity in one thousandth of the extract of a 1 ml extract of hypothalamus--would be present in those brain fragments in *minute* quantities. In fact, it was known that the specific activity of vasopressin and oxytocin was extremely high, [one] could show biological activity on nanograms of those two peptides. So very early it became obvious that this was going to be a *big* project. We started publishing a few papers about this, which were fairly well received in the literature--while there was a great deal of hesitation by the rest of the academic world to consider this concept of brain cells secreting molecules of their own which would control function of the pituitary. I published a couple of notes about this.

IV. COLLÉGE DE FRANCE (1960-1963)

Guillemin: Then in the early 1960s, I was invited to give some lectures in Paris at the Collége de France--at least give one lecture--about all these things. There was in France a group--there were actually two groups--which also had been interested, mostly in the neuroanatomy between brain and pituitary in birds: the group of Jacques Benoit and somebody at the Collége de France [who] had this chair of experimental endocrinology. The man was older--way older than me--had just been made permanent secretary of the French Academy of Sciences, and he invited me to give this lecture, I think it was either one or two, which I gave. It was very well received, somehow. At the end of that he asked me if I would consider coming back to France in this laboratory and most likely get the chair when he would retire for good. This was never said explicitly, but it was implicit.

Chappelle: This was Robert Courrier?

Guillemin: That was Robert Courrier--you are quite right--who actually was rather famous in those days because he had been one of the first people to purify some of the early hormones from the secretion of the ovarian follicle. Also, he had been, probably, the very first person to produce thyroid hormones that were labeled with radioactive iodine. Collége de France had had its small cyclotron, which the Germans had never been able to get into during the war, and some of the local physicists had started making radioisotopes, including iodine-131. Courrier and a couple of his collaborators had been able to make radioactive thyroxine, or radiothyroid hormones. He was actually a man of good standing. So to cut a long story short, in 1960 the whole family moved back to France where I was the associate director of this laboratory at the Collége de France. The wonderful part of that was that Courrier--being with the academy and so

on--we were housed in one floor of this beautiful chateau, a castle of the French Academy of Sciences in a suburb of Paris, and since housing was difficult in those days, we were really more than fortunate. So we worked in that laboratory. There was a very good chemist called [Marian] Jutisz--who had studied at Berkeley with Herbert Evans and C. H. Li, the famous chemist--who [Jutisz] was to be the chemist of whatever I [inaudible] handle over there. So we started organizing things--not with the tissue cultures anymore, because that would have been a big thing to start in the Collége de France, but with simpler bioassays.

Andrew Schally requests a position in the Baylor laboratory

By that time I had received a letter from somebody whom I had never met, Andrew Schally, who was a graduate student at McGill--after I had left Montreal--with somebody called Murray Saffran. They were also interested in this concept of hypothalamic pituitary control. He [Schally] had actually been in an early paper with Murray Saffran and somebody called [Bruno] Benfey, and so he knew what this field was about. He wrote me a letter saying that he was going to get his degree a few months later and that he would like to join my laboratory to go after the isolation of these hormones of the brain because he thought, also like his master Saffran, that this was something to be done. So I wrote to Saffran to find out who this fellow was--I never met him--and Saffron wrote me a nice note about Schally, saying, “He is a young fellow, and I think he is reliable and he is honest,” and so on. Eventually, I wrote back to Schally and said, “Fine.” I met him at one of the Federation [Federation of American Societies for Experimental Biology] meetings in Atlantic City--where they took place in those days--and I agreed to hire him to come to my laboratory when he would get his degree a few weeks after that. And sure enough--that would have been late-1951 or so--Schally came to my laboratory. [A position in chemistry was available] because Hearn, the chemist who was with me at the beginning, had actually moved for family reasons to Iowa, he was in Iowa City. When I had agreed to go to Paris to the Collége de France, I had, of course, discussed that with the chairman of the Department of Physiology at Baylor, Hebbel Hoff. Hebbel was such an extraordinary man. He was very well educated; he was very learned in the history of medicine. In fact, we had published together quite a few papers about the history of medicine. We had discovered the early manuscript of a famous book by Claude Bernard--when I was at the Collége de France on that first visit--which we decided we would translate into English. Hoff told me--I will never forget that either--he said, “I agree with you, you should go back to France since you are being asked to go to this rather prestigious place--that’s fine.” “But,” he said, “you know you have been in this country for what, almost fifteen years; you don’t really know these French people anymore; you don’t know how they work and how they act. So by all means go, but I insist--I want you to keep this laboratory working.” And Schally was there--at that time he had arrived--and I said, “Fine.”

Chappelle: Who did you put in charge?

Guillemin: Well, Schally was, indeed, in charge of the chemistry part of it. For the physiology--for the bioassays--the idea was still to look for this corticotropin, ACTH-releasing factor. For the bioassay, there was this young fellow--who just passed away last month, by the way--called Harry Lipscomb. And so the laboratory was actively working in Houston, and I was starting the other one in Paris. And, *literally,* I commuted between Houston and Paris, three or four times a year, running the two laboratories. Hebbel Hoff, in his generosity, had organized my being interviewed by the president of something called the Houston Foundation. Sure enough, in twenty-four hours they gave me one hundred and fifty thousand dollars as a grant to take care of the travel expenses for me and for students, which I would take to Paris and vice versa. It was an incredibly constructive time. Meanwhile, Schally and Lipscomb were still going on with the purification of the corticotropin-releasing factor.

The search for thyrotropin-releasing factor (TRF) and luteinizing hormone-releasing factor (LRF)

In Paris, I decided that--with Jutisz as the chemist--we would start looking for another of these hypothetical hypothalamic substances, which would control the secretion of TSH (thyroid-stimulating hormone. There were good reasons [namely] from the early work of Harris and his stimulation or [creating of a] lesion in the hypothalamus that there was a controlling molecule of brain to pituitary for the secretion of thyrotropin, of TSH. I devised a very simple, incredibly simple, bioassay using the radioiodine that Courrier's laboratory had available over there, a very quick bioassay stimulating the secretion of TSH. And within a year, we were able to publish a note in the French *Comptes Rendus* of the academy demonstrating the presence in hypothalamic extract of some molecule, which stimulated the secretion of thyrotropin and, eventually, thyroid hormones. It was still the early days of purification, but it was obvious that this was the way to go. We also, either the same year or the following year--based on a new type of bioassay that had been devised by somebody called Al Parlow--[decided] to look for the secretion of gonadotropins, mostly what we call LH, luteinizing hormone. It was a rather strange bioassay in which we were measuring the ascorbic acid content of a stimulated ovary--[stimulated] by LH and FSH. It was actually working well--when you would measure the purified, mostly, LH [inaudible]. But it was still bioassay. But with this rather complex way, we were still able to show and publish what I consider to be one of the very first demonstrations of the existence in those hypothalamic extracts of an LH--luteinizing hormone-releasing substance--gonadotropin-releasing substance. Geoffrey Harris in England and Sam McCann in Texas had both published [an] earlier paper--earlier than mine--showing that there was such a substance, based on various assays of their own, including ovulation in the rabbit and so on, but the test that we were using with

this new Parlow test was way faster than what they had. So there was no doubt that there was this new hormone, LH-releasing factor, that had to be also further purified and looked for, regarding isolation.

All of this was going on; and in my commuting between Houston and Paris, it became obvious to me that we were doing way better in Paris on the purification of these new molecules for the release of thyrotropin and the release of LH with Jutisz as the chemist, than we were doing on the CRF, the corticotropin, the ACTH-releasing factor--with Schally. And we actually had published several papers with Schally as first author in the chemistry of this, but I was not particularly impressed about what was going on. On one of these trips, I told Schally--I said, "You know, you have been telling me you are in charge of the chemistry; we have been looking for this molecule, and you are telling me we are going to get it in the next six months, but that hasn't happened for the last four years, and we still don't know what we are talking about." So I said, "You know, you should look for your own ways." And so I asked him to leave the laboratory. And he actually left the laboratory and got himself named as--in the laboratory, which he would run, in the VA system in New Orleans. He actually had--by phone--already established some connection with somebody, who turned out way later to be incredibly bright, Cy Bowers. So the laboratory in Houston was now without a chemist.

And for a strange reason--which I never quite understood, which had nothing to do with the quality of the research involved, but which had to do mostly with a strange interpersonal relationship with Courrier, the old man, and so on--the climate became very negative in the laboratory at the Collége de France. So I decided that this was not my cup of tea--far from it--or French wine for that matter, and I decided that I would just leave. The laboratory in Houston was still working in full, so we left the Collége de France in late 1963 to come back to Houston. To this day, I think my wife never totally forgave me for taking her away from her chateau in Louveciennes to go back to Houston, Texas. But we survived.

V. BAYLOR COLLEGE OF MEDICINE (1963-1970)

Guillemin: So we came back to Houston, to Baylor. By that time I had been so convinced that it would take huge amounts of hypothalamic tissue, eventually, to isolate enough of these molecules [in order] to determine the molecular structure, that I had made arrangements with a company in Paris, which was specializing in getting samples of tissues from animals at slaughterhouses and other [sources] and deliver [the samples] to laboratories. I had made a contract with one of these companies to obtain hundreds of thousands of fragments of sheep hypothalamus. Why sheep? Because I had gone to the slaughterhouse myself and I had noticed that the skull of sheep--what we call the clinoids of the sella turcica--were very flat, so that if we were moving the brain out of the skull, we would not damage the part of the hypothalamus that we were interested in;

while using pig brain--like we had also tried--the clinoids were so vertical that by moving the brain away from the base of the skull, very often we would damage this part of the tissue. In those days by the way--in all of those three years in Paris--I had received money from the NIH to pay for the research, which we were doing over there. And that money, the French structure had nothing to do with it, so that I could do practically what I wanted with it in the laboratory. And I used those monies from NIH to buy something like half a million fragments of sheep brain. When I came back to the United States--I had organized things to ship and I had some problems going through customs with half a million sheep brains--I had organized this to go through. And we came back with these very large amounts of frozen, on dry ice, fragments of sheep hypothalamus, which went immediately to the isolation program at Baylor.

The recruitment of Roger Burgus contributes to the isolation of TRF

Since Schally had left the laboratory at that time, I had to look for a new chemist because I am no chemist--I never claimed that I was--and I really needed somebody for this field, for this project, who knew how to purify [and] isolate these peptides--because we were now convinced that the molecules we were looking for were indeed small peptides, maybe a little larger than the oxytocin/vasopressin, but still small peptides. So I placed an advertisement about this and a few months later, I hired--in the laboratory--Roger Burgus, who strangely enough was from Iowa State University, and he had strangely enough--I repeat--he had worked with Hearn, when Hearn went back to his family things. So Burgus was well aware of the project that I was involved with and what was the goal and what [was] to be done. So Roger Burgus came to the laboratory, and we immediately started a wonderful collaboration; he was a wonderful, younger man knowing very well these things, and I realized very quickly that he was a way better chemist than Schally had been in these things. Very, very rapidly within less than two years after Burgus came in--well, actually, it may be a little later because we had to accumulate enough of the starting material. In 1969, we were convinced that we had pure thyrotropin-releasing factor, TRH (thyrotropin-releasing hormone)--TRF, we called it in those days, and that it was a small molecule composed of three amino acids. We knew that for a fact. We had unquestionable evidence that the molecule which we had *isolated*, and we had evidence--I repeat--that what we had isolated was essentially composed of three amino acids: glutamic acid, histidine, and proline *in* an acetate form, and it was in pure form. So we decided that we really had now the stuff, so to speak.

Tucson Conference (1969)

But just a few months before that, we had gotten some very unpleasant news from the NIH in which they said that all their advisory committees had said that there was a group of people who were getting hundreds of thousands of dollars from the NIH looking for elusive brain hormones--which probably were

just part of their imagination--and that nothing had come out of all of that and all of these monies, and that the NIH should really look into that and cut it off if need be. The NIH organized a meeting in Tucson in 1969--early in the year, I remember--at which meeting those of us involved in the search for those molecules would be speaking: that was Schally--there was nobody else from his group, it was just he--and my group, which was essentially me talking, Burgus talking, and I think that Wylie Vale, who was still a graduate student with us, was also at that meeting. And the NIH would have a bunch of referees listening to all of that to advise them whether to keep giving money or just turn off the faucet.

Chappelle: Was it just those two groups, your group and Schally's group?

Guillemin: There was also the group of McCann. There were three groups from this country to which NIH had been giving money. Yes, Don McCann was at that meeting, absolutely. They had also invited Geoffrey Harris to come and talk about this whole thing, so it was a rather high-level scientific meeting. But I knew all along that the people at the NIH--there were people of the study section, who were in the audience, that were really looking or listening to what these two groups, Schally's and mine, were going to say. By that time Schally had actually published that they had claimed to have isolated the thyrotropin-releasing factor, the TRF, and that it was indeed composed of three amino acids, the same amino acids which we had ourselves found in the laboratory, glutamine, proline and histidine, but that they had obtained synthetic molecules from the Merck group of all the possible combinations of these three, namely, nine [combinations]: Glu-His-Pro; His-Pro-Glu, and so on, and that they had tested them in their bioassay and that none of them had any biological activity. So they actually *published* that TRF had nothing to do with those three amino acids. We came to the meeting, and a few *weeks* before the date of that meeting, we had obtained our ultimate results showing *unquestionably* that the pure substance releasing TSH was, indeed, composed of these three amino acids. Was it three, six, nine, a polymer? We had no idea, but we knew that there was nothing else, besides the sodium salt, than those three amino acids. I remember Burgus and Wylie Vale saying, "Should we reveal that at the meeting, or just keep it [to ourselves]?" Because we knew that we were now *days* away from a structure. I remember saying, "No, you know the odds that everything in the field may be cut off are such that we must show what we have even though we are going to reveal to competition what we have and that they had missed." So at the meeting in Tucson, I discussed the bioassays, and Burgus showed the chemistry--for which, by the way, the credit is his--showing that we had, indeed, isolated a molecule with all the activity of the thyrotropin-releasing factor we were looking for, composed of these three amino acids and nothing else, and that we were convinced that it was now a matter of weeks for us to get the sequencing and get the structure.

Meanwhile, I remember I called on the telephone--from that meeting in Tucson--friends of mine in Switzerland with the Sandoz people asking them if they could synthesize for us all the combinations of these three amino acids. Actually, I had earlier called the Merck people to see if they would still have some of these compounds that they could send us, and they said, "No, we gave everything to Dr. Schally." I asked Schally whether we could share in these compounds with him since we didn't know what to synthesize, these molecules. He wrote back and said, "There is no way it could be done because the FDA did not allow sending peptides across state lines"--some strange response. So that's why I called the people in Switzerland, and we did receive those nine synthetic peptides, the tripeptides. By the way, we still did not know whether the active molecule, the native molecule, was three, six, nine amino acids, but we postulated that it might be a tripeptide, which it was. We tested all these compounds and none of them were active, just like what Schally had said earlier.

Obtaining the structure of TRF and confirming it through mass spectrometry

At that time Burgus, being the good chemist he was, said, "If you look at vasopressin and oxytocin and a few other peptides"--biologically active, which had been purified in a different field by [Vittorio] Erspamer in Italy--"the N-terminus is always protected, so maybe it's not glutamic acids; it's pyro-Glu." So we immediately transformed the Glu-His-Pro and the other nine compounds, we changed the N-terminus by cyclization. Sure enough, to our delight, only one sequence showed low level, but unquestioned TRF activity; that was the sequence Glu-His-Pro, which we had transformed into pyro-Glu-His-Pro. At that time, by the way, we had units for these activities, just like NIH had units for the purified ACTH and FSH and so on. So if our native TRF--the most purified--at, say, 50,000 units per milligram of activity, this synthetic molecule, which we had changed the Glu, to pyro-Glu, was active--at say 10 units per milligram. So we knew that there was still something else missing. And here again, Burgus said, "Ah, but maybe the C-terminal has to be protected, too." So we protected that C-terminal--I have forgotten exactly how it was done--and we got this molecule, pyro-Glu-His-Pro-amide, which had the *full* biological activity of the 50,000 units of the native TRF.

We still did not know for sure that the native--this was a synthetic molecule--we still did not know for sure that the native molecule was indeed the same as the tripeptide. At that time we thought--and it was again Burgus's conclusion--that the best approach to do that would be to get together with another young fellow at Baylor, who had just moved to Baylor from the NIH in collaboration with somebody called Evan Horning, in a new so-called lipid research center at Baylor, and they had brought mass spectrometry. They had a high-resolution mass spectrometer and a couple of lower resolution mass spectrometers. So we got together with this young man. I talked to Horning, and I said, "Do talk to

this young fellow in the laboratory called Desiderio"--I have forgotten his first name--[Dominic] Desiderio was his name. And in no time, we were able to derivatize the synthetic molecule so that it would be volatized enough to go into the mass spectrometer, which in itself was relatively new for small peptides; it was very much the beginning of separating peptides in the mass spectrometer to establish the various fragments. We were able to obtain a perfectly reliable mass spectrum, low resolution, of the synthetic pyro-Glu-His-Pro-amide. Then we put the native molecule in the same system, and, lo and behold, we had absolutely identical mass spectra. So there was a fateful date, which I think was June 19, 1969, where for the first time Burgus was able to write on the blackboard the structure of a native thyrotropin-releasing factor. We published that immediately in the French *Comptes Rendus* because in those days those French *Comptes Rendus*--in contradistinction to *Science* or *Proceedings,* which took weeks and months of reviews--the publications go very fast. And there is no doubt in my mind that we were--our group was the first--in that publication--to report the complete structure and final structure of the thyrotropin-releasing factor as pyro-Glu-His-Pro-amide and show the mass spectra of both the native molecule and the synthetic tripeptide, which our friend from Switzerland had synthesized for us. So that was the major thing that happened in the field.

Now, meanwhile, what was Schally doing? Well, after this meeting in Tucson, when he realized that they had missed something, he associated with somebody who was not in his group, who was a well-known senior chemist called Karl Folkers, who was at that time at the University of Texas. So he and Schally got together on this thing. Eventually, Karl Folkers became convinced that what Schally had claimed earlier to be his isolated material was not pure at all. It may have been a single peptide, but it was so contaminated with all sorts of things coming from their way of separation that they had missed the concept that the peptide part of what they had was the active molecule. But Folkers--being as I said [a senior chemist]--was able to go through that. They also realized the significance of the pyro-Glu--which we had published earlier, by the way--and probably the amidation of the C-terminal. They somehow did not have access to mass spectrometry--which still surprises me to this day. The following year, or maybe the same year but several months after us, they published a note saying that based on seventeen different paper chromatography systems that the molecule of TRF was most likely pyro-Glu-His-Pro-amide, and eventually they did mass spectrometry. I have forgotten who with, but it was at least one year later. So that was their claim also to have isolated and gotten the structure of TRF. That was to me--what I have called, earlier--the inflection point in that field of research, the structure of TRF. Then the next step, of course, was to go after the other molecules, the one releasing gonadotropins, releasing growth hormone--which we knew had to exist and, of course, we had no idea what they were--and also ACTH--the CRF molecule still had to be characterized, the corticotropin-releasing factor.

VI. SALK INSTITUTE (1970-1989)

Chappelle: How did you come to be chairman of the laboratories for neuroendocrinology at the Salk Institute?

Guillemin: Ah, good question, good question. So, of course, we published our results with the isolation of the TRH/TRF and the molecular structure. We also had published enough to show our involvement in the mechanism of secretion of the gonadotropins, particularly LH, and it was *obvious* that if we could control the secretion of the gonadotropins, we may well look into some totally new approach of fertility control. In those days there was a division at what was called AID, [United States] Agency for International Development, which was deeply involved in the problems and the concept of population control. Their scientist advisors read what was in the literature, and I was approached by them: Would I agree to sign a contract; whereby, they would provide millions of dollars, by the way--on an annual basis--to support the research of my laboratory. So, of course, I agreed and shifted most of the funding from NIH (National Institutes of Health) to this AID. At about the same time, I was asked by the new president of the new campus of the University of California at Irvine--they asked me to join the faculty at Irvine, and they offered me the possibility of running a big department of physiology, pharmacology and biochemistry--combined--which I thought was a lot. So I discussed this with Hebbel Hoff at Baylor, and he said, "Well, you never know." He said, "Why don't you go and see." The generosity of this man, Hebbel Hoff, was so astounding. So my wife and I went to Irvine to the new campus, which was *a building*--it was still building--and got to see the president there. We discussed what they wanted, and I started telling them, "You know this is an enormous venture you want. It seems to me that you need at least two people, rather than just one; in fact, it would be best if you had three departments: physiology, biochemistry, and pharmacology. They may be in the same building, but these are three different entities." We kept talking and so on. The man who was in charge of [our itinerary], who was an MD himself at Irvine in the beginning of the school--that evening, since he was in charge of all the arrangements of our visit--I'll never forget--he took us for dinner to a restaurant on the coast, and the restaurant was called Victor Hugo, which was a good beginning. It was right on the beach, and to our amazement, for the first time in our lives, my wife and I, we saw whales cavorting on the beach; this was the time of year when they would migrate from Alaska to the places on the Pacific side of Mexico. There were a series of beaches where they would actually have their calves and get inseminated again and go back to Alaska, three months later.

[Interruption]

Chappelle: So you were watching the whales at the Victor Hugo [Restaurant] ?

Guillemin: Yes. And during this very pleasant dinner, our host was called on the phone--the maître d' apologized--and he came back a few minutes later, and all of a sudden he said--we were still looking at the whales--"Jonas would like to speak to you." And I said, "What do you mean, does this have to do with the whales?" He said, "No, no, no, the real Jonas, Jonas Salk wants to speak to you; he found out where you are." So the next day, I sort of declined, closed out the proposal of the people at Irvine; that three department [arrangement], it didn't make any sense to me. So we closed that proposition, and then my wife and I, we drove to La Jolla to meet with Jonas Salk, whom I did not know. I had never met him and I had never seen the Salk Institute, either. When I got there that next morning to meet with Jonas and saw the place, I was so *moved*--moved is the word. I said, "Whatever the offer of Jonas is, the answer is yes." [I would] spend the next twenty years of my life in such an *extraordinary* place. The meeting with Jonas went *very* well. It turned out that at that time of year the Salk Institute had, in [its institutional] structure, the group of what they called non-resident fellows--I had no idea of the structure of the faculty--and those non-resident fellows were *extraordinary* people. They all had a Nobel Prize. There was Jacques Monod, Francis Crick--who else was there?--anyway, these absolutely superb people. So they interviewed me, not only Jonas, but all of them. And apparently we got along well, and I said, "You know I do want, in the next steps to bring higher system of separation and realizing--establishing molecular structure of these peptides, [and] also get into the synthesis." The fellow who had just published the solid-phase synthesis for peptide [was there as well], and he indeed did receive the Nobel Prize a few years later. So it was the very beginning of all of this. And I said, "I want to bring mass spectrometry, NMR, (nuclear) magnetic resonance, and start a program of peptide centers." So we got along fine and I agreed to join the faculty at the Salk Institute.

When I went back to Houston, I told all of this and showed pictures to the group, the young people around me, which were still Burgus, Wylie Vale, who was completing his dissertation for the PhD degree, a young woman in the laboratory called Catherine Rivier from Switzerland--she was working for a PhD degree from the University of Lausanne, but there was an agreement, which the dean at Baylor had agreed upon; whereby, she would do all the work in my laboratory, I would be the senior advisor for her committee, but she would get her degree from the University of Lausanne. So I proposed to all of them to move en masse to the Salk Institute where I was given ten thousand square feet of laboratory space to organize and so on. And that is the way we moved to the Salk Institute with all our equipment, which had been bought by

AID and NIH monies. The people at Baylor were open to this sort of move, which was in keeping with the spirit of academia. We established ourselves in the laboratory at Salk Institute. I had worked with local architects to have the inside of the laboratory built exactly the way--since we would be the users--we would want it, and for twenty years we used that laboratory as we had designed it on day-minus-one, so to speak, without changing anything, it was such a superbly functioning laboratory. So we moved over there.

In pursuit of luteinizing hormone-releasing factor (LRF)

There was a new postdoc called Max Amoss, whom I had asked to set up a new radioimmunoassay--it was the very beginning of those radioimmunoassays--for the gonadotropin, for LH. Max had actually started a radioimmunoassay for LH of the rat. We were getting antibodies from the NIH and various other people, and I knew that the next step to isolate this gonadotropin, this LH-releasing factor (LRF), would be by using the radioimmunoassay, which was *far more* sensitive than any bioassay we had used earlier and also extremely fast, as compared to older days [when] we had to wait for the ovulating animals. So we are now at the Salk Institute, and within *weeks* we started generating results. And it is obvious that this molecule, which we are looking for--to the release, to stimulate the secretion of LH--is also a peptide, as the theory would have had it, and it is a much bigger molecule than our three amino acid residues for the TRF. And we have a highly purified material, and we showed that it is composed of nine amino acids on acid hydrolysis. We sent the results to the people at AID in Washington because we were supposed to keep them informed every three months of all the results, since they were [supplying] all the funds for this. We knew that this was not the end of the chemistry, far from it. We knew also that we had done only one acid type of hydrolysis and that the next step was to do alkaline hydrolysis to see if we had been missing something.

And it was that time of the year when the Endocrine Society was preparing for the meeting of the year, and I was on the committee to review abstracts that were sent and that were to be selected for presentation and so on. And *sure enough*, I received in that pile of abstracts--there was one from Schally's laboratory with two Japanese collaborators, one called [Akira] Arimura, the other called [Yoshihiko] Baba. They had the same eight amino acids, which we had found in our own laboratory. I felt very uncomfortable about knowing that. By the rules, people submitting abstracts to the Endocrine Society were not supposed to publish them before the meeting, which was where you showed your latest results and so on. And all of sudden, I knew what was going on in Schally's laboratory, and I felt a little uncomfortable about it. So I wrote a letter to Schally, a personal letter, telling him I want you to know that I have seen your abstract, and I want you to know that several months ago we found exactly the same amino acids that you have, as per the report we sent on such and such date to AID--to show that I was not bluffing. The meeting took place

in June, or whenever it was, of the same year in San Francisco. At that time we were purifying some more of the LRF by the method that we had used earlier because we needed some more to get the sequence. At the meeting of the Endocrine Society, there were several symposia, and I was asked to be the chairman of a session where this problem of hypothalamic control of pituitary function would be discussed, and Schally was one of the speakers. How could I forget that?

At that meeting Schally got up and said, "Here is the structure of the peptide releasing LH. Actually, it's not eight residues--there is an additional tryptophan. It is a decapeptide; there are ten residues." Sure enough, he showed the complete structure, the complete sequence, because Arimura, who had been with Schally--who was essentially a biologist--had brought into Schally's laboratory a superb chemist from another university in Japan, Hisayuki Matsuo, who had devised this specific method to characterize tryptophan residues in small peptides. And he took charge immediately of all the chemistry of what Schally had purified for this LHRH, or LRF molecule, and Schally showed for the first time the correct and complete structure as the *most likely* substance with the activity of LRF. They even said that they had the synthetic material that had the full biological activity. So, obviously, we had missed one tryptophan residue because we were still in the process of doing some more [research], and there is no question that Schally's credit is to have shown the first correct structure of the decapeptide LRF. And about two months later, we had isolated enough of the material of our own of ovine origin--Schally's work was with pig material, so it was the structure of the porcine LRF that he had given, and we did not know what would be the structure of ovine LRF, which turned out to be identical to the structure of the porcine material, which by the way is the same as the human; we isolated that from human brain later on, and it is the same structure. So there is no question that the credit for that first correct structure of the decapeptide LRF goes to Schally's laboratory, and the *ultimate* credit is really to Matsuo, who was a superb chemist in his own right, no question about it.

Somatostatin

Meanwhile, we are still doing our work on these hypothalamic extractions, and it is obvious that the next step is to go after the postulated molecule that stimulates the secretion of growth hormone. There was a paper going to back to 1960 by Seymour Reichlin, who had proposed--on very clever reasoning based on data, which had been obtained not only by him but by other people, also, in rats that had been rendered obese by hypothalamic lesion in a way which was almost classical--he had noticed that these animals, while being obese, also were shorter in size and that their epiphyseal cartilage were reduced. So he said, "With these hypothalamic lesions, we render these animals obese, but we also inhibit the secretion of something that must be a growth hormone-releasing factor." So we said, Well, okay, it is rational that

there should be a growth hormone-releasing factor. So we go back to the old tissue culture technique, and we have a freezer full of extracts of our hypothalamic tissues from the TRF project and the LRF project. By the way, over the years, we handled in the laboratory close to five million sheep brain; we manipulated, I think, over a ton and a half of brain fragments.

So we start looking for this growth hormone-releasing factor with the tissue culture, and I had asked a new postdoc in the laboratory, Paul Brazeau from Montreal, to set up a radioimmunoassay for rat growth hormone. We had gotten antibodies, specific antibodies, from a couple of friends at Scripps Memorial Hospital in San Diego, and he set up a radioimmunoassay for rat growth hormone, which was extremely sensitive and very specific. So we started assaying our extracts of hypothalamus on our tissue culture setup, and to our *amazement*, instead of stimulating the secretion of growth hormone, we *repeatedly* see a fall of the secretion of growth hormone within *minutes* after adding the hypothalamic extract. I still remember telling Paul Brazeau when he first showed me the results, "Come on Paul, why don't you do it right? Do it again." Which he did, and sure enough, a week later, he came up with the same results. So we looked carefully [to see if there] could there be anything wrong in the setup, and we said no. So we re-did the experiment once more--I did it with him--and we came to the same conclusion: that there was in this hypothalamic extract some substance inhibiting the secretion of growth hormone, and there was really no good evidence that there was such a thing. There had been a paper by McCann's group in which they had done multiple small biopsies, so to speak, of fractions of cubic millimeters of rat or rabbit hypothalamus, and they had claimed that there were regions that would inhibit secretion, others would stimulate secretion. But I had not taken that paper seriously because statistically the results were really not significant. So here we are, is this a total artifact, or is it real life? But the results were so stunning and so much in keeping with a real fact; we had perfectly logged those responses between the amounts of extract we would add, to the decrease of growth hormone. So we decided to find out what that was.

Within a couple of weeks, Roger Burgus and Jean Rivier, who was in the laboratory--not only in charge of the NMR, but also a part of the chemistry--isolated a molecule, which turned out to have fourteen amino acids. Burgus started sequencing it--in those days by the Edman method--all we could do manually was one residue a day. In the next two weeks, Burgus showed a complete structure of a fourteen-residue peptide with a sixteen cyclic bridge. Jean Rivier synthesized that molecule; we confirmed the molecular structure by mass spectrometry, which we had introduced at the Salk Institute with Nicholas Ling being in charge--who came to us from [Carl] Djerassi's laboratory up in Stanford. And we published that. I named the molecule somatostatin, meaning that it stops at least the effect of the growth of the organism, and we sent this note to--I think it was either *Science* or *Nature,* I have forgotten which--and that was published and attracted a great deal of

attention because people reproduced the data and everybody agreed that what we had stated was correct. I had also immediately realized the significance of such a molecule in the treatment of pituitary adenomas, particularly in the case of acromegaly where the tumor secretes huge amounts of growth hormone. In collaboration with my colleague-clinician here in San Diego, Samuel Yen, we published that injection of this purified peptide or maybe the synthetic one--one of the two--in these patients with acromegaly--where we would measure blood growth hormone by radioimmunoassay--would, indeed, lower immediately the concentration of growth hormone in the blood. It was obvious that this would be of significance in the treatment of acromegaly, possibly also in the case of juvenile diabetes, because we knew from the work of Houssay and others that there was this competition between growth hormone and insulin secretion in those patients. So we published that. And, as I said, it attracted a great deal of attention. As you know, nowadays, simpler analogs of somatostatin--fewer amino acids than the fourteen--are part of the classic treatment of acromegaly, also of other types of pituitary tumors, by the way, particularly those secreting prolactin, which--not all of them, but most of them--are sensitive to somatostatin along with dopamine. It is turning into a very complex, very interesting sort of thing--still going on with new molecules being synthesized both in industry and in academia for the treatment of these patients.

On the discovery of the somatostatin-secreting cells of the pancreas

As part of my philosophy over the years, whatever we had in the laboratory, I always agreed to share with anybody, free of charge; after all, we were working on public monies. The only thing that I would request would be the courtesy of letting me know what kind of results they would get out of it. We did not claim anything else, nothing in publication, and so on. So one day, we got a request for this new somatostatin peptide from somebody whom I had actually never met, at least I don't think so, called Charlie Gale, who was a young physiologist in Seattle at the University of Washington. They were working with baboons, on the secretion of growth hormone in their baboons, and so on. They wanted to get some somatostatin, so we sent him a few hundred milligrams of the somatostatin. Maybe six months later, we got a phone call from Charlie Gale saying, "Your stuff definitely lowers the levels of growth hormone in the blood of our monkeys, but we have almost lost three of our animals due to hypoglycemia; so somehow there is a problem with the secretion of insulin and of glucagon with this molecule." We had never seen anything like this; we repeated [our work] and in the rat and we never saw any effects on the blood level of insulin and glucagon. Their observation was of such importance, I said, "My god, there is no way that somatostatin from the hypothalamus could travel to the pancreas"--knowing what we knew of the half time of the molecule and the circulation time in the animal. So I said, "Well, it may be the nerve endings of the vagus," which we knew innervate the pancreas, "maybe they release somatostatin, locally, in the islets." By that time

we had generated some--not very good--but we had some antibodies to somatostatin, which were perfectly good to do histochemistry, but not good enough for radioimmunoassays. I remember sending some of those antibodies, frozen, to a fellow whom I had met earlier in France, called Maurice Dubois, who was essentially an histologist. I sent him some of these; I said, "Look for the possibility of this molecule at nerve endings of the vagus in the pancreas." He wrote back and said, "Okay, I'll do it." He was not particularly enthusiastic, but the professor had asked him to do that, so he would do it. And sure enough, maybe a few weeks later, he called me on the phone from France to the laboratory here in San Diego, saying, "I want you to know, your somatostatin is all over the pancreas, not by the nerve ending, but it is in the special cells which we have called delta cells for all these years, and nobody knew what those delta cells were actually synthesizing." The beta cells make insulin; the alpha cells make glucagon; but now those delta cells, we know, make somatostatin, and that explains the effect that I had been seeing on the secretion of both glucagon and insulin. So we published those results, which were so unexpected. *Unknown* to me, Rolf Luft in Stockholm and Thomas Hökfelt had made the same observation on their own--with antibodies of their own--and they also published, independently from us, this observation of somatostatin-secreting cells in the pancreas, which was also confirmed later by Lelio Orci in Geneva. This was really a totally unexpected discovery, and it attracted a great deal of attention. The clinical application of this observation--I have mentioned earlier--are such that analogs of somatostatin are, indeed, to this day part of the treatment for acromegaly and several types of other pituitary adenomas, and so on. So that was part of what happened with somatostatin.

Sequencing of enkephalins; isolation and characterization of endorphins

We still had to find the molecules, of hypothalamic origin, releasing growth hormone, of which--as I said earlier, based on the earlier results of Si Reichlin--such a control should exist. About that time--I have forgotten exactly the year, probably 1975 or so--I was asked to give a speech about what we had been doing on the hypothalamic peptides to the equivalent of the Tripoli Association of Canada in Toronto [Canadian Association for the Advancement of Sciences], so I went there. The man who had organized that session of the meeting, I don't remember his name, asked me on that occasion what did I think of this paper which had just appeared a couple of days earlier from the laboratory of [Hans] Kosterlitz in Scotland--in Aberdeen, Scotland--about the characterization of molecules which were ligands of opiate receptors in the brain, including the human brain, which they had called enkephalins. They were small peptides, but they didn't have a sequence. I said, "My god, here is the clue." I knew perfectly well as a physician that injection of morphine in humans, in patients, stimulates secretion of growth hormone, and it does so also in laboratory animals. I said, "We now know that there are opiate receptors in the brain; these fellows are now finding ligands, which are

peptides. Here is the answer." But they had no structure. It was obvious when I read the whole thing that they really were not equipped to do that. So I decided when I came back from that meeting, *immediately*, to look into that. But I had to have a bioassay for those unknown opiate-like peptides or molecules. In going over the literature, it was obvious that there were a couple of bioassays, which I had never heard of, like the gastrocnemius muscle or some strange thing, which I had never even heard of. But there was a group in San Francisco who had been looking for those opiates, endogenous opiates, potential molecules; they were using one of these bioassays. Here again the name escapes me; it is embarrassing. I wrote to the chairman [Avram Goldstein] of that laboratory, and I told him that I really needed to learn those bioassays if I wanted to proceed with the isolating of these [inaudible], would he agree to teach me how to do this bioassay. He immediately wrote back and said, "Of course, we would be glad to," knowing, by the way, that I would immediately become a competitor for what they were doing. They were generous. I went to San Francisco, learned the bioassay from these colleagues, came back, set it up in twenty-four hours, and that was the easiest thing I ever did. In less than one month, I had *isolated* from our extracts of both the hypothalamus and posterior pituitary--of which we still had large quantities--three molecules, based on their separation on simple chromatography, that had opiate-like activity. And it was obvious, very early, that the molecules I was dealing with were much larger than those that these people in Scotland had reported. They had said that there were five amino acids in their molecule; whereas, in my case, one of those had thirteen residues, another fourteen, and the other was actually thirty-one residues. We said, Well, we better get into the structure of all of them.

We were now very well equipped in the laboratory, based on our years with the earlier peptides, including somatostatin. So we started sequencing the smallest of these molecules, which was thirteen residues. The day after Christmas of that year, which was I think 1975, we got our copy of *Nature* in which the group of Kosterlitz in collaboration with two other chemists--again the name escapes me--they had established the sequence of their five residues, opiate-like peptides, which they called enkephalins. And as we were starting to get the sequence of our thirteen residue molecules, I had decided to call these molecules endorphins. I did not coin the name; it was coined by somebody else from New York University, again the name [Eric Simon] escapes me. And to our absolute *amazement,* the first five residues from the N-terminal of our peptide of thirteen residues were identical to the sequence of this leucine enkephalin that the group of Kosterlitz had just published a few days earlier. And we proceeded to get the structure of that thirteen-residue endorphin, and it included the whole five enkephalin, plus eight more residues. The next one, called gamma-endorphin, had one more residue, fourteen residues. Then we started to go after the longer peptides, which had these thirty-one residues. I had been asked to deliver the Harvey Lecture at Rockefeller University that day, sometime in the middle of January, and I went there and showed in that lecture the results which we had obtained just a few days earlier with these new

opiate derivatives of the brain. That made, of course, a lot of noise--and came back in the laboratory.

So we are still in the process of sequencing the thirty-one residue, which should be called gamma-endorphin--since [it was the third to be characterized and they were being named in sequence] alpha, beta, gamma. And then I got a phone call and a letter from C. H. Li, the chemist of Herbert Evans at Berkeley, who had isolated ACTH, got the structure of ACTH, and he had also isolated another hormone, another molecule, which always makes people uncomfortable because nobody could find any biological activity for it, except a minor lipotrophic effect, which he had called beta-lipotropin. And since it became obvious, gradually, that our thirty-one residue was part of the structure of the molecule of C.H. Li, he asked me and begged me to call this molecule beta-endorphin rather than gamma to make sure that it would show the parenthood with his beta-lipotropin, and I said, "Of course, yes." By the way, it was so touching because C. H. Li passed away, maybe a year later, and there was a big [memorial], of course, at the University of California in San Francisco [inaudible]. And I was the only person outside of that group who was invited to be at the memorial; I went, of course. So that is how we established also the structure of beta-endorphin, which is a thousand times more potent than the enkephalins of Kosterlitz and company. Now we had those molecules.

Determining the structure of growth hormone-releasing factor (GRF)

With Nicholas Ling and Jean Rivier, we synthesized the full beta-endorphin, and we tested for release of growth hormone: inject it in rats and, sure enough, it is as potent as morphine was, extremely potent, to stimulate secretion of growth hormone. We put it *in vitro,* directly on the pituitary--no effect. So, obviously, we did not have the right stuff. We had something that worked like morphine, but that did not stimulate the secretion of growth hormone at the level of the pituitary per se. So we go again. At that time a couple of papers had appeared in the literature of very rare cases--in fact, only three had ever been reported--of patients who had full acromegaly, fully acromegalic, and they had no pituitary tumor. The suspicion was that they always had some tumor somewhere else, and removing that tumor would cure the acromegaly--the idea was that the tumor was secreting growth hormone, which a tumor can do, secrete all sorts of things--and that would take care of it. But we also heard of two cases where those tumors did not contain growth hormone, did not release growth hormone, but these people had acromegalic levels of growth hormone. So the idea occurred, at least to me, that those tumors might secrete some peptides similar to the hypothalamic peptide that would stimulate the secretion of growth hormone without being growth hormone per se. We obtained two such tumors, one from somebody called Mike Thorner from the University of Virginia, who had recognized one such tumor of this young woman acromegalic, who had a tumor of the pancreas, I think. He was keenly

aware of all these concepts and so on, and he measured the growth hormone level of that patient before and right after removal of the pancreatic tumor, and sure enough, her blood growth hormone decreased in hours, to normal. He had saved some of that tumor, and some of it went to the laboratory of Wylie Vale and the other part went to mine. Meanwhile, I had given a big lecture in Paris to the French Endocrine Society members about what we were doing, and I said, "You know, we still don't know what is the controller of the secretion of growth hormone." I talked about such patients as had been seen either with a tumor secreting growth hormone or a tumor possibly secreting an analog of the endogenous releasing factor, and I remember saying, "If any of you in your clientele or in the department hospital ever see such a patient, call me on the phone, let me know, and I will send you a round trip ticket to San Diego, so long as you bring me the tumor." *Sure enough*--it is so amazing--a few months later I got a letter from this young woman [Geneviève Sassolas] who was a resident in the Department of Medicine in Lyon telling me that they had a patient with full acromegalic, had no pituitary tumor, but they could not find any tumor anywhere else. I wrote back and made a few suggestions, and a week later got another letter from her saying, "Yes, indeed, you were right. He had actually two tumors in the pancreas." So I said, "You remember what I said, your roundtrip ticket is ready." She said, "No, please come [to Lyon] and we will do it together to get the tissue." I couldn't go because the laboratory was working full [inaudible] on something, so I sent to Lyon this young woman who was in my laboratory, Fusun Zeytin was her name; she was involved in tissue cultures in my laboratory and she spoke perfect French. So she went there, got together with Geneviève Sassolas and the surgeon, and two days later was back in the laboratory with a frozen tumor of 100 grams from that patient. In *no time*, in actually less than a week, we were able to show that part of the tumor was--strangely enough--loaded with somatostatin, and the other part was loaded with this growth hormone-releasing substance. In a couple of weeks we established the complete structure of that peptide which turned out to be three residues more than the one which we had gotten from Mike Thorner, and we published that. Wylie's group published also their results. That was the growth hormone-releasing factor, which is forty-four residues, native form.

Wylie Vale isolates the corticotropin-releasing factor (CRF)

Meanwhile, by the way, the group of Wylie Vale in 1981--by that time Wylie had a laboratory of his own, still at the Salk Institute, with Jean Rivier, Catherine Rivier, and a couple of other people, and they had been the ones who isolated the CRF, the corticotropin-releasing factor, which was really an extraordinary thing. We had been looking for it since 1955, and we were in 1981. And to this day, what has come out and what is still coming out from Wylie's laboratory in this field is of superb quality and makes me very happy and proud, to be sure. So that is where we are.

Isolation of fibroblast growth factors

And in 1975, after the endorphin story, we starting looking for some of these growth factors with Bob Holley, who had just received a Nobel Prize a couple of years earlier, was now interested in those, but they were not at the Salk Institute. [His group] did not have the facilities to sequence whatever they were isolating, so we started doing this work with them, and we went ahead and isolated several of the fibroblast growth factors.

On receiving the Nobel Prize (1977)

So as all of this was going on with these growth factors, and after the endorphins, and a series of analogs synthesized and tested with Nicholas Ling, one good morning about four o'clock the phone rang in the bedroom, and at four o'clock in the morning being woke up by the phone is not my favorite way. So I got up and rather gruffly picked up the phone, and on the other line I hear, "This is Professor Luft calling from the Nobel Committee." So I immediately became a little more congenial. [laughs] And sure enough, that is when I was told that I had received the Nobel Prize of the year--that was 1977--and that I would share that Nobel Prize with Andrew Schally, which sort of surprised me, and with Rosalyn Yalow for all the work she and Sol Berson, who had just passed away the year before, had done on the establishing of all these radioimmunoassays, which were really a revolution in the practice of laboratory medicine in all sorts of ways. So that's the Nobel Prize. I was a little uncomfortable, to be honest, to see that Schally was also part of that because I really wondered why and on what basis. There was no question that his laboratory--with Matsuo and Arimura from Japan--had come up first with the right structure, the right molecular structure, of the LRF, of the gonadotropin-releasing factor--but anyway. So I went to Stockholm for the Nobel Prize, and as you know, it is quite a show, and everything went very well. It was extremely pleasant, extremely congenial. And at the big ceremony, in front of hundreds, maybe a thousand people in this big auditorium, and so on, the chairman of the committee--they give the Nobel Prize for the various fields: physics, chemistry, physiology or medicine, and the newest one in memory of Alfred Nobel--in economics. Everybody is there on the podium, and the chairman of the committee for physics, chemistry and physiology gets up, and the king is there and the queen and so on. The chairman calls your name so you get up, and he reads the citation that goes with it, at which time you just move on the podium to the king, who is now standing up, and who hands you your diploma of the Nobel Prize and the small box containing the gold medal. You bow to the king, bow to the audience and you go back and sit down. And the next call--this is alphabetical order--and Schally is called, same thing and so on, and then Roz Yalow. Then we still have to have the naming and giving the prize for

economics. And as we are all re-seated in our chairs, in front of the whole thing, we open our book to see--usually the diploma is always there with special engraving--so we look at it, and what do I see? I have in front of me the Nobel Prize with the name of *Schally*. So meanwhile he opens his book and he sees that he has the Nobel Prize book in the name of *Guillemin*. He sort of fidgeted and said, "What do we do?" I said, "Let's do nothing in front of everybody; we will exchange those things"--all of this from the corner of my mouth--"we will exchange those things after the end of the ceremony, and so on," which is what happened. So we went to this room to remove our [ceremonial attire] and get our normal clothes back, and at that place Schally comes to me and he has this thing, and I said, "Okay, Schally, I am giving you your Nobel Prize, and you received mine." And he never said a word. So that was my conclusion of the episode [laughs] *in toto*, so to speak--not quite, but good enough. We went back to the [Salk] Institute; Schally went back to his place in New Orleans, which sadly enough was completely destroyed by Katrina. He moved; to my knowledge, he is now in New Orleans [and] has a laboratory of his own. I don't know exactly what they do.

Inhibin and activins

We went back to the Salk Institute, where we completed--we went on with the work on these growth factors. We also clarified, once and for all, something that had been hanging for twenty years in the clinical and research laboratory literature regarding the possibility of the existence of a molecule called inhibin, which was postulated as an inhibitor of the triggering of puberty in both boys and girls. We started looking for such a molecule, and in no time--again, because we were so well equipped in terms of the methodology in the laboratory--we isolated a series of very complex molecules, which were indeed accounting for all the activity of the inhibin. It was Nicholas Ling who recognized that these were heteromeric molecules. And then--and I don't remember exactly how it started--it became obvious to us that some of these fragments of the full molecule also existed, isolated, and they could recombine to make molecules which had the opposite biological activity, in other words, stimulating the secretion of LH and FSH, which I called activins, against the concept of inhibins. This has been confirmed many times, ever since, by all sorts of groups.

Retirement (1989) and the Whittier Institute

So all of this brings me to a retirement age, and we closed the laboratory at the Salk Institute. I was asked by a very wonderful colleague from the Scripps system to come, with parts of the laboratory, to this Whittier Institute for Diabetes and Endocrinology--just across the street practically from the Salk Institute, which we did for a few years. In fact, I was even on the board of that group for a few years.

VII. SALK INSTITUTE (1997-present)

Guillemin: But because of structure--the financial thing with Scripps--the thing did not subsist, but I was then asked by the faculty of the Salk Institute to reintegrate into Salk, which I did. I am still over there with an office of my own. I still have the same secretary; after thirty-seven years, Bernice [Walker] is still my secretary. Three years ago I was asked by the board of trustees to take over the presidency of the Institute because the then president, Richard Murphy, had resigned for various reasons. And while the board was still looking for a new president, they asked me to take over as president on an interim basis, so I signed for six months. It lasted about two years, but we now have at the Institute a president who is a wonderful person, Bill Brody, who was the president of Johns Hopkins for twelve years. So this new life for the Salk Institute, and mine is advancing in age.

VIII. THE ENDOCRINE SOCIETY

Chappelle: I want to ask you something about the Endocrine Society. What were the most compelling issues that you were involved with as president of the Endocrine Society?

Guillemin: That is a very good question. I was actually president-elect, and Sid Ingbar was the president, and he and I were, of course, on the best of terms. We learned, simultaneously--he and I through different [sources]--in my case because the news came to me from France--that it was obvious that there was a major problem of some contamination in the human growth hormone that was being distributed, essentially by the NIH at that time, for those children with panhypopituitarism or growth hormone deficiency. They were being treated with injection of human growth hormone and were doing very well with it. But it was obvious--based on two cases in England, at least three or four in France and, I think, one or two in this country--that there was something contaminating that growth hormone, which produced Creutzfeldt-Jacob disease, the equivalent of what we call mad cow disease in humans. So I remember getting together with Sid Ingbar on the phone, and we said we must advise the FDA, we must advise the NIH to stop delivering these preparations because we don't want to see this Creutzfeldt-Jacob contamination spread all over the place. To make us feel even stronger about this immediate closing of the distribution of the extracted purified human growth hormone, the people at Genentech, with whom we were in close touch, showed us and told us [that] they were ready to put on the market synthetic human growth hormone, which obviously would not be contaminated with Creutzfeldt-Jacob and so on. So all of this combined, we--the Endocrine Society--became public, and said, We don't want to distribute the growth hormone--to keep distributing the growth hormone, which you are used to--because of [the] contamination problem, which we didn't quite understand, by the way, at that time, but there is now

available for your patients these new synthetic molecules coming from Genentech on which you can rely with absolute certainty. This was the transition. We insisted with the FDA--I remember talking to people in the FDA, to make sure that the Genentech molecule would be cleared and FDA approved, as soon as possible, which it was. That is the way we handled this in this country, which was really wonderful. The French went a different way; it is embarrassing. They kept distributing their preparation, which was heavily contaminated with those viruses called prions, and they really ran into a fair number of children who became infected with this Creutzfeldt-Jacob, but eventually they stopped that, of course, and came back to the proper way of--actually, it is now all synthetically DNA produced kind of hormone. So that was one of the major things, in fact, *the* major thing that happened. At the meeting today, by the way, around the table of the breakfast of the old past presidents, three of us who had been involved with this at that time were still there, and we were able to talk about it, including Mel Grumbach, this leading pediatrician who had been involved with the early treatment with human growth hormone for all these children and teenagers.

Chappelle: Thank you.

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Interview History—Roger Guillemin, MD, PhD

Dr. Guillemin was interviewed by Michael Chappelle on June 19, 2010, during the Endocrine Society's Annual Meeting held at the San Diego Convention Center. The interview lasted one hundred and thirty-nine minutes. The transcript was audit-edited by Mr. Chappelle and reviewed by Dr. Guillemin 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 four (4) 45-minute mini DV cam tapes, is in the Library holdings and is available under the regulations governing the use of permanent noncurrent records*. Records relating to the interview are located in the offices of the Clark Sawin Library's Oral History of Endocrinology Project.