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JEROME M. HERSHMAN, MD

Interview conducted by
Michael Chappelle
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INTRODUCTION

Jerome M. Hershman, MD, is Distinguished Professor of Medicine at the David Geffen School of Medicine at UCLA, and Associate Chief of the Endocrinology and Diabetes Division, Department of Medicine at the West Los Angeles VA Medical Center. He pioneered the interrelationships of thyrotropin, chorionic gonadotropin, and their receptors, and he was among the first to point out the effects of vasopressin, tumor necrosis factor, transforming growth factor, thyrotropin-releasing hormone, and cytokines on thyroid function. Dr. Hershman served as chief of the Endocrinology and Diabetes Division at the West Los Angeles VA Medical Center for three decades, where he completely transformed it into one of the leading endocrine units in the country.

BIOGRAPHICAL SKETCH

Dr. Hershman was born in Chicago, Illinois in 1932. He graduated from Northwestern University in 1952, earned a degree in chemistry at the California Institute of Technology under the guidance of Linus Pauling in 1953, and received his MD degree from the University of Illinois Medical School in Chicago in 1957. Following an internship at Cook County Hospital in Chicago and a residency at Beth Israel Hospital in Boston, he served in the US Air Force as a Captain and internist from 1959 to 1961. After fulfilling his military obligation, he took a two-year fellowship with Ted Astwood at the New England Center Hospital in 1963, where he studied the effect of the antithyroid drug, propylthiouracil, on the deiodination of thyroxine. He next took a metabolic residency with Maurice Strauss at the Boston VA Hospital. Later, on the advice of Strauss, he accepted a position as a VA Clinical Investigator at Northwestern University in 1964. While at Northwestern, Dr. Hershman pioneered the development of a radioimmunoassay for bovine TSH. In 1967, he was recruited by Jim Pittman to the University of Alabama and the Birmingham VA Hospital as an assistant professor of medicine and Assistant Chief of Clinical Nuclear Medicine, eventually becoming Chief of the VA Endocrine Section in 1971. His accomplishments in Alabama include the development and application of an immunoassay to measure TSH. Also while at Alabama, following the elucidation of the structure of thyrotropin-releasing hormone (TRH) in 1969 by Roger Guillemin and Andrew Schally, Dr. Hershman undertook early and important clinical studies with synthetic TRH, establishing its dose-related effects on TSH regulation and demonstrating its use in the evaluation of patients with pituitary disease, work done in collaboration with Jim Pittman and Charlie Baugh. In 1972, David Solomon recruited him to the University of California Los Angeles as Professor of Medicine in residence and Chief of the Endocrinology and Metabolism Division, West Los Angeles VA Medical Center. In Los Angeles, with long-time collaborator Gene Pekary and fellow John Morley, Dr. Hershman continued his work on TRH, establishing its presence in tissues outside the hypothalamus, pancreas, and reproductive tract. In addition to this work, his group went on to study placental thyrotropin and prove that it was HCG; study patients with hyperthyroidism due to placental tumors secreting excess HCG; identify the HCG effect on the thyroid in normal pregnancy and hyperemesis gravidarum; and investigate TSH regulation in non-thyroid illness. He also collaborated with Clark Sawin on studies of TSH and thyroid hormones in aging. Dr. Hershman is a past president of the American Thyroid Association and the founding editor of *Thyroid*. He has 300-plus published scientific journal articles and has written more than 100 authoritative book chapters and reviews about thyroid function and disease. More recently his research has contributed to our understanding of the mechanisms of formation and growth of thyroid tumors and the role of the sodium/iodide symporter.

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I. FAMILY BACKGROUND AND EARLY YEARS

Chappelle: Dr. Hershman, would you please tell me a little bit about your family background starting with your grandparents?

Hershman: My grandfather--my mother's father--came here from Poland. He was in the Russian Army. So he was unique by having traveled as a young man. He came here around the turn of the century, 1899-1900. He then established himself and brought other people from the little shtetl that he came from. My mother came here when she was two-years old. My father was also an immigrant from the same shtetl in Poland--came here as an older teenager because his older sister had come here, again through my grandfather. His parents never came here. My grandparents, I think, were merchants. In Poland, my father's father was a feather merchant and my mother's father was in the grocery business and had a very successful business in Chicago.

Chappelle: When and where were you born?

Hershman: I was born in Chicago, July 20, 1932, and I was the second child in the family. I have an older brother.

Chappelle: What's his name?

Hershman: My older brother's name is Marvin.

Chappelle: What did your mother and father do for a living when you were growing up?

Hershman: When I was very young, my father had a laundry business. I think he had very little capital, and you can get into that business without much capital. And he always had in mind to have a shoe store, and he did--around 1939 or 1940--go into the shoe business. And he had a shoe store and continued that throughout his career.

Chappelle: Did the Depression have much of an effect?

Hershman: He earned enough, I think, to keep the family well fed and in a nice apartment, so we were really fortunate. My father was extremely hard working and, I think, was a good role model in that respect.

Chappelle: Was education a priority in your family?

Hershman: It was. My mother's education was only through high school, and my father went to night school after he came to Chicago. Education was a priority in Jewish families of that era in Chicago, so the parents hoped the children would go to college.

Chappelle: In Chicago, did you grow up in a Polish-Jewish neighborhood?

Hershman: It was a neighborhood that was mainly Jewish, but not exclusively. So it was kind of a mixed neighborhood, and people came from all different parts of--probably, initially--Eastern Europe, but diverse places. Not as diverse as nowadays.

Chappelle: What kind of education did you have?

Hershman: I went to grammar school and high school in Chicago. At that time the schools were very good. The high school I went to, Roosevelt High School, was a good school and there was an emphasis on academia, social life, and sports.

Chappelle: And what were your favorite subjects?

Hershman: I liked just about everything. I enjoyed English. I took Latin because there was an outstanding Latin teacher there. I had an excellent English teacher who also ran the school newspaper and encouraged me to join the newspaper. And the science subjects, unfortunately, were weak. Math was just so-so, but I enjoyed those subjects and probably did some learning on my own.

Chappelle: What about your extracurricular activities?

Hershman: I was active in sports. I loved basketball and probably devoted too much time to it. We had a mediocre basketball team, and after my third year on the team, I left it because I was asked to be the sports editor, and so instead of participating, at least in basketball, I wrote. I was also on the tennis team as a senior, but again it was a pretty mediocre tennis team. On the other hand, I love tennis and have continued to play tennis since then.

Chappelle: Did you ever consider a career in journalism? Was that possible?

Hershman: I did not consider a career in journalism. I enjoyed the writing but did not go on with it. But on the other hand, I learned to write, probably through that work.

II. NORTHWESTERN UNIVERSITY (1949-1952)

Chappelle: Why did you choose to go to Northwestern for undergraduate?

Hershman: Well, I did not have broad horizons in terms of leaving the Chicago area or the state of Illinois, so I applied to Northwestern and received a full-tuition scholarship. They had a good reputation and it seemed like a good place to go, and I have never regretted it.

Chappelle: And what was your major?

Hershman: I majored in chemistry because--I was a premed when I went there and some of the chemistry courses for premeds were watered down; I avoided those and just took chemistry courses with people who wanted a career in chemistry. So I had some wonderful chemistry teachers. I did take biology courses as a part of premed and enjoyed them, and then I became interested in economics and had a minor in economics as well as in biology.

III. CALIFORNIA INSTITUTE OF TECHNOLOGY (1952-1953)

Chappelle: But you were always thinking in terms of premed even when you switched to chemistry and even when you took economics?

Hershman: I was. For a while I flirted with going on for a year in economics and getting a master's degree in economics, but not seriously. I knew that I wanted to go into medicine. I finished Northwestern in three years by going to summer school for two summers, so it looked like I had some extra time, and after I was accepted at medical school, I decided that I wanted to leave Chicago--do something different--and late in my senior year I applied to graduate schools in chemistry. I had a close friend, Albert Claus, who had thought more about chemistry because he knew he was going to go on in chemistry graduate school. And at that time it was easy to be accepted to graduate school if you were a good student, so I was accepted at diverse places I applied to, but because he chose Cal Tech, and had thought it over pretty carefully, I decided to go to graduate school at Cal Tech. I had been accepted at medical school at University of Illinois and at Northwestern with scholarships to both, so I remember it was with some regret that I called them to tell them that I was going to go to graduate school in chemistry instead. Northwestern held my acceptance, perhaps because I was in undergraduate school and held my scholarship, but the University of Illinois, being more bureaucratic, would not do that. So then I went to Cal Tech, starting there when I was just twenty-years old as a graduate student.

Chappelle: Were you worried about having to postpone your situation at the University of Illinois or...

Hershman: I wasn't, because I could have gone to Northwestern and I wanted the experience of being a graduate student and of going somewhere else rather than spending all my time in Chicago. So it was kind of a fling that I thought about very seriously and for a long time. I never regretted it because it was at Cal Tech that I developed a much more serious interest in science and in research.

Chappelle: How were you supported both in medical school and at Cal Tech?

Hershman: Well, at Cal Tech--

Chappelle: I'm sorry--before medical school--in college and at Cal Tech.

Hershman: In college, I lived at home and commuted, so I did not have to pay for living expenses. I earned some money selling shoes at a chain store, which was popular among my friends, and actually earned more money than I could spend. It wasn't a lot of money, but college and my work kept me very busy so that I really didn't have time to spend the money that I had, a very modest amount. And when I graduated from college at Northwestern, I had more money in the bank in a very small account than I did when I started. At Cal Tech, my parents did not support me at all. I had a teaching assistantship that paid for living expenses and a scholarship for my tuition. And so I got along on kind of a meager budget.

Chappelle: What was it like studying science at Cal Tech in the early 1950s?

Hershman: Cal Tech was a very exciting place from a scientific point of view, and it was a small place compared with Northwestern. It was a small university, and people were very friendly. I got to know people in other fields in addition to medicine--in addition to chemistry. There was more biochemistry in the biology department than there was in the chemistry department, but the people in chemistry were interested in proteins, peptides, and in DNA (deoxyribonucleic acid). The head of the department, Linus Pauling, was already a very distinguished scientist, and he did make an effort to meet all of the graduate students and provide them with some counseling about their research project. Even though I intended to stay there for just enough time to get a master's degree, he did counsel me about research. We were required to do a research project in order to receive a master's degree.

Chappelle: And did you have other mentors besides Linus Pauling?

Hershman: Well, Linus Pauling advised me to work with a young man named Alex Rich, who had received an MD from Harvard Medical School, and because he had a medical background and--[knowing] I wanted to go into medicine--Pauling thought it would be a good combination.

Alex Rich was a very charming fellow who was interested in DNA--really in the structure of DNA--which a number of people were working on around the world. That was a hot topic. Pauling had an interest in that too, particularly in the association of the strands of DNA. Alex Rich was interested in the crystallography, and he had devised a method called streaming birefringence for determining the molecular length of DNA; it was a kind of Rube Goldberg apparatus in which there were two concentric circles, the outer one whirling around and causing an alteration of the path of polarized light going through it when there were large polypeptides, or other really very large molecules, that

would cause an alteration of this polarization. And since DNA was a very long molecule, that would fit the bill. So I did these measurements using this apparatus, which tended to float around the room while the motor was going, so it took two people, one person to hold the apparatus down and the other person to make the measurements--and I isolated the DNA and did all of this work myself and then did the measurements and wrote a thesis. I was told I was the first person to receive a master's degree by completing a thesis in just one year of work--along with course work and doing some teaching of a physical chemistry course for geology students in order to justify my teaching assistantship.

IV. UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE (1953-1957)

Chappelle: And then once you had your master's, you had to reapply [to medical school]?

Hershman: Well, during the course of that year, I reapplied to the University of Illinois Medical School. I had been influenced by a friend of my brother to go there in preference to Northwestern. I also knew a couple of other people--friend of the family, who thought it was a wonderful medical school. And in some ways it was more appealing than Northwestern because University of Illinois had two clinical years--or two years of basic science, and then two clinical years--whereas Northwestern had three years of more didactic work. It was at that time [considered] appropriate to change into more of a clinical emphasis during the last two years. So I did go to University of Illinois School of Medicine in Chicago.

Chappelle: Is there anything that stands out regarding your medical-school training?

Hershman: During medical school--in the first year--we were encouraged to meet with faculty members in regards to choosing a research project. Not everybody did that, but I was quite interested in that--perhaps because of my training and research in chemistry at Cal Tech. So I interviewed with a man named Howard Armstrong, who was at University of Illinois but mainly based at the Cook County Hospital. He had a research laboratory at the Hektoen Institute at the Cook County Hospital, which was just across the street from the medical school. He was a very charming fellow. He had done work on the physical chemistry of plasma proteins with Scatchard and Oncley in Boston. He had come from the Peter Bent Brigham Hospital in Boston, and I decided that I would work with him. So, all four years of my medical school--on a part time basis--I worked in his research laboratory. I think the University of Illinois had outstanding teachers in basic science as well as in the clinical years, so I was very pleased with the training that I received there, both in basic science related to medicine and in clinical years.

Chappelle: Did you interact with Dr. Armstrong socially?

Hershman: I did, in that he used to invite me to lunch at the Cook County Hospital--with members of the faculty--when I was a freshman and sophomore. That was quite an honor to be in their company. And then after I was engaged, I remember [that] he invited me to dinner at his home; he was a very cordial person. He was well rounded, played the piano, had an apartment on the top floor of the Cook County Hospital in a residence hall called Karl Meyer Hall.

V. COOK COUNTY HOSPITAL: INTERNSHIP (1957-1958)

Chappelle: How did Dr. Armstrong influence the direction of your career?

Hershman: He influenced it in a very substantial way, both from the point of view of my doing research during medical school and getting some publications from that--more so than I had ever thought about--and by recommending that I apply for residency in Boston. I had decided, because I knew Cook County Hospital well--I had gone to a lot of lectures and seminars there as a medical student--that I wanted to intern there, so I did. I wanted to go into medicine, but at that time there was a rotating internship where we also got experience in surgery, pediatrics, and obstetrics as part of the internship. But it was at the end of my senior year that he encouraged me to apply for residencies after the internship year in Boston, so I did go out there to interview at places for which he had provided letters of introduction.

Chappelle: Now, were you interested in endocrinology or the thyroid at this particular time?

Hershman: I did have some interest in the thyroid because we had some lectures about thyroid disease. At that time radioiodine was very exciting to use as a tracer for visualizing the thyroid and doing some diagnostic tests. I remember our surgery department wanted to remove the thyroids all the time because the head of the department, Warren Cole, had made a reputation out of removing thyroids and finding a lot of thyroid cancer in what were called cold nodules of the thyroid. The diagnostic test was just radioiodine imaging, and then the patients would go to surgery. Ted Schwartz, who was in the department of medicine--really based at the Presbyterian Hospital--said that you didn't have to remove all those thyroids. You could treat people with thyroid hormone--which actually Astwood, who will enter the picture subsequently, had pioneered--and some of the nodules would shrink--or some of the goiters would shrink. I enjoyed this contrast between medicine and surgery, and I was influenced to some extent by Ted Schwartz as far as finding that endocrinology was exciting. At Cook County Hospital there was also a very dynamic endocrinologist, Sheldon Waldstein, who probably provided some subliminal influence in my choosing a career.

Chappelle: Were you doing any research at that time?

Hershman: During the internship, there was no time for research. It was very busy.

Chappelle: How did you come to do your internship at Cook County?

Hershman: Because I had worked at Cook County doing research in Armstrong's laboratory, I learned a great deal about County. I wanted to stay in Chicago. I had thought about the University of Illinois Hospital, but at Cook County the interns could take more responsibility than they were given in a university hospital, and that appealed to me. So I chose that and the residents there were excellent; I had good training from them, and the attending physicians were generally outstanding.

Marriage

Chappelle: Did you get married at this time?

Hershman: I got married during my internship--about halfway through the internship. I had met my wife a year and a half before that. After a year we were engaged. In fact, she was in graduate school when I met her--she was in graduate school in biology at Northwestern. She started Northwestern after I left, so I never met her there, but I met her on a tennis court in Chicago. We became engaged about a year later. Before we were engaged, she spent a summer at the Woods Hole Oceanographic Institute as part of her graduate work. I went to Boston in June--shortly after graduating and before starting my internship--and interviewed at hospitals in Boston for my residency; I went to the Beth Israel Hospital where Hermann Blumgart was chief of medicine. And although I interviewed at some other places, I was very honored to have been accepted on the spot for a residency after I finished my internship. So I took that position and then went back [and] did my internship, and halfway through--I remember toward the end of December in my surgery clerkship--we got married. That was unusual--being married during surgery--because it was supposed to be very difficult with no time off. But it was the end of December, elective surgery was down, and they gave me permission to get married and take a week off.

Chappelle: What is your wife's name?

Hershman: My wife's name is Fleurette Kram Hershman.

Chappelle: And what was her career?

Hershman: She was interested in biology and she--I met her when she was working for a summer at a hospital taking EKGs (electrocardiogram) before starting graduate school. It was just a summer job at a hospital that her father worked at as a surgeon. He worked with the surgical group at that hospital on the north side

of Chicago. I went to play tennis at a park court and she was playing on an adjacent court with her sister. We got to talking; I saw her that night, there was a courtship, and it has been a very happy marriage. It is now fifty-one-years old.

VI. RESIDECY AT BETH ISRAEL HOSPITAL; TEACHING FELLOWSHIP AT HARVARD MEDICAL SCHOOL (1958-1959)

Chappelle: How did your residency at Beth Israel shape your career?

Hershman: Beth Israel really opened my eyes because most of the residents had gone to Harvard Medical School since it was a Harvard teaching hospital, and they had different vistas. They were interested in academic careers. They were interested in going to the NIH for a period of additional training, postdoctoral training. I could not do that because during my internship, I had signed up for the Berry Plan, which was a plan whereby doctors could volunteer for the military instead of being drafted--since the doctor draft was still on. But at Beth Israel, I became more interested in an academic career. For the next year I had planned to take a metabolic residency at the Boston VA that I thought would have given me a different exposure, but I could not do this unfortunately because the Air Force, which I had volunteered for, would not give me a deferment for additional years of residency training. So after the one year at Beth Israel, I had to start my Air Force training--Air Force experience as a physician.

VII. UNITED STATES AIR FORCE (1959-1961)

Chappelle: What were your duties in the Air Force?

Hershman: In the Air Force I was an internist--even though I had one year of training--and I was assigned to a fifty-bed hospital, which had not been built. We operated out of a ten-bed dispensary, so I did mainly outpatient internal medicine. People were hospitalized for minor illnesses at the dispensary. The air base that I was assigned to, Beale Air Force Base in north central California, was not far from the Travis Air Force Base, which was a larger base that had a very nice hospital. I had time to go there a couple of days a month to attend their endocrine clinic, which was staffed by a fellow named Russ Randall, who subsequently went to the Boston VA Hospital. So [it was] an introduction to outpatient endocrinology.

Chappelle: And how did you feel about this experience in the Air Force? Did you look on these as lost years for your career?

Hershman: Well, they were the easiest years I've ever had in medicine because, at least initially, our base was not that busy. We did have some time to think. I did a lot of reading. I was in charge of the laboratory in our dispensary, which of

course was just minor administrative job. I arranged for some seminars that our group of eight physicians attended. We would each pick a topic and talk about it, and I learned how to practice outpatient internal medicine, taking care mainly of minor illnesses. I enjoyed it, but I didn't regard it as a challenging experience. I think it further shaped my decision to go into academic medicine--if I could develop a career that way--rather than practice internal medicine, mainly taking care of outpatients. And that was quite a contrast because in the previous years I had been taking care of very sick patients in the hospital instead of healthier outpatients.

VIII. FELLOWSHIP WITH DR. E. B. (TED) ASTWOOD AT THE NEW ENGLAND CENTER HOSPITAL (1961-1963)

Chappelle: So, you had planned--before you went into the service--to do a fellowship.

Hershman: I had planned to do a fellowship. I had not quite decided exactly what it would be. I was leaning toward endocrinology pretty strongly, and I did take a course in endocrinology while I was in the Air Force--a five-day course in San Francisco, UC San Francisco, and that strengthened my interest. And then at the end of the first year of my Air Force tour, I interviewed for fellowships in Boston--I did want to return to Boston. So I interviewed with Sidney Ingbar at the Boston City Hospital--the Thorndike Institute there--met some of the people that worked with him that were very early in their careers: Lew Braverman, Bill Green--and thought that was a lot of fun. I remember that my talk with Ingbar lasted over two hours; afterwards, I had a headache. And in the afternoon I was scheduled to meet with Ted Astwood. Ingbar was very intense. I remember he said that he would like to offer me a fellowship, but I wouldn't find out until September. At that time my wife and I had had our first child, and I knew I had to have a job. When I went to visit Astwood, I found him to be a very charming man, very straightforward. The group with him was very cordial; his setup looked just right. He offered me a job and I accepted on the spot. So I went home with a job and feeling very good about that.

Chappelle: Would you comment on Dr. Astwood's scientific stature and accomplishments?

Hershman: Ted Astwood was somewhat senior at the time I met him, and he had already become famous for two things. One, he had developed the antithyroid drugs--he did this while he was at the Peter Bent Brigham Hospital--and those drugs were the first treatment, medical treatment, for hyperthyroidism, so they were used widely. He initiated the treatment with the antithyroid drugs, which he developed going from understanding something about thyroid physiology, working with rats to see which drug was most effective in interfering with the synthesis of thyroid hormone, and then taking it to patients. First he developed propylthiouracil and--just a few years later--methimazole: propylthiouracil about 1943-4, methimazole in clinical use from 1949. And those two drugs

have remained the mainstay of the medical treatment for hyperthyroidism up to this time, sixty years later. So he was quite well known for that. In addition, he had purified ACTH (adrenocorticotropic hormone), so he had an interest in the pituitary and in pituitary protein polypeptide chemistry. He was just a very wonderful, nice man who was nondirective. At the time I started to work there, he was not doing much clinical work, but he had a colleague, Carl Cassidy, a member of the department who was the clinical endocrinologist in the group. I wanted some clinical endocrinology training, so another fellow--Jim Givens--and I decided that we would divide up the first year of doing clinical endocrinology--it was not required--and we alternated at three-month intervals of working in clinical endocrinology with Carl Cassidy, both in the outpatient setting and in the hospital consultation setting.

Chappelle: Would you speak a little bit about the development of clinical research centers and the role of federal government during this time?

Hershman: During the second year of my fellowship, there was a first clinical research center at the New England Center Hospital. Astwood was well connected with the NIH and was granted a clinical research center for the New England Center Hospital--Tufts Hospital. And so he asked for projects for that clinical research center. They were presented to a committee, and if successful, then you could start your clinical project. I had worked on the antithyroid drugs studying the effect of propylthiouracil on deiodination of thyroxine, a metabolic pathway for thyroxine. At that time it was not appreciated that thyroxine was converted to triiodothyronine (T_3). It was thought to be just totally deiodinated, which it is, but not converted to the more active thyroid hormone, T_3. I showed in working with rats--with a faculty member who had come from Tennessee and used to spend his summers at Astwood's lab, Les Van Middlesworth--that propylthiouracil interfered with the deiodination of thyroxine. That was a hot topic then. And Astwood had a drawer full of other antithyroid compounds that he had tested. So we tested the effect of these other antithyroid compounds--with structures that were somewhat similar to propylthiouracil--for their effect on the deiodination of thyroxine in rats given radioactive thyroxine. We measured urinary radioiodide after injecting thyroxine labeled with radioiodine as a way of showing that there was increase in deiodination, an increase in urinary radioiodide from rats who were in metabolic cages. I found that 5-propylthiouracil was more effective than 6-propylthiouracil, the one that is used clinically, so I synthesized 5-propylthiouracil because there wasn't enough of it to use for clinical studies, and was able then to put it in capsules and give it to patients, something that would be totally unheard of now, and did this in the clinical research center at the New England Center Hospital. We showed that 5-propylthiouracil was a potent inhibitor of deiodination of thyroxine.

Chappelle: What was Lester Van Middlesworth like as a mentor or personality?

Hershman: He was a very dynamic fellow who appears to be high strung, but he was really a very, very nice man, a warm and cordial person. In July when I started my fellowship, he was looking for someone to help him with this project, which might go on in the summer. So I offered to do that. It was quite a contrast to picking a project in Astwood's laboratory because Astwood was completely nondirective. He encouraged you to think about possible projects that you could do. There were several faculty members--and you would talk to the faculty members, see what they were doing and then pick a project. Or it could be entirely of your own creation. So instead of working on a project that I had created myself at the time, I worked with Van Middlesworth, and it did probably help me to a fast start in research. I studied, subsequently, the effect of these compounds on the binding of thyroxine to plasma proteins, which was also a topic of interest at that time.

Chappelle: Did you meet Clark Sawin at this time?

Hershman: Clark Sawin came to the laboratory when I was in the second year of the fellowship. That was the start of his fellowship. He was in the Army right before that, and so we did strike up a friendship, which lasted until his untimely death. We did a lot of collaboration through the years on research projects and were close friends for all of these years.

Chappelle: What was he like as a personality and a medical scientist?

Hershman: Clark was a wonderful person, very tall, kind of slender fellow with an imposing presence. He had gone to Boston Latin School and Brandeis University. He had an encyclopedic mind and near-photographic memory and was very analytic. We did not work on any projects together during the fellowship. He chose his own work, and was very well thought of. He then went on to the Boston VA Hospital where he had the largest part of his scientific career.

Chappelle: How well did your time with Dr. Astwood serve you in your career?

Hershman: I think it convinced me that I wanted to stay in academic medicine. During the fellowship, I decided to enlarge my horizons by working on projects that required various techniques from organic synthesis--which I had not counted on--to developing apparatus for work in which I perfused a dog thyroid gland that had been removed surgically by residents who were using the dogs for surgical procedures. So I developed an apparatus for perfusing the thyroid, which taught me how to utilize sort of a Rube Goldberg scientific apparatus that had been developed for rat hearts, but I adapted it to the thyroid. So I learned various techniques. I had in mind--if there was any philosophy at all to my research fellowship--enlarging my horizons from the point of view of

techniques, and I was given a good recommendation by Astwood for subsequent training and an academic career.

IX. BOSTON VA HOSPITAL: A SECOND RESIDENCY (1963-1964)

Chappelle: Why did you choose to do a second residency at the Boston VA Hospital?

Hershman: Well, late in my second year of fellowship, I decided that if I were to work on a medical faculty and do clinical medicine and endocrinology that I needed more hospital training in medicine because I had been away from it for four years--two years with the Air Force and two years of the fellowship. Because I had been interviewing at the Boston VA before that--I had arranged this metabolic residency that I couldn't take when I went into the Air Force, instead--I interviewed again with Maurice Strauss and told him that I would like to be a *senior* resident, but I would want some time to rotate through this metabolic residency--which was more of a nephrology, a salt and water background training; that is, the disorders that they would take care of. It also gave me some time to continue the research that I was doing. So I spent six months on the wards as senior resident and six months in the metabolic residency. And it was during that time that I decided I was interested in an academic career and started looking around for a job. I met with Maurice Strauss because one of the jobs that I was interested in was the position of VA clinical investigator, which you could take with you around the country: you could apply to any one of a number of VAs and get a position as a VA clinical investigator. My wife and I decided that we wanted to return to Chicago because we had been away from it for essentially six years, so that was a good time to do that.

Chappelle: What was Maurice Strauss like as a leader, a mentor?

Hershman: Maurice Strauss was a wonderful man, a very impressive clinical mentor. He met with the senior residents each morning to review the admissions of the previous night and he would ask very incisive questions. You really had to know your patients; and in doing so, he was an extremely good teacher. And he was available for consultation at other times. His presence on the medical service of the Boston VA was very strong. There was a good faculty, but he was certainly the most impressive of the teachers, and I enjoyed my experience there a great deal. I felt I learned a great deal of medicine, giving me the confidence I'd hoped to achieve in terms of taking care of hospitalized patients.

Chappelle: How far had your career progressed at this point?

Hershman: At this time, I had decided that I wanted to stay in academic medicine and I applied for a position as a VA clinical investigator, as I mentioned earlier. I went to Maurice Strauss to ask him about the future of the VA and he told me--this time was 1964--that when he came out of the military, nearly twenty years

before that, along with some other physicians that went on to senior positions--but were of course much younger then--that many of them had said that there was not going to be any future in the VA. And he said that those people had had a number of positions in different institutions since then, whereas he had stayed at the VA. And he thought that the future of the VA was bright for an academic career associated with universities. So he encouraged me to apply for the VA clinical investigatorship, which I did at the VA associated with Northwestern.

X. VETERANS ADMINISTRATION RESEARCH HOSPITAL AND NORTHWESTERN UNIVERSITY MEDICAL SCHOOL (1964-1967)

Chappelle: Why did you pick that particular VA?

Hershman: I wanted to return to Chicago, and so there were two places. One was University of Illinois and the other was the one at Northwestern. There was also the Hines VA, but I decided that the affiliation with Northwestern would be more interesting. There was no one working at that VA who could be my mentor--and I also wanted to be independent--I actually liked that idea rather than going somewhere where there would be a so-called mentor who might direct me a great a deal. I wanted to be *undirected* and to just work on my own.

Chappelle: How did your family feel about moving to Chicago?

Hershman: My wife and--at that time--our two children thought that was fine. We had remained close to our family in Chicago, so returning to Chicago was a good idea as far as the entire family was concerned.

Chappelle: What were your duties at Northwestern?

Hershman: At Northwestern, as a VA clinical investigator, I had about three-fourths, or a little more than that, of my time for my research. I made rounds as an attending physician two months a year, and then I also attended an endocrinology clinic at the VA, and occasionally an endocrinology clinic for some months--on a monthly rotation--at the medical school. The head of our endocrine group at the VA was a fellow named John Colwell, and his interest was in diabetes. He had a laboratory across from mine doing diabetes research. We had a lot of interactions but did not collaborate in research.

Chappelle: How did you divide your day?

Hershman: I spent the vast majority of my time in my research laboratory. So I had a technician. I continued my work in deiodination of thyroxine, but I also started some work on sulfonylurea drugs, perhaps because of John Colwell. At that

time there had been a claim that they affected the thyroid gland and thyroid hormones in blood, and so I studied the binding--the interference by sulfonylurea drugs with binding to the thyroxine-binding globulin. I also did some work on the effect of iodine given with TSH as a mean for interfering with the peroxidase enzyme system--resulting in a paper that is very seldom quoted nowadays, I must say. And then I became interested mainly in radioimmunoassay of TSH and developed a method for bioassay of TSH. That is, I took the McKenzie mouse bioassay and set that up to compare the bioassay with immunoassay. The immunoassay work, I just started--and didn't take very far, but I did start working on the radioimmunoassay of bovine TSH.

Chappelle: Did you have collaborators?

Hershman: At Northwestern, I mainly worked [by] myself. I worked with some students who came to work in the laboratory, but I did not have an active collaboration with others. I had a person in physiology I would review my work with, Allan Lein , who had had a career in thyroid research related in some ways to the deiodination of thyroxine.

Chappelle: How did you manage to balance career, family, and social life when you were in Chicago?

Hershman: As best I could, because I did work hard in my research work. I commuted for about forty minutes each way. I used to go into the hospital and my laboratory often on the weekends, but it all worked out. I think mainly because my wife was very strong in terms of raising the children, and did not expect me to have to spend a long time with the kids other than doing social things and picnics and meeting with family on weekends, usually Sunday afternoon.

XI. BIRMINGHAM VA HOSPTIAL AND THE UNIVERSITY OF ALABAMA SCHOOL OF MEDICINE (1967-1972)

Chappelle: How did it come about that you became the chief of the endocrine division and chief of nuclear medicine at Birmingham VA Hospital and also professor of medicine at the University of Alabama?

Hershman: Well, at the end of the three years of the VA clinical investigatorship, I decided to look around for another job. That was just a three-year position. What Northwestern suggested was that I go to the Cook County Hospital, which didn't have a very good setup for me in endocrinology. I looked at a position at Indianapolis. I remember turning it down because I decided it wasn't just right. And no sooner had I turned it down--calling the fellow that had offered me the job--than I had a call from Jim Pittman at the University of Alabama in Birmingham and the Birmingham VA, saying he knew I was looking for a job. Well, I had gone through this interview process and turned it down and decided to look around some more. I said, "No, I wasn't looking for a job. I just turned

one down." He said, "Yes, I know. I just talked to Leo Oliner." So he was very persuasive, and he persuaded me to come to Birmingham to look at the job, even though I had never lived in the South--and didn't know much about it. So I went there to visit, and it was a wonderful position: the laboratory was a new lab and came with a number of technicians, and it was an excellent division of endocrinology that Pittman had developed, with a lot of excellent medical scientists in different areas. He had an interest in the thyroid as did his wife, the late Constance Pittman. So I saw it as a great opportunity, and I remember meeting with my father-in-law about leaving Chicago. My father-in-law knew that I wanted an academic career, and he said I should take the best job that was available. And this was clearly the best job. So I moved to Alabama and worked hard. At that time, I was successful in setting up a TSH radioimmunoassay. There were a number of things that just came together while I was there. I had good person power; I had good grant support, and it was a very formative time for moving ahead in the areas that I have worked on most effectively in my career in academic endocrinology and, particularly, thyroid research.

Chappelle: You mentioned your immunoassay for TSH, would you say a little bit more about that?

Hershman: Yes. The radioimmunoassay for insulin had been developed by Berson and Yalow, and that technique was applied to growth hormone. And then several people tried getting this to work to measure TSH. The leaders in the field were Bob Utiger, who was at Washington University, and Bill Odell, who was with the NIH. Utiger, actually I think had been at the NIH working with Odell as well. So I visited both places--Utiger at Washington University, Bill Odell at NIH--and saw how they were doing their radioimmunoassays. The main thing was separating the antibody-bound TSH from the unbound TSH--there were a variety of methods. And I took what I thought was the best of both methods and set it up myself. So it was a small step that I think was perhaps a slight improvement--I'm not sure Bill Odell would have agreed with that. But anyway, we did have an assay that was set up and which could measure TSH in the *above-normal* range very effectively, and slightly into the normal area.

Around the same time, the structure of TRH (thyrotropin-releasing hormone) had been determined by Schally and Guillemin--really [by both of them in their separate laboratories] around the same time [in 1969]. Jim Pittman and I went to visit Schally at the New Orleans VA and learned something about the structure. We went back and talked to a solid-phase chemist at the University of Alabama, Charlie Baugh; although it was a tripeptide, it was a tricky one to synthesize. So he said he could synthesize it for us, and then I was to watch him, and then go ahead and do it on my own. Well, that was impossible because the reagents that he used had to be specially purified. So the work had to occur in his lab, and indeed he had a wonderful technician who did this after he designed the synthesis. So I worked with her, did the synthesis, and went

back to his lab again--working with his technician--and did the synthesis. And at that time you could synthesize a compound and then use it in patients. There was not the kind of restriction that you have nowadays--just cleaned it up and purified it and used it. And so I had the opportunity to give TRH to patients--with a fellow working with me in endocrinology--and measured the increment in TSH that occurred after giving the thyrotropin-releasing hormone. Jim Pittman and I applied this to various clinical scenarios. [We] showed that in *hypo*thyroidism there was an elevated TSH with an exaggerated rise after giving TRH; that in patients with *hyper*thyroidism, who had a very low TSH--it was suppressed by the high serum concentrations of thyroid hormone--that there was no rise; and in pituitary conditions of different sorts there was an increment that tended to be delayed if there was a hypothalamic lesion, but if the pituitary was wiped out there was no TSH increment. So we published a number of papers on using TRH. We established dose-related effects in terms of TSH increments.

Chappelle: So it worked out for you that you had this assay right at the moment when TRH was discovered.

Hershman: Yes, it worked out very well in that respect. And I had an excellent technician who could do the assay.

Chappelle: The *New England Journal of Medicine* published a paper that you coauthored in 1971 with Jim and Constance Pittman on hypothalamic hypothyroidism. What was the significance of that paper?

Hershman: The idea that if you had a lesion in the hypothalamus you could become hypothyroid was known, and there were animal models showing that, but there had never been a patient in whom that had been demonstrated. So it was a patient that Connie had as her patient who was a youngster--teenager--with diabetes insipidus and growth hormone deficiency. We showed that when that young person--the little boy--was given TRH there was a rise in TSH, but it was delayed--as one might expect if there had been a lack of TRH, and yet the pituitary was intact. So it was the first published case--I believe--of hypothalamic hypothyroidism. It was a brief case report, but it was a first.

Chappelle: In 1974 you wrote a medical progress report in the *New England Journal of Medicine* on the clinical application of TRH. Have you already told me what those applications were?

Hershman: Right. Mainly they were the applications I told you about--showing the application of TRH to diagnosing *hyper*thyroidism and the failure of TSH rise after TRH because the normal TSH could not really be measured with precision then. So it was a failure of a *rise* of the TSH that was important for diagnosing milder hyperthyroidism, in which TSH is suppressed. And, again, we showed if the pituitary was wiped out--by pituitary tumors, for example, or

the treatment of the tumor--that there was no TSH increment. So the review was reviewing the data to date, which had also been going on in various laboratories: Norm Fleisher in New York; Schally cooperated with people in Mexico to do similar studies. So there were studies going on all over the world--eventually quite a few studies, excellent studies in Europe.

XII. WADSWORTH VA HOSPITAL AND THE UNIVERSITY OF CALIFORNIA LOS ANGELES (1972-present)

Chappelle: How did you become chief of the endocrine section at the Wadsworth VA Hospital and professor of medicine at UCLA?

Hershman: After I had been in Alabama four years, I was promoted to professor of medicine. And at that time, Jim Pittman left to take a position in Washington as the head of research in the VA. I decided that was probably a good time to consider other positions. I stayed there for a year, which was also productive. And then was offered, during the fifth year I was in Birmingham--which I enjoyed living in by the way; people were very nice, very cordial--nice university community. But I was offered this job to head my own division, and I wanted to do that. I had not been chosen be head of the division of endocrinology at the University of Alabama. A fellow who had an emphasis on diabetes--well known to the local people there--was chosen, instead. And so I was recruited for the position at UCLA, really at this VA Hospital--West Los Angeles VA, known then as the Wadsworth VA Hospital--to run the division here, really to get it going again because it had fallen into disuse. The previous head had left two years before, had not been replaced, and they were looking for somebody. The chairman of medicine at UCLA at that time in 1972 was David Solomon, who had actually worked in Astwood's Lab, was an endocrinologist of excellent stature. And he recruited me along with the chief of medicine, Seymour Dayton. When I came out to visit, it looked like an excellent opportunity. There was a fly in the ointment in that six months later the hospital was closed because it was considered earthquake vulnerable because of the earthquake in 1971--that happened after I accepted the job. The VA closed the hospital. I remember Jim Pittman called and told me. He said there was going to be another hospital built. He wasn't supposed to tell me that at the time, but since we were close friends, he did. He encouraged me to go ahead with my move if I chose to. And, indeed, all of that did happen.

Chappelle: So you were recruited to build a division?

Hershman: I was recruited to build a division because there were no full-time people here, then. So I brought in a diabetologist--because we have a lot of patients with diabetes--Seymour Levin, who has remained a life-long colleague. And then I brought in--the following year--another person, Harold Carlson, whose expertise was in the pituitary. We collaborated together to do a lot of work, again TRH related. I developed with the help of Henry Friesen--who had been

a fellow with me at Astwood's Lab--who had developed--who had purified prolactin, developed an antibody to it. So Harold Carlson and I set up an assay for prolactin in my laboratory here. I had a very good TSH assay that I'd worked on, but we set up the assay for prolactin, and we and others showed that TRH caused a rise in prolactin. And that was work that Harold Carlson did because he was interested in prolactin. So, we were a nice team. He worked on prolactin. I worked on TSH. And, we did a lot of work in neuroendocrinology at that time in that respect.

Chappelle: Now in your early days at UCLA, how did you divide up your day?

Hershman: Because I was initially just a one-man program--I had recruited two good fellows in my first year, who I worked with clinically. I was fortunate that they came here, and one of them, David Geffner, has remained on our clinical faculty all of these years and is an outstanding teacher. But, I was responsible for the hospital consultations; I ran our endocrine clinic. I was in charge of the Endocrine Fellowship Program and did rounding--we actually had an endocrinology ward at that time, subspecialty ward, and I was responsible for that. So I really had to work very hard during the first two years I was here.

Chappelle: What were your teaching duties?

Hershman: I was responsible for teaching residents who rotated through our endocrinology ward, and I was also attending physician in general medicine doing two or three months each year in general internal medicine. But, I nevertheless did have a high proportion of my time for my research.

Chappelle: Did you bring anybody with you from Alabama to work in your lab?

Hershman: In Alabama, I had recruited a PhD named Jim Kenimer, who worked with me for one year *there*. At that time I had begun the work on placental thyrotropin and was particularly interested in HCG (human chorionic gonadotropin) as a thyrotropin. So, Jim came with me; he was an expert in protein purification. And a Japanese fellow, Akira Kojima, who had worked with me, also came with me. So, two people came with me and that was very helpful in getting my research laboratory going.

Developing assays for thyroid-stimulating hormone, thyroxine, triiodothyronine, and thyrotropin-releasing hormone

Chappelle: What was the status of your TSH assay at this point?

Hershman: Well, in the early years here, I also recruited a PhD who had an excellent background in physical biochemistry, Eugene Pekary. He and I worked together to improve our TSH assay, and I believe that at the time--we

published about 1975, but we worked on this for three years--we had the most sensitive TSH assay in the world. It required a very long incubation, so it wasn't so practical, but nevertheless there wasn't anything better: all the TSH assays required several days of incubation before you got a result. And Gene and I did a lot of work on TSH radioimmunoassay because we could now measure the normal range. And [I] actually collaborated with Clark Sawin to do some studies about the changes in thyroid hormone levels that occurred after giving TRH. TRH would cause an increment in TSH, which would increase thyroid hormone levels. And we did some collaboration on that--I also worked with other people here on that. I also had radioimmunoassays for thyroxine and triiodothyronine and got some help from Inder Chopra, here, who was a pioneer in the development of thyroid hormone radioimmunoassays.

Chappelle: How did the emerging realization of the complexity of TRH affect your research or the field in general?

Hershman: After a few years it was realized that TRH was a ubiquitous neurotransmitter--that it was present in other regions of the brain aside from the regions in which it was produced and secreted from--that trickled down through the portal venous system from the hypothalamus to the pituitary, increased TSH secretion, and arranged a set point for TSH secretion. It was found in other regions of the brain by a radioimmunoassay for TRH that Bob Utiger did. And, we also developed a radioimmunoassay for TRH--Gene Pekary did that. And we studied its presence in the reproductive tract. And, so it was found that TRH was a ubiquitous neurotransmitter. We showed that it was present in the pancreas. My colleague Seymour Levin was studying perfused rat beta cells from the pancreas of rats, and we showed that TRH altered insulin secretion when the pancreatic beta cells were perfused with TRH. And, indeed, it was present in what are called the delta cells, I think, of the pancreas. It's role there in regulating insulin secretion is really unknown. But I think it is a ubiquitous neurotransmitter, somewhat like epinephrine and norepinephrine.

On the teaching of fellows

Chappelle: Would you speak a little bit about the teaching of fellows?

Hershman: I've been very fortunate to have wonderful fellows. I've actually had fifty-seven postdoctoral fellows who have worked in my laboratory or with me in clinical research. Much of the work I've done has been clinical research, but many have worked in the laboratory mainly, or done both. And five of them have gone on to be heads of endocrine divisions. So I've been very pleased with the fellows. Generally, unlike Astwood, I would make a few suggestions for possible projects that they could work on, based on what was available in my laboratory and in regard to colleagues, but I never just pigeonholed a fellow and said, "Do this" as I think many mentors did. But Astwood never told a fellow what to do at all. You just went to him if you had an idea and he

would tell you if it was a good idea or a bad idea or he didn't know about it. I tried to be a little more directive, but wanted fellows to work on something that they had a specific interest in. And, one of the advantages of being here is that Los Angeles is an attractive area for young people, so a lot of fellows who trained elsewhere decided to come to Los Angeles for fellowship, and I was fortunate to have some wonderful fellows who were high achievers in many respects. And I would allow them to--as they progressed--develop their own projects.

Demonstrating that placental thyrotropin is identical to human chorionic gonadotropin (HCG)

Chappelle: Would you say a little bit more about placental thyrotropin and the idea that TSH was made in the placenta?

Hershman: In Birmingham, our laboratory did some work on purification of bovine TSH. And even in Chicago--the last year I was there--I developed interest in the possibility that the placenta secreted a thyrotropin because the placenta secreted placental lactogen--it's similar to growth hormone, similar to prolactin. And the concept had arisen that the placenta was sort of a pituitary gland. It has not entirely held up. But nevertheless the concept that the placenta secreted a thyrotropin was there. So, I started extracting placentas in order to find a thyrotropin. And I had a bioassay for TSH that I could test it in, and I had the immunoassay for bovine TSH. And, indeed, I found that there was some cross-reacting material that I could extract from placentas in Birmingham. I also collaborated with obstetrics in that respect. They would provide placentas to me. But it turned out that I could not repeat that work when I came here. And I realized that probably the columns we used had been contaminated with bovine TSH even though we went to great lengths to perfuse the columns, get rid of any contaminating material. Because when I came here and tried to repeat that work, it wasn't repeatable. But, instead, I found that the thyroid stimulator could not be separated from HCG. And this thyroid stimulator that we worked on was provided from hydatidiform moles (placental tumors) by a fellow named Pat Higgins in Toronto, who worked with me. He actually did the clinical work on patients with hydatidiform mole who were hyperthyroid, and he sent me these placental tumors--the hydatidiform moles--which we extracted to purify the thyroid stimulator and then tested the various fractions by bioassay, and then we would do immunoassay for HCG. And we could never separate the biologic activity from HCG. So, lo and behold, one time Jim Kenimer--[who was a fellow] in the first year that I was here--and I said, We can't separate it. They must be the same. And, indeed, we got some highly purified HCG from Robert Canfield of Columbia and showed that that had thyroid stimulating activity. Now, one of his other collaborators (Bruce Nisula) had done that at the time as well, so we both concluded that HCG was the placental thyrotropin.

Then I started studying variants of HCG in the hydatidiform moles--because it varies in its glycosylation, and the more basic forms have stronger thyroid stimulating activity in *in vitro* bioassays. But, on the other hand, if you remove the sialic acid so it gets more basic-- because it's a glycoprotein, so, it's got a lot of carbohydrate on it. And, if you remove that sialic acid its halftime of disappearance in serum is less. So there are two camps. Some people say it has to have more sialic acid to be a good thyroid stimulator, but in a bioassay, the less sialic acid it has, the more thyroid stimulating it is. And, I had a wonderful Japanese fellow, Masayoshi Yoshimura, who worked with me on that aspect of it, and I had some collaborators here, Murphy Goodwin at USC, who provided hydatidiform mole tissue.

Chappelle: Were there any therapeutic applications?

Hershman: The applications, I think, in clinical medicine have actually become broader because not only was it realized that HCG--when it was secreted in extremely large amounts by placental tumors--was a thyroid stimulator. But with improvements in TSH assays and good HCG immunoassays, I showed that early in pregnancy there was a suppression of TSH, and this coincided with the peak HCG at ten to twelve weeks of pregnancy. So I developed the concept that HCG had a role as a thyroid stimulator in early pregnancy, but that it didn't raise thyroid hormone levels outside of the normal range. We found that they were slightly increased. Others didn't find that. It has been very controversial. But I think there has been general agreement [that] thyroid hormone levels are slightly increased early in pregnancy as long as iodine supplied for making thyroid hormone was okay, and that TSH is suppressed. Everybody agrees on that. It's suppressed when HCG is high. So I think that HCG stimulates thyroid function, albeit within the physiologic range early in pregnancy. Daniel Glinoer produced some very nice data on that. We had two studies showing this inverse relationship between HCG and TSH. So, I think the concept that HCG has a role in normal pregnancy has been accepted. And there is a condition of pregnancy in which there is severe vomiting, called hyperemesis pregnancy. There, HCG levels are high and some of the women with hyperemesis gravidarum actually have hyperthyroidism related to it when the HCG levels are high, and that concept has also been widely accepted. And in collaboration with Murphy Goodwin and the group at USC, we were able to show that and show that the thyroid stimulating activity in serum was proportional to the HCG content of the serum.

Investigating endemic goiter

Chappelle: What led you to investigate goiter in New Guinea and Central Africa?

Hershman: In the early '70s, when I had a good TSH assay, people working in Central Africa--the Belgian Congo group--contacted me about measuring TSH. Patients had goiter, had iodine deficiency, and they wanted to determine

whether there was an increase of TSH in these people. And we did show that by measuring TSH, supplying the data to them, that TSH was increased. It was increased in many of the subjects to levels that would be considered *hypo*thyroid levels here. I collaborated with an Australian group, Basil Hetzel and his colleagues, who were doing similar studies of severe endemic goiter in New Guinea.

Chappelle: What were the therapeutic implications of that data?

Hershman: It was hard to tell clinically by examining these people that they were hypothyroid, even though they had big goiters, because of communication problems, because of insensitivity of determining hypothyroidism when it was mild. So, when the TSH was elevated, I think that was additional evidence that there was a problem in regulation of the thyroid, in producing enough thyroid hormone, and eventually I think it was accepted that an elevated TSH was indicative of hypothyroidism, and I think these were early studies that evolved that way.

Studying TSH regulation in non-thyroid illness

Chappelle: What is non-thyroid illness syndrome (NTIS) and what led you to focus on it?

Hershman: Well, non-thyroid illness syndrome is a condition in which there are abnormal--usually low levels--of thyroid hormones, the T_4 and the T_3 in serum in patients who are severely ill with other conditions, such as pneumonia or people in intensive care units with multiple organ failure, but nevertheless sustainable. And that was a syndrome that had a lot of focus about twenty years ago. People didn't understand it: did the low levels of thyroid hormone indicate hyperthyroidism? It really wasn't clear. So I did some studies of that in our patients with chronic renal failure on dialysis. We found actually their TSH measurements--that healthier people were normal. And, in general, the TSH was normal in the people with non-thyroid illness and low thyroid hormone levels, and as the people would recover, the TSH would rise higher. An Australian group showed that. I collaborated with our chief resident here at that time, Greg Brent. He was a resident and became chief resident and then went on to a very successful career in endocrinology and is now *my* chief. I recruited him to come back here after he spent ten years in Boston to join our faculty. After thirty years as chief of endocrinology here, I stepped down, and he stepped up. He is now the chief of our endocrinology and diabetes division. Anyway, we did some very good studies on non-thyroid illness including, I believe, the only study in which we gave thyroxine to these people with very low thyroid hormone levels, in an effort to see if that would improve the outcome of their condition. Unfortunately, no, it did not. The mortality predicted for these people was very high based on their very low thyroid hormone levels. There actually was a correlation with severity of illness. And

by giving thyroxine, which would raise the free T_4 and depress the TSH a little bit, there was no improvement in the outcome of these patients.

Thyroid cancer and the sodium-iodide symporter

Chappelle: Why did you begin to focus on thyroid cancer in the midnineties?

Hershman: Around 1992, a fellow named Nat Ross came to join me; he had trained in molecular biology--took over the position as assistant chief. At that time I had shifted my interest to some extent and became interested in thyroid cancer. I worked with another fellow on a review of the medical treatment of thyroid cancer. Thyroid cancer is a condition that endocrinologists see a lot because those patients keep returning to see us for follow-up of their thyroid cancer. We got some thyroid cancer cells from a collaborator at UCLA named Guy Julliard--actually a radiation oncologist who developed thyroid cell lines. And we studied the effect of the cytokine tumor necrosis factor-alpha, on these cells and their survival--had a paper in *JBC (Journal of Biological Chemistry)* on that. And then we continued to do studies on TNF-alpha. Now, it was really TNF-alpha that brought me to this--because TNF-alpha is a cytokine secreted in severe illness. I hypothesized that it was responsible for lowering the thyroid hormone levels. So in a rat model, in which we administered TNF-alpha--that makes animals sick if you administer it--we showed that there were lower thyroid hormone levels: that the synthesis of TSH was reduced--and in some early molecular biology work we showed that the messenger RNA of the beta subunit of TSH was reduced. We speculated--based on this data--that the whole system was damped down in non-thyroid illness. But, then I moved the TNF-alpha work into this thyroid cancer model to see what effect it would have on the thyroid cancer cells. It inhibited their growth. Unfortunately, it did not inhibit the growth of other papillary thyroid cancer cell lines. So, it was not generalizable. But it did inhibit growth of this the first papillary thyroid cancer cell line that we tested.

Chappelle: Did the transition to cancer research entail much reorganization of your lab?

Hershman: It did in a sense. After the work without TSH radioimmunoassay, we evaluated the commercial immunoassays for TSH. I initially got involved in testing of some of the commercial tests, and it was clear that they were much better, and there was no reason for my lab to continue [developing tests]. And work with TSH wasn't as interesting anymore, in terms of finding out much new. We did a number of clinical projects on it, but I decided to move in the area of thyroid cancer. The work that I became interested in doing was mainly at a basic level because, even though we have thyroid cancer here, the population that we have to follow is much smaller than those of big cancer centers, so I decided to focus more on the basic science of thyroid cancer. I was fortunate to have two excellent molecular biologists join me. One of them, Michael Fenton, is continuing to work with me. And I was also interested in

the sodium iodide symporter--which Nancy Carrasco cloned, now almost fifteen years ago. We found, as did others, that the symporter was relatively inactive in thyroid cancer cells. We decided to work on trying to improve that, as have other groups--trying to activate it [the symporter], so that thyroid cancers--papillary cancers--could be treated with radioiodine. So in order to improve it, you have to find out exactly why it's not working. Well, this led to studies on the molecular regulation of the sodium iodide symporter. We've studied the far-upstream enhancer. A Japanese postdoc came to my lab, Katsumi Taki, and worked on this and found that there was a region in what was called the far-upstream enhancer of the gene that had some regulatory components. And we found that a binding factor--necessary to activate it, bound to this upstream enhancer, and would activate the symporter--but it was deficient in a line of papillary thyroid cancer cells. And Mike Fenton, who joined me subsequently, showed that the missing factor was a transcription factor called CREM (Cyclic Adenosine 3', 5'-Monophosphate Response Element Modulator)--C-R-E-M--which has a lot of other roles in cells of the body. And so that was the main contribution in recent years of our work on thyroid cancer; it was really on the regulation of the sodium iodide symporter. I have continued to focus on that, and the work that I am doing now is--

Chappelle: Excuse me just a minute. Would you say what the sodium iodide symporter is?

Hershman: The sodium iodide symporter is the protein that concentrates iodide. The thyroid cell is unique. There are some other cells that also concentrate iodide, like the salivary gland and the stomach, and they also have this symporter. It is called the symporter because sodium also travels into the cell along with iodide in a way to provide electrical neutrality, and so the iodide is transported in along with sodium, that's why Nancy Carrasco named it the sodium iodide symporter. And the regulation of this protein has become a big focus of work in many laboratories, so that was my focus.

Chappelle: And you were saying your contribution--?

Hershman: Our contribution was to show that there was this far-upstream enhancer that was important for regulating the expression--the turning on of the sodium iodide symporter. It was unusual to have something that was almost ten kilobases upstream that was a component of this enhancer, so we called it a far-upstream enhancer in the human gene.

Chappelle: What were the therapeutic implications?

Hershman: The goal is to activate it when it is inactive so that thyroid cancers can be treated with radioiodine. They *are* treated with radioiodine, but more than half the time the thyroid cancer cells--that are called differentiated cells because they still have morphology that is similar to normal thyroid cells, different but similar, and ideally they will be treated with radioiodine--but more than half

the time you can't treat them with radioiodine because they've lost this important component of thyroid cell function. They still secrete the major thyroid export protein called thyroglobulin, so they have *some* of normal thyroid function, but they lack the concentration of iodide because the symporter is not functional. So the goal is to make it functional. And a number of laboratories, including ours, have tried a pharmacologic approach, and we have had some partial success with that. Hopefully, with pharmacologic manipulation of the symporter, we can activate it and then patients with metastatic thyroid cancer could be treated with radioactive iodine more successfully.

Chappelle: What is sunitinib?

Hershman: Sunitinib is a drug used for treating kidney cancer and a gastrointestinal-type of cancer, and it has also been tested with thyroid cancer. I became interested in it because it causes hypothyroidism and the mechanism by which it causes hypothyroidism is unclear. I am currently studying the possibility that it blocks the thyroid peroxidase enzyme--in a clinical research project. Our laboratory had shown that it does not block the symporter activity in a thyroid cell model. Others had speculated it did, and that's how it caused hypothyroidism. But I don't believe that's the mechanism. I think the mechanism is either that it compromises the vascular supply to the thyroid cells--which it is known to do because it inhibits the vascular endothelial growth factor receptors, that's one of its main anticancer actions, reducing the vascularity of cells--but it is also possible that it is blocking the peroxidase enzyme, and so we are pursuing that.

Perchlorate studies

Chappelle: Would you speak a little bit about your role as a consultant on toxic substances and the thyroid?

Hershman: I was asked a number of years ago by the University of California to be a consultant in regard to perchlorate contamination of drinking water. Perchlorate has contaminated drinking water because industry, mainly defense industry, rocket industry, has used it as a component of solid rocket propellant. It is a very strong oxidizer, and so when they mix up a batch of it--this is a reconstruction I've got from old-timers who worked in that industry--they'd mix up a large batch of rocket propellant, put a lot of it into the rockets, and then they would just throw the rest of it away because they could get away with it at that time. And the perchlorate is very soluble, so it would just trickle into the water supply, and eventually contaminate wells, rivers, and drinking water. And it is known that it will interfere with the uptake of iodide by the thyroid. The thyroid needs iodide to make thyroid hormone, so perchlorate, if the concentration is high enough, will block the uptake of iodide. We showed that the thyroid transports perchlorate. The symporter is responsible for transporting perchlorate into the thyroid. The thyroid transport proteins

affinity for perchlorate is between ten and fifty times as great as iodide, so if there is enough perchlorate, you don't get any iodide in. I reviewed the literature about this and wrote a report for the State of California. This is a controversial area because there are two camps. One is that the amount of perchlorate has to be two hundred times higher than what is in the drinking water currently, perhaps six parts per billion, and the other camp is that more than one ppb is bad. I think the State of California has reached sort of a compromise. And so, anyway, it was mainly literature review, but it did get me very interested in the role of perchlorate in thyroid cell economy, as a contaminant.

Chappelle: What about perchlorate as a therapeutic solution?

Hershman: Perchlorate was used in the 1950s as an antithyroid substance because it prevents the thyroid gland from synthesizing thyroid hormone by blocking the iodide uptake into the gland. It had been tested as a treatment for hyperthyroidism and was given in large amounts, but it was found that with chronic administration it was toxic in these large amounts, which are several orders of magnitude more than the contamination of the water that one would ingest if you received it in that way. So perchlorate therapy of hyperthyroidism was dropped after a number of years because of its toxicity. But at the same time, there is a possibility to use it to prevent the uptake of radioactive iodine from fallout from a nuclear bomb--I-131 is a part of that fallout and caused the thyroid cancers from the Chernobyl catastrophe, the cancers in the children. Iodide is used to prevent the uptake of the radioactive iodide, currently; there's a stockpile of iodine tablets--I am studying the possible role of perchlorate to be given for short periods of time to prevent the uptake of radioactive iodine causing DNA damage in thyroid cells.

Chappelle: Who is working with you on that?

Hershman: There is a fellow, Armen Okunyan, who worked with me as a student who is now working in my lab on that. I am collaborating with a group at UCLA interested in protection against radiation.

XIII. AMERICAN THYROID ASSOCIATION

Chappelle: You were president of the American Thyroid Association from 1992 to 1993. What were the most significant issues you had to deal with as president?

Hershman: The organization was running very well at that time, so I was not confronted with any crises. The secretary of the association at that time, Len Wartofsky, was in his fifth year, so he was very experienced. He would handle more day-to-day matters, and we would have a near weekly conversation about such things as the financial aspects of the ATA and interaction with other groups--it was in the early days of the creation of AACE (American Association of

Clinical Endocrinology), this clinical endocrinology organization, and our interaction with them. I had an opportunity to develop a leadership policy then. Usually the president would focus on one thing, and I decided that we should raise money for research to help young investigators, because it was getting hard at that time for young people to get their first grants. So we were fortunate to raise some money, actually it was raised more by one of the people in the organization who had an inheritance from a relative who passed away and wanted to leave a sum of money for scientific research.

Chappelle: Who was that?

Hershman: Frances Carr who did some excellent molecular biology of TSH and is now at the University of Vermont. That was kind of a seed grant. And then I steered the organization into getting money for research from donors who provide money to charitable organizations. So we got started in raising money. And Reed Larson, who succeeded me as president, agreed with me that he would move it along; we got together on this. And indeed, it has blossomed into providing research funding for young investigators for a two-year period to work on a project of their own to get them started. They are small grants, but they are quite decent.

Chappelle: Would you say a little bit about how funding and trying to raise support has changed since you first started out?

Hershman: I was fortunate to have started at a time when research funding was fairly easy to obtain by comparison with nowadays. It was at a time when 40 or 50 percent of grant applications were funded. Your track record meant a lot. If you had a good track record and a reasonable idea, you received funding without providing a lot of pilot data, as is necessary nowadays. Now it is very difficult. You have to have a lot of pilot data and show that your laboratory is fully capable of doing that work. And that has been the change that makes it very difficult to get grants nowadays. People plan on applying several times before getting their first grant, a contrast with the time when I started when you were nearly assured of a grant.

XIV. THE ENDOCRINE SOCIETY

Chappelle: What has been the nature of your relationship with the Endocrine Society over the years?

Hershman: Well, I joined the Endocrine Society in 1964. At that time you had to show some research accomplishment in order to get in, and fortunately during my fellowship I published several papers, so I joined in 1964. I have been on several of the committees including the postgraduate education committee, and I was able to develop the postgraduate program--it was called the Postgraduate Assembly--in Los Angeles. It would move around every year. It was a very

substantial three-day program, which would move from city to city, once a year. And so we had it here. I was on the Research Affairs Committee. I've been on the Publications Committee--serving a couple of terms on that. And I have found that it is a wonderful organization. It has become quite large because it is a large umbrella for many aspects of endocrinology. It has undertaken a much more active role than it did at the time I joined, when it had essentially one person who was the only administrative employee to now having a large number of people working in it.

Chappelle: What will you be doing at the Society's annual meeting this year?

Hershman: Well, this year I'm asked to give "The Year in Thyroid" lecture which I have found is a big job--reviewing a lot of literature and picking out what I think is the best literature to present. So that has been occupying a good portion of my time, including the last weekend trying to search for the best articles.

XV. CURRENT VIEWS OF THE FIELD

Chappelle: What are your current views of the field?

Hershman: The field of endocrinology has enlarged a great deal since I went into it when it was more physiologically oriented. Now the emphasis is on molecular biology on the one hand and on evidence-based medicine on the other hand, in regard to clinical applications. I think there is probably some more separation between clinical endocrinology and basic science endocrinology. Fortunately, the Endocrine Society has an annual meeting at which both are presented. I think that it is still a wonderful field with a lot of challenges. We have a large number of applicants for fellowship, mainly one in clinical training, but research training as well, and so I think the field has done very well and will continue to change in ways that are probably completely unpredictable at the present time.

Chappelle: Thank you.

[End of Interview]

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Interview History—Jerome M. Hershman, MD

Dr. Hershman was interviewed by Michael Chappelle on March 22, 2010, in his office at the West Los Angeles VA Medical Center. The interview lasted ninety-seven minutes. The transcript was audit-edited by Mr. Chappelle and reviewed by Dr. Hershman 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 three (3) 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.