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FRANCIS S. GREENSPAN, MD

Interview conducted by
Adolph Friedman, MD
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FAMILY BACKGROUND AND EDUCATION

- Dr. Friedman: Frank, am I doing this with your permission?
- Dr. Greenspan: Yes.
- Dr. Friedman: When and where were you born?
- Dr. Greenspan: I was born in Perth Amboy, New Jersey, on March 16, 1920.
- Dr. Friedman: Did you grow up in Perth Amboy?
- Dr. Greenspan: Yes, I grew up in Perth Amboy, went to high school there, then went to Cornell University undergraduate school, and Cornell Medical College.
- Dr. Friedman: Did you have any siblings?
- Dr. Greenspan: Yes, I have an older sister and an older brother. My mother died when I was born, and my father re-married, so I have a half-brother and I had a stepbrother.
- Dr. Friedman: What does your sister do?
- Dr. Greenspan: My sister was a teacher; she taught in the New York school system. She was a high school teacher.
- Dr. Friedman: What about your half-brother and sisters?
- Dr. Greenspan: Let's see, my half-brother is a stockbroker in New York--my stepbrother, actually--was in sales. He died at an early age of a stomach cancer, and then my real brother was in sales, and he died, also of a malignancy, when he was about sixty years old.
- Dr. Friedman: What about your parents? Where were they born? Did they have any vocations or avocations? What kind of education did they have?
- Dr. Greenspan: My father was born in Russia. Actually, he was born in a little town called Ostrog, which was about forty miles from Chernobyl. He came here in about 1890 with his several brothers. He originally came to New York, and then to New Jersey. He was in the grocery business, and they had a wholesale grocery operation in Perth Amboy and in northern New Jersey. My mother was born in--let's see--her family originally came from Russia, migrated through Sweden, and then to New York. I think she was born in

New York, New York City. My father met her when they were living in New York, and they were married and moved to New Jersey. My mother was a schoolteacher; my father was essentially in business.

MARRIAGE, MEDICAL TRAINING, AND MILITARY SERVICE

Dr. Friedman: When did you get married?

Dr. Greenspan: When did I get married? I got married when I was about twenty-five after I graduated from medical school; I had an internship and assistant residency at New York Hospital. Then I went into the Service for a year and a half, and then I met my wife when I was in the Service. I was stationed in San Francisco, and I met my wife in San Francisco. We were married in 1945, actually, when I was about twenty-five.

CHILDREN'S CAREERS

Dr. Friedman: Besides a daughter who has already achieved her own reputation, tell me about your children--I want to hear about her, too. Tell me about your children?

Dr. Greenspan: Well, we have three children. My oldest boy graduated from Stanford, and he is teaching in the California community college system at Alameda College. He teaches automotive mechanics and lives in Alameda. My second son also lives in Alameda--Alameda is a suburban area right across the bay from San Francisco--he's in real estate--real estate multiple listing service for a real estate operation. My daughter is a physician. She graduated from Stanford and then went to Boston and has been very active in treating patients with osteoporosis. They just moved to Pittsburgh where she is going to be in charge of a women's health program in an osteoporosis set up.

MEDICAL TRAINING

Dr. Friedman: That sounds great. As far as your hospital education is concerned, did you have any training in endocrinology, or was it all part of your residency?

Working with Ephraim Shorr in gynecological endocrinology

Dr. Greenspan: No. I did before I went into the Service. And while I was at New York Hospital, I worked with Dr. Ephraim Shorr. Dr. Shorr was the endocrinologist for New York Hospital and a very, very nice guy.

Dr. Friedman: I know of him.

Dr. Greenspan: Did you know Dr. Shorr?

Dr. Friedman: I know of him.

Residency at Cornell and Stanford; working with Tom Addis on the endocrine aspects of renal disease and the relationship between creatinuria and thyroid function; Bob Williams arranges a position in endocrinology with Evans and Li

Dr. Greenspan: He was particularly interested, actually, in gynecological endocrinology, and he worked with Dr. Papanicolaou. Papanicolaou developed the Pap smear, and he was studying the effects of estrogen in humans using the Pap smear as an indicator of estrogenic effect--a very gentle and very wise man. Then when I got out of the Service in 1948, I went back to Cornell for a one-year residency and then came out to Stanford where I finished my residency program. While there, I did some work with a Dr. Addis--Tom Addis--who was actually a nephrologist but was interested in the endocrine aspects of renal disease, and we did some work on the relationship between creatinuria and thyroid function. And as you know, in hypothyroidism there is diminished creatine excretion, and in hyperthyroidism there is increased creatine excretion, and we were studying this as a part of the possible application to the diagnosis of the disease. It didn't work out; it was a little too crude, but it was a nice project. Then, after I finished my residency, I had been following the work of Dr. Williams--Bob Williams--and I wanted to go back and take an endocrine fellowship with him. Actually, I was accepted to his program in Boston, but at that time he had just accepted a position as head of endocrinology in Seattle. So he called and said that he would be glad for me to come with him to Seattle, but he was afraid that--since he was just moving there--that it would be difficult to get anything going, and he recommended that I not go with him and rather that I arrange for another fellowship. What he did, which was really nice, he came out to San Francisco and talked to Dr. Herbert Evans, who--at that time--was head of the

Institute of Experimental Biology. He and Dr. Evans and Dr. C. H. Li were actively engaged in isolating and purifying pituitary hormones. He arranged for me to meet with Dr. Evans. Essentially, he arranged for me to obtain a fellowship to work with Drs. Li and Evans for a year as a graduate student in endocrinology, which was sort of equivalent to the fellowship program. Although it was all in basic work, there was no clinical work at that time.

Developing a bioassay for ACTH; working on a tibia test for growth hormone

Dr. Friedman: Did this continue on to your nuclear medical training?

Dr. Greenspan: No, actually the year that I spent there was mostly in hormone bioassay. We worked out a method for assaying ACTH by using the depletion of ascorbic acid in the adrenal glands of guinea pigs, and then I worked on the tibia test for growth hormone. In this system, we used hypophysectomized rats, and we administered growth hormone, and measured the thickness of the tibial plate, which grew as growth hormone was administered.

EVANS AND LI PURIFY AND WORK ON STRUCTURE OF HUMAN GROWTH HORMONE

Dr. Friedman: What age were the animals? You used immature animals?

Dr. Greenspan: Yes, but they were hypophysectomized. It is a crude but reliable method. It required a fair amount of hormone but was only useful for purification of pituitary hormone. That was one of the basic tests that was used by Evans and Li as they purified and worked on the structure of human growth hormone.

STANFORD UNIVERSITY: SETTING UP AN ENDOCRINE CLINIC; STARTING ON THYROID PROBLEMS

Working in nuclear medicine with Robert Newell; radioiodine uptakes and scans; working on an assay for TSH with P-32

Dr. Friedman: Then what did you do after that?

Dr. Greenspan: After I finished the fellowship, I actually got a little tired of working in the laboratory and wanted to get back to patients again, so I joined the staff of Stanford University, and there I set up an endocrine clinic. I set up a laboratory, and it was there that I

started to work a little bit with thyroid problems. The chap that was in charge of nuclear medicine was a Dr. Newell. I worked with him doing radioiodine uptakes and scans at the same time. I was working on a method for the assay of TSH--using the P-32 uptake of a chick thyroid following an injection of human serum. We were also using urinary extracts to see if we could measure TSH in urine--using the P-32 uptake of the chick thyroid following the injection of TSH. I haven't thought about this in a long time.

Dr. Friedman: You sort of have a conflict there because using the serum you have both TSH and T₄, and it is sort of hard to figure out which one is going to affect the chick more.

Dr. Greenspan: That's true; that's one of the reasons we were hoping that we could do something with urine. But at that time there was no appreciation that TSH wasn't excreted in the urine, and we were not able to detect urinary TSH. The method was not sensitive enough to pick up TSH in serum, even though it was quite good for pure TSH.

Dr. Friedman: Did you do any other work with the adrenal and cortisone except in relationship to the ACTH studies in pituitary?

Dr. Greenspan: No, I seemed to have gotten mostly involved--I sort of got into more thyroid work after I went to Stanford, and the other thing I did--which was probably the most productive--was to set up an endocrine clinic, which was very effective and worked out very well.

Working with Joe Kriss on radiophosphorus uptake by chick thyroid as a bioassay for TSH

Dr. Friedman: I noticed in your bibliography you did some work and had some contact with Joe Kriss.

Dr. Greenspan: Yes, I had a great deal of affection for him.

Dr. Friedman: Tell me more about him, and what was your relationship with him?

Dr. Greenspan: Well, Joe was a wonderful guy, and what had happened was that he had been trained--he had trained, I think at St. Louis--and then moved to Portland where he married and was living in Portland, working at a hospital there. But he really didn't like it and decided to get back in academic work. He came down to Stanford and was working with Dr. Newell, the chap I mentioned in nuclear medicine, and we got to know each other through his work in nuclear medicine. I was in endocrinology and in medicine, and he

was in nuclear medicine and doing some endocrinology in that area. As a matter fact, we wrote some papers together. Can I see my bibliography?

Dr. Friedman: Sure. Go ahead.

BECOMING DIRECTOR OF THE THYROID CLINIC AT UCSF

Dr. Greenspan: Well, Joe and I used the chick thyroid. We looked at the uptake of radiophosphorus by the chick thyroid and thought that to be a much more sensitive method for the bioassay of TSH. Again, that worked very well for the pure hormone. But it was not sensitive enough either for serum or for urine. We worked together for about ten years and then in about 1950--let's see, I started in 1948, and in about 1958, Stanford decided to move their medical school out of San Francisco and down to Palo Alto where the undergraduate school was located. Joe decided he would go down with them, and I decided I would stay in San Francisco. When Joe went down to Stanford in Palo Alto, he became head of nuclear medicine at that time. Dr. Newell had retired. And then at that time, I moved over to the University of California and became director of the Thyroid Clinic at UC and continued to do some research work at the University of California.

Dr. Friedman: About what year was that?

Dr. Greenspan: This was about 1958. They moved, and we split; I stayed in San Francisco, and Joe went down to Palo Alto.

ON JOE KRISS'S ATTEMPTS TO DEMONSTRATE HOW ANTIGENS FROM THE THYROID MIGHT HAVE GOTTEN INTO THE ORBIT

Dr. Friedman: I observed from your CV--but before we get into that, you didn't do any of the work with Joe on the orbitopathy?

Dr. Greenspan: No, I had--we set up the method, the McKenzie method, for the assay of long-acting thyroid stimulator (LATS) and studied that in a dynamic way, but I was not involved in any of Joe's work on the pathogenesis of the orbitopathy. Remember, he did that neat study where he injected iodine into the thyroid gland and showed that there was a retrograde circulation and the material that was injected into the thyroid moved up the cervical chain rather than down. He thought the antigens from the thyroid might have gotten into the orbit via retrograde cervical lymphatic drainage.

Dr. Friedman: I remember reading that.

Dr. Greenspan: I'm not sure that idea is valid. Now we know, actually, that lymphocytes throughout the body are sensitized to thyroidal and orbital antigens. So it doesn't necessarily require the movement of an antigen from the thyroid into the orbit since the orbital fibrocytes already have TSH receptor in them, and, therefore, they have the antigen. But at the time it was a very attractive hypothesis--but he did a lot of very nice work on orbitology.

Dr. Friedman: Anytime you want to stop to rest or want to drink, just tell me.

Dr. Greenspan: Okay.

Dr. Friedman: But, I noticed from your CV, also, you had done a few papers on thyroid and gonadal relationships and also on thyroid and breast cancer. Would you also like to discuss them with me?

Dr. Greenspan: Yes. What happened with that was that I was asked to write a chapter for a GYN textbook. I actually hadn't done any primary research in that area but essentially reviewed the literature. I wrote a chapter on thyroid physiology in particular reference to female endocrinology, but that was really for a textbook on gynecological endocrinology. I wrote that chapter for a couple of years, and then I stopped it. The other question you asked me was--

WORK IN THYROID AND BREAST CANCER: STUDYING THE POSSIBILITY OF THYROID DISEASE AS A PRECIPITATING FACTOR IN BREAST CANCER

Dr. Friedman: The other question was, what was some of the work in thyroid and breast cancer?

Dr. Greenspan: The thyroid/breast cancer project was very interesting. What had happened is that several radiologists had conducted surveys where they asked the patients who were coming in for a mammography what illness they had. And they were impressed with the fact that many women had thyroid problems and were on thyroid medication. So they postulated that the presence of thyroid disease was a precipitating factor in patients with breast cancer. Now, we decided to look into that. What we did is--we ran a survey on a large group of women with breast cancer, and we used it--controlled women without breast cancer using statistics and data from a large group of women who had been followed in San Francisco. The bottom line was it turned out that the incidence of thyroid disease in the non-breast cancer group was exactly the

same as the incidence in the breast cancer group. The thing that had surprised everybody was that there was a relatively high incidence of thyroid disease in women in both the pre- and postmenopausal age--which now comes as no surprise because we all know that. But at that time it was surprising. I did that with Dr. Piero Mustacchi.

Work on demonstrating thyroid therapy is not a cause of breast cancer with Piero Mustacchi

Dr. Friedman: Please spell that?

Dr. Greenspan: That's M-u-s-t-a-c-c-h-i. The first name is P-i-e-r-o. Piero was an epidemiologist and helped to get together the statistics on that. Essentially, what we were able to show was that thyroid therapy was not a cause for breast cancer. We were able to show that the two diseases were totally unrelated. The fact was that a lot of women had thyroid trouble and a lot of women had breast cancer; and there was simply the association that they were both occurring in women, females.

Dr. Friedman: It sort of was a coincidence?

Dr. Greenspan: Right, right.

Dr. Friedman: Is there anything else you want to tell me about your thoughts or your views on that?

Dr. Greenspan: About the breast cancer thing?

Dr. Friedman: Yes.

Association is not causation

Dr. Greenspan: I think it's a good illustration as a fact that you have to be careful about associations and when you're trying to relate to dissimilar situations. You have to be careful that the fact that two things occurring in one individual doesn't necessarily mean that they are associated; they may be totally independent observations, and that was certainly true in this situation.

PETER FORSHAM, A CO-EDITOR WHO SURVIVED ALMOST SIXTY YEARS ON INSULIN THERAPY

Dr. Friedman: I noticed, from the CV again, that you co-edited a text with Peter Forsham. I haven't seen or heard of anything about him for some time. Is he still living?

ORIGINS OF THE LANGE PUBLISHING COMPANY

Dr. Greenspan: No, Peter died about three or four years ago. Peter was head of the endocrine department at UCSF (University of California, San Francisco). He was mostly interested in diabetes and was a very wonderful teacher and a very fine individual. He himself had diabetes, which I think developed when he was about nine years old, and he was one of the first ones to go on insulin. He survived almost sixty years. He died when he was about seventy, so he survived almost sixty years on insulin therapy, which was really remarkable. The way we got into this--there was a chap by the name of Lange. Dr. [Jack] Lange was a UC graduate, and when he was in medical school, he used to put out or publish the lecture notes, which students could then purchase and help them get through the course.

Dr. Friedman: A good businessman?

Dr. Greenspan: He decided that this was important enough, so he essentially began to publish a series of volumes on medicine, neurology, surgery, anatomy, physiology, biochemistry. These were paper bound books, which were coauthored or authored by multiple authors, and were relatively inexpensive. They sold for twenty to twenty-five dollars and were updated every couple of years, so they enabled medical students to purchase very good text at a very reasonable rate.

Dr. Friedman: You were telling me--is there anything else about this?

Dr. Greenspan: Yes. I was telling you about Jack Lange and the Lange Publishing Company. Jack felt there would be a need for a textbook of endocrinology, and he asked Peter Forsham to edit it. He had asked Peter for several years, and Peter kept saying that he would do it when he had time, and he never had time. One day I was sitting next to Jack at a meeting, and he said, "Frank, would you be willing to be a coeditor of a textbook of endocrinology," which would be published by Dr. Lange. I thought that was a great idea, and so I said, "Yes, I would."

Coediting with Jack Lange

Dr. Friedman: We were talking about this Dr. Lange.

Dr. Greenspan: Anyway, so he asked me if I would coedit it. Actually, it turned out that Peter was involved in many other things, so I actually did most of the editing of the book. What we did is, we invited mostly a UC (University of California, San Francisco) group of authors to write the various chapters, and it was a good book, and it was well received, and it worked out very well. Actually, we have gone into five editions, and right now we are working on the sixth edition. I was with the book the whole time. My coauthors have varied, mostly because the editors either moved or had other projects in mind. But right now, the current edition will be coedited by myself and Dr. David Gardner, who is a very good endocrinologist at the University of California in San Francisco.

Dr. Friedman: Will they at least give you the credit of having it called Greenspan and Gardner?

Dr. Greenspan: Yes, it'll be Greenspan and Gardner. The Greenspan part has been there all of the time. Yes, the others have varied, and depending on availability--

PUBLISHING WITH SUSAN GREENSPAN

Dr. Friedman: I noticed--again from the CV--that you started to publish with your daughter [Susan Greenspan], approximately in 1988. Tell me something about her and your relationship to her career and her work, et cetera.

Dr. Greenspan: Yes. She is a very independent individual, and actually she decided to go into medicine and to explore the area that she has explored. She went to Stanford Medical School. She met her husband, Dr. Neal Resnick, when he was a senior and she was a sophomore--I think she is about two years behind him--and then he took an internship at Peter Bent Brigham in Boston, and she transferred from Stanford to Harvard. She actually graduated from Harvard Medical School. She took her internship at Beth Israel Hospital. Then after she finished, she went to Massachusetts General Hospital where she worked with Dr. Chester Ridgeway and Dr. [Farahe] Maloof in the endocrine department at MGH (Massachusetts General Hospital). She really developed her own interesting career very effectively and did an excellent job.

A transcontinental project with Susan Greenspan: the effect of thyroid therapy on bone metabolism

Actually, what had happened was that the issue of thyroid and bone had come up--as to what effect thyroid therapy had on bone metabolism. There was experimental work, but there wasn't much

clinical work on it. I was running a thyroid clinic at UC and also had a private practice where I saw a lot of thyroid patients. We thought that group of patients might be interesting to look at, in terms of bone structure. So we took a large group of patients--

Dr. Friedman: Excuse me, when did she come back to the West Coast?

Dr. Greenspan: She never came back to the West Coast. She stayed in Boston, and so this was a transcontinental project; the work was actually done in San Francisco, and the bone mineral density studies were done by--Dr. Genant had set up the bone mineral density studies. He was sort of a pioneer in developing quantitative methods for measuring bone density. So she was the one who thought it was a good idea, and I was the one who had access to the patients. And so we set up a protocol. We took a group of patients who had been on thyroid for a long time. We didn't have TSHs--TSH--but we had total thyroxine levels and the free thyroxine index. We had made an effort to keep the free thyroxine index within the normal range. What we did was, we looked at the bone mineral density. This was at the end of a long period of thyroid therapy. It turned out that there wasn't any significant difference between our patients who were treated with thyroid--a normal group--we did have a large normal reference group. There was a small group that had Graves' disease, and if you look at that group that had Graves' disease, they did have a slight degree of demineralization; but overall, thyroid therapy did not seem to have any major effect on bone mineral density. This was one of the first papers that came out in this regard. My daughter's name is Susan--Susan Greenspan. More recently, she decided to do a sort of a meta-analysis of a great many papers that had reviewed this problem, and we put this together in the form of a review article, and, again, the bottom line was that in men and premenopausal women the administration of thyroid has very little effect on the bone because the steroid hormone--estrogen or testosterone--will maintain bone structure. However, in the postmenopausal women on suppressive thyroid hormone therapy, there is evidence of increased bone loss. And in this group of patients--the postmenopausal women on suppressive therapy--the administration of an antiresorptive agent is important and helpful and will prevent excessive bone loss in that group. That's the last paper--that was the other paper we did together, and that was recently.

Dr. Friedman: What would you say the percentage difference is between the postmenopausal woman who's not on thyroid suppressive therapy as compared to the postmenopausal woman off estrogen--and a postmenopausal woman on estrogen?

Dr. Greenspan: I'm sorry, say that again, I didn't--

THREE SITUATIONS REGARDING POSTMENOPAUSAL WOMEN AND THYROID THERAPY

Dr. Friedman: First, if you can, I'd be interested in the comparison between the postmenopausal woman who's on suppressive therapy with thyroid versus the postmenopausal woman who's not on thyroid; and then the relationship of the postmenopausal woman on estrogen--on or off thyroids.

Postmenopausal woman on replacement thyroid therapy; postmenopausal women not on estrogen and on doses of thyroxine; postmenopausal women on suppressive therapy who take either estrogen, bisphosphonates, or a SERM

Dr. Greenspan: I think we can look at three situations: First, the postmenopausal woman on replacement thyroid therapy has no problem with bone. Let's say she is no different from a postmenopausal woman not on thyroid, so that replacement therapy doesn't do anything different. She would still be subjected to estrogen lack, but she would not lose any more bone than any other postmenopausal woman. Second, the postmenopausal woman not on estrogen therapy and on suppressive doses of thyroxine or the postmenopausal woman who has Graves' disease or toxic multimodular goiter will be subject to very rapid and severe bone loss, and she can get into bad trouble with osteoporosis. Third, the postmenopausal woman on suppressive therapy who then takes either estrogen or bisphosphonates or a SERM (Selective Estrogen Receptor Modulating) drug, like Evista (raloxifene), will be completely protected against bone loss. If the excessive thyroxine therapy stimulates both bone formation and bone loss, and the bone loss is greater than formation, you end up with osteoporosis. If you block bone resorption, either using estrogen or bisphosphonate or raloxifene, then actually the net result may be an increase bone formation, and the patient really does quite well. This is an important observation and important in terms of therapy.

PART-TIME PRIVATE PRACTICE, PART-TIME RESEARCH, AND TEACHING

Dr. Friedman: Is there anything else you'd like to tell me about your own work or your own practice? Your practice has always been associated with the medical school, and you haven't been in private practice.

Dr. Greenspan: No. I have been in private practice. As a matter of fact, for the years that I was at Stanford and also for much of the time at UC, I

was on the clinical faculty, and I essentially supported myself by private practice. I had an office and then was doing part-time practice, part-time research, and teaching. It's only recently--I'd say over perhaps the last ten or twelve years--that I've been set up where I'm on fulltime university staff. More recently, I've been on halftime staff. I still see patients, but I'm salaried by the University, and the patient income goes into the professional pool. I managed to survive the academic stress and the practice stress by maintaining this bi-fid relationship.

Dr. Friedman: What is the obligatory retirement age out in California?

Dr. Greenspan: Fortunately, there is no obligatory retirement age, and so you're allowed to both practice and teach and participate as long as you want, as long as you are functionally active. There had been an initial retirement age of sixty-five and seventy, but the State Legislature felt that this was discrimination against older people, and so the State Legislature essentially ruled that there was no obligatory retirement age, and there isn't any at the University.

Dr. Friedman: That's great.

Dr. Greenspan: That's very nice.

ETHICS AND BUSINESS IN BIOSCIENCE: DR. DONG, UC, SYNTHROID, BOOTS PHARMACEUTICALS, AND SELECTIVE PUBLICATION

Dr. Friedman: I'm going to ask you a question, which everybody who knows you probably asked you, but would you mind discussing with me the problem and the work with Dr. Dong and the impact of the drug company on this?

Dr. Greenspan: Oh, my goodness. Sure. Okay, one of the questions that came up while I was chief--in dealing with thyroid patients--was the question of replacement therapy and the adequacy of therapy. One thing I did was, when I first started running the Thyroid Clinic, I brought a pharmacologist into the clinic group. Her name was Betty Dong, and she's a doctor of pharmacy. She was very useful to us in terms of helping us to find out about the drug effects on thyroid function and drug interactions and appropriate drug therapy for different diseases, so we'd worked together for a long time. She did a study in about 1985, I think. A patient came into the clinic who had been on a proprietary drug called Synthroid, was doing well, and then she was switched to generic, and she became markedly hypothyroid, actually myxedematous. And in looking at

this we found that the generic drug that she was on essentially was devoid of--or was very low in--thyroid hormone content. Dr. Dong wrote this up as an illustration of the fact that at that time we had to be very careful about generic drugs. At about the same time, two things happened. One, the FDA recognized the problem with generic preparations and passed the regulation that all USP (United States Pharmacopeia) preparation of thyroxine had to be standard by high-pressure thin-layer chromatography as to determine the actual content of thyroxine in the tablet, and the content had to be between ninety and one hundred and ten percent of its stated potency. Once they did that, the generic preparation--which was now USP generic--had the same potency and the same hormone content that the proprietary drug had. That sort of stabilized that situation. At the same time, the Flint company [Flint Laboratories, Inc., original manufacturers of Synthroid] came to Dr. Dong and wanted her to do a study comparing generic to proprietary drugs; in this situation, Synthroid with generic preparations. Flint Company was bought out by Boots [Boots Pharmaceuticals], an English company, and then Boots continued this project; I'm not sure that they were aware of the new USP requirement. However, even if they were aware of the USP, they must have thought that their drug was different. I think they had the idea that if they could get a clear demonstration that generic drugs were inferior, this would be a very good marketing tool.

Dr. Friedman: Do you want to stop for a minute? Only if you do--

Dr. Greenspan: No no, I'll keep going. So they and Dr. Dong set up a protocol where a group of about twenty-four patients were selected, and they were to be given six weeks on Synthroid, six weeks of another proprietary preparation called the Levoxyl, and then six weeks on each of two generic preparations, which were Rugby preparations, which did not have any proprietary name. Then we looked at their serum thyroxine levels, free thyroxine and TSH, and the rise in hormone levels above the base line following oral administration of the drug to get an idea of whether they were comparably absorbed. Actually, the protocol was primarily set up by Dr. Dong and the Boots representatives; I was the medical consultant. Dr. Dong was not a physician; she was a pharmacologist, and so I was the medical consultant to this. I reviewed the protocol and worked with Dr. Dong, although she did actually most of the work in terms of patient management and blood drawing and organizational stuff. The Boots people were very anxious that there would be no slip up in this, so they decided that all of the testing--that is the TSH, free thyroxine, and total T₄ would be done by one laboratory. They selected Dr. DeGroot's

laboratory in Chicago to do these. So we collected all the specimens, kept them frozen, and then sent them to Dr. DeGroot--who did all of the testing merely by numbers--so he did not know who had what preparation; the testing laboratory was blinded in that sense. Then he sent back the information, and we analyzed it. Well, what happened was that the Boots people were very happy with this whole program until Dr. DeGroot did the tests. Then it became apparent that there was no difference between the proprietary and the generic preparations. As a matter of fact, the blood levels were the same, and the absorption was the same. This provoked a tremendous consternation on the part of the Boots people, and at that point they started to raise a number of minor objections. A patient came in late to get their blood drawn and, therefore, that blood shouldn't be taken. There were just a number of other absolutely inconsequential, insignificant things that they tried to raise to question the accuracy and validation of the data. Dr. Dong tried very hard to clarify the questions that they brought up, and she did answer them all. Finally, she said that she was going to publish this regardless. I forgot to mention that in the contract for this research program it was stated that the results could not be published without the permission of the Boot's Company. Dr. Dong took this contract to the UC lawyer at that time; he said, "Oh, that's a standard contract, it has never been used, and the company would never do [so] because of the adverse publicity that they would get. So don't worry about it; just sign it." However, the Boots people stated that we had signed a contract; they would not allow publication. Incidentally, the data that was put together was sent to the *JAMA* and was accepted for publication. Dr. Dong told Boots that it was accepted. They came back and said that if this were published, they would sue Dr. Dong, all the authors, and the University for any loss of income, which would have occurred as a result of the publication of this article. [interruption]

We were just talking about the fact that when the paper was accepted for publication, the medical director of Boots informed us that they would sue the authors and the University for any loss of income that would have occurred as a result of publication of this article, and also they would be sued for breach of contract. Well, when you think of the possibility that the sales of the Boots product, namely Synthroid, might have been materially changed if people recognized that the generic preparation was equivalent, this could amount to many, many millions of dollars. And if the authors were responsible for that--obviously, this was a threat that we could not accept. We went to the University lawyers. They said that the only way that we could publish this would be if we were able--legally--to break the contract, and, in order to that, we

would have to go to court, and it would take a year and a lot of money to do that, and they weren't willing to go through all of that to break the contract. And so, we were left largely up in the air with a completed manuscript that we were unable to publish. Boots held on to this restrictive attitude for some time until a reporter from the *New York Times* heard about this and did some investigation and printed an article, which essentially brought this to the attention of the public.

- Dr. Friedman: I thought it was published in the *Wall Street Journal*.
- Dr. Greenspan: Excuse me, not the *New York Times*. It was the *Wall Street Journal*. It was in the *Wall Street Journal*. And once it became public, then there was a big outcry, and there were a lot of efforts made. Finally, Boots allowed this to be published, and it came out, and it was accepted. There was some controversy over it. The question of whether we selected an appropriate group of subjects to do this was probably the major criticism. But on the other hand, the fact of the matter is that these preparations are equivalent. Other papers have come out to substantiate this fact, too. That was a major crisis in the thyroid field and still is simmering; in the sense that, some of the HMOs have now sued Boots for false advertising, and Boots has had to put up a lot of money to settle those cases, and they are still fussing around.
- Dr. Friedman: Well, there were a couple of guys--I think if I'm not mistaken--wrote a paper or something saying there was something wrong with the study, and it surprised me.
- Dr. Greenspan: It surprised me, too. Boots has an extensive consultative group, and the doctors who wrote on this were all members of their consultative group and, I think, have a little bias in their attitudes. I felt that despite their eminence there was a little bias in their attitude.
- Dr. Friedman: My point has always been that regardless of which preparation you have them on once--you stick to the preparation. In other words, I don't believe in writing a prescription for a generic--I'd say levoxyl if I want to save the patient money. But the point is then you know--that getting the same USP product continuous--so you can adjust them if you have to raise or lower the dose; in fact, you can do it.
- Dr. Greenspan: Adolph, for many years, I did that same thing. And I felt that particularly with the early evidence of the inadequacy of the generic thyroxines. I actually refused to use generic thyroxines.

However, right now there is abundant evidence to suggest that these are absolutely interchangeable. This is like Squibb's aspirin and Bayer aspirin; you simply can't tell the difference. They have the same content of thyroxine, they absorb equally, there is absolutely no difference. You can change from levoxyl to Synthroid to Levothroid with no difference whatsoever. Over a period, you will have to monitor the patient periodically, which you do anyway. If you change the dose, you have to monitor them. But there is absolutely no difference in these preparations.

FAILED ATTEMPTS AT TRYING TO SEPARATE THYROGLOBULIN FROM ITS ANTIBODY

Dr. Friedman: Good. In terms of the last couple of years of work, you still seem to be working in the research aspect of thyroid function in endocrinology--aside from the fact that you were working on the guidelines. Would you like to discuss those points, one at a time?

Dr. Greenspan: At the laboratory, we were working for a long time on attempting to separate thyroglobulin from its antibody to see if we could detect thyroglobulin in the presence of antibody. I must say that I spent several years trying to do that and was unsuccessful. We never published that because we didn't succeed in splitting it. I thought that we could split the antibody from its antigen, that is, split thyroglobulin from its antibody, either by chemical means or by possibly modifying the antibody itself. But it turned out that that's a very, very tight relationship, and it is very difficult--at least we were unable to split that. But then in the last several years, I gave up the laboratory, and the only work we can do now is some clinical research, which is essentially on individual patient problems.

EARLY DAYS AT THE INSTITUTE OF EXPERIMENTAL BIOLOGY WITH DRs. EVANS, LI, AND SIMPSON

One of the things that, if you'd like, I'd like to talk about for a minute are the early days at the Institute of Experimental Biology with Dr. Evans, Dr. Li and Dr. Simpson. This was a very powerful group. Dr. Li was a brilliant biochemist who did a great deal of work on protein separation—

Dr. Friedman: You mean C. H. Li?

Separation and purification of six pituitary hormones; discovery of vitamin E

Dr. Greenspan:

C. H. Li. Dr. [Miriam] Simpson was a very good biologist, and she worked on the biology of these preparations. Dr. Evans was a very powerful and brilliant guy who supervised all of this. Over a period of years that group separated out the six pituitary hormones, including ACTH, FSH, LH, TSH prolactin and growth hormone; and they purified and repurified all of them. These were bovine preparations; they weren't human preparations. They really set the stage for our understanding of pituitary hormone physiology with the preparation of these purified hormones. Another interesting thing was that--as a side issue--they (Evans and his group) discovered vitamin E. Now the way that they discovered vitamin E was in a rat colony; they fed rats a preformed diet to which they added all the known vitamins, and the rats did okay except that they didn't reproduce. Evans felt that there was one other substance that was necessary for reproduction in the rat. They thought it was a fat-soluble vitamin, and eventually they came around to the discovery of vitamin E, alpha-tocopherol. They discovered vitamin E, but the only usefulness for vitamin E at that time was to improve the fertility of rats, and no one ever expected that vitamin E would have any human or general usefulness. It's sort of fascinating for me to see, now that vitamin E is a major antioxidant, and people are taking it in large quantities, and they feel that it is helpful in the prevention of cancer and the prevention of heart disease. If Dr. Evans had ever known this and could see what his finding of this factor that preserved fertility in rats developed into, he would be both happy and surprised.

ASSESSMENT OF ANTIOXIDANTS

Dr. Friedman:

What is your personal opinion about the antioxidants?

Dr. Greenspan:

Well, at first I thought that this was overdone, but as one follows the literature, there does seem to be increasing evidence that they may be useful in terms of both malignancy and cardiac disease. I think that the final word has yet to be spoken, and one of the difficulties is the difficulty in measuring antioxidants in clinical situations. You really can't show the evidence of deficiencies of vitamin E. And all you can suggest is that, perhaps, with excess of it--may be helpful. But again, this is a very difficult concept to prove in clinical studies. The clinical studies really haven't been done to prove this, but I would say there's a possibility that there is benefit in it. Again, the surprising thing was that, when they first discovered it, antioxidants were not even thought of, and it was

never thought that vitamin E would develop into the kind of preparation it has developed into.

CLINICAL GUIDELINES

Dr. Friedman: I had asked you about the guidelines, do you think that we are making too much to do about the guidelines nowadays, or do you think it is a worthwhile devotion of time?

Medical uncertainty; strengths and weaknesses of guidelines; guidelines and cost effectiveness

Dr. Greenspan: Well, the guidelines are a kind of mixed blessing. On the one hand, there was a lot of uncertainty as to how to deal with thyroid nodules, how to deal with hypothyroidism, how to deal with hyperthyroidism in terms of both diagnosis and management, and it seemed appropriate to at least lay out some suggestions as to how these illnesses might be both diagnosed and managed. Actually, Dr. Peter Singer in the Thyroid Association did a really heroic job in working this out. The problem with it is that guidelines get fixed into rules, and you can't always follow a rigid set of rules in either diagnosis or therapy when patients don't always fall into very specific categories, and so you have to have flexibility. And the other thing that is difficult is that "managed care" and the whole question of cost effectiveness come up. Any deviations from the guidelines may be considered not to be cost effective and, thus, will not be paid for by the insurance company and may result in a blocking of other areas of diagnosis in management. For example, when guidelines were written, we didn't know the usefulness of the recombinant TSH, so that wasn't at all included. So an HMO that strictly follows the guidelines would not allow the use of recombinant human TSH. So again, the answer probably is that the guidelines have to be rewritten every few years to be sure that we do not lock ourselves into an obsolete method of either diagnosis or treatment.

Dr. Friedman: After today's discussion at the meeting, they ought to start rewriting them now.

Dr. Greenspan: I would agree with that. Again, I think that guidelines can be useful "guidelines," but they are not a rigid rule. I think the problem comes out when either individuals or organizations or lawyers or legal maneuvers start to use them as the absolute rule, and then we can get into big trouble.

THYROIDITIS

Dr. Friedman: I noticed you had one or two papers on thyroiditis, was that strictly the discovery of patients, or did you have a particular reason? One you wrote in 1998 on Riedel's thyroiditis, and then you wrote on lymphocytic thyroiditis this year.

Dr. Greenspan: Those were two totally different problems. The first was a patient who presented with a rapidly growing huge thyroid mass, which was obstructing the trachea and producing massive discomfort, even respiratory distress. And an attempt was made to biopsy it surgically, but it was so wide spread, and it couldn't be removed, and the patient was rapidly getting sicker.

Dr. Friedman: Excuse me, this was Riedel's thyroiditis?

Dr. Greenspan: Yes. Riedel's thyroiditis is an acute inflammatory thyroiditis with the position of much scar tissue and fibrous tissue, so it presents a rocky, hard mass in the neck. I thought this might be actually an end stage of a severe Hashimoto's thyroiditis--an end stage of chronic lymphocytic thyroiditis or Hashimoto's thyroiditis--and that it might respond to steroids and thyroxine. Thyroxine would turn off TSH, and steroids would block the immunological activity, which I thought was present there. Indeed, this patient made an actual dramatic response to the combination of steroids and thyroxin. We had, I think, two other patients who also responded to this type of therapy. And since this was such a life threatening disease, which did respond to really relatively simple medical therapy, we thought it was worth writing it up.

Dr. Friedman: Definitely worth writing. Let me ask you what happened to the size of the goiter, did it diminish significantly?

Dr. Greenspan: It melted away. I still see the patient, and she has no goiter. She's on thyroxine of course, and she is feeling fine--been through two pregnancies, and she has just done wonderfully well. It really was a dramatic and life saving therapy.

Dr. Friedman: What was the age of this one, and were they all three female?

Dr. Greenspan: They were all three females. The initial case was about twenty-five when I first saw her. The other cases were a little bit older, they were in the thirty to forty range. But they were young adults, females.

Dr. Friedman: That's unusual that you saw three cases. I don't think I've ever seen one, or else I could have missed it.

Dr. Greenspan: No. I don't think you'd have missed it.

Thyroiditis as a possible protection against the growth and spread of malignancy

Dr. Friedman: I don't think I ever saw one.

Dr. Greenspan: Fortunately, they are very rare, but when they occur, they look like an anaplastic carcinoma, and they grow and spread rapidly. They are very frightening and upsetting. The other paper on thyroiditis-- a different problem. We had done a survey of about seven hundred patients with thyroid cancer that we followed over a period of twenty to thirty years. I felt that we needed to clarify the use of the Cancer Society's staging system as applied to the thyroid. You remember the staging system; it is the so-called TNM--T standing for the state of the thyroid, N for the presence of lymph nodes, and M for distant metastatic disease. This TNM (Tumor, Node, Metastasis) staging system was being used widely in all of the hospitals to stage other cancers, but we never really knew what this staging system would tell us about thyroid cancer. Therefore, we took our seven hundred cases on whom we had pathology and we staged them according to the TNM, and then we looked at their follow up over the twenty-year period. We were able to show that the stage ones and twos did very well and the stage threes and fours did very badly. We were able to use this to predict the outcome of thyroid cancer in a large group of patients. Now, one of the other questions that came up was what is the effect of Hashimoto's thyroiditis when it occurs with the cancer? Is that good or bad? In other words, if a patient had cancer and thyroiditis are they likely to do better or worse? So we took a subset of these patients who had thyroiditis and compared them to a comparable group of patients who didn't have thyroiditis. Interesting enough, it turned out that the patients who had the thyroiditis did better than the patients who did not have thyroiditis. So the thyroiditis may have a certain protective effect in the patients with thyroid cancer, and it certainly does not have an adverse effect.

Dr. Friedman: Did you venture to say it's autoimmune?

Dr. Greenspan: Yes. I think the autoimmunity may in some way protect the patient against the growth and spread of the malignancy. So, then in some way this may be protective in terms of body defenses. It

was interesting that it turned out that the patients with thyroiditis had a better prognosis than those without it, and so thyroiditis may be beneficial rather than a detrimental factor in thyroid cancer.

Dr. Friedman: This is interesting because I wasn't aware--I don't think there was an increase incidence of thyroid cancer in chronic lymphocytic thyroiditis, but there is an increase incidence of lymphoma in chronic lymphocytic thyroiditis.

Dr. Greenspan: That's correct. And that is really unique to the thyroiditis, and it occurs in patients particularly with widespread and long-standing thyroiditis. But we weren't looking at that group of patients. We were looking at the group of patients with papillary or follicular thyroid cancer whose pathology showed evidence of either focal or diffuse thyroiditis contrasted to those who did not show that. Fortunately, we had the pathology on all of the patients, and we had the follow-up in terms of their recurrence rates and deaths, and follow-up of the effects of the cancer. Thus, we were able to develop a very interesting observation.

ON THE DEVELOPMENT OF ENDOCRINOLOGY OVER THE COURSE OF HIS CAREER

Development of radioiodine; introduction of anti-thyroid drugs; molecular mechanisms and the genetic level

Dr. Friedman: Well, I'm sort of at the end of my questions, but I was wondering if there was anything else that's come up in your mind in the course of our discussion that you think might be a helpful additive to this interview and your history?

Dr. Greenspan: Well, I'm not sure that my history would be helpful to the field of endocrinology, but I have had an opportunity to watch endocrinology develop over many years. It's very interesting to see how it progressed from initially just observation--where we had the observation of individuals who had gross changes such as myxedema or Graves' disease with eye signs, or Cushing's disease, or acromegaly--and from there, to the recognition of which glands were involved and how they were involved, to the knowledge or to the recognition that these could be controlled. In [the] case of the thyroid, the discovery of radioiodine--that came in really in the late forties and early fifties--and the introduction of anti-thyroid drugs--again in the early or mid-forties--modified our treatment of hyperthyroidism, so that we began to develop techniques to control the function of the thyroid gland.

Now, what we are seeing--you've seen it at the meeting, and I have, too--we are getting down even deeper to the molecular mechanisms of hormone synthesis and secretion and the genes that are involved with it. This opens the potential for modifying diseases by changing the gene structure--or modify the gene activity either with drugs or with other techniques. Thus, what started out as a totally empirical type of science has now made enormous progress. I think we understand a lot, but there is a whole new range of options, opportunities, and knowledge that is opening up--particularly utilizing the molecular mechanisms of disease and the modification of these molecular mechanisms.

Dr. Friedman: That's true, particularly with the gene work. Well, I guess I'll have to thank you very much for your time and your help, and after I get this typed up, go over it, and see if I can fill in any of the blanks. Then I will mail you a copy. Now, I may have to mail you a copy, and ask you to send it back to me corrected, but eventually I'll send you a copy, as they say, "for my grandchildren."

Dr. Greenspan: Right, okay, no problem.

End of Interview

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