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JOSEPH W. GOLDZIEHER, MD

Interview conducted by
Adolph Friedman, MD
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EARLY YEARS IN BUDAPEST; IMMIGRATION TO THE UNITED STATES

Dr. Friedman: Dr. Goldzieher, am I doing this with your permission?

Dr. Goldzieher: Absolutely!

Dr. Friedman: According to your records, you were born in Budapest, Hungary, September 21, 1919.

Dr. Goldzieher: That's correct.

Dr. Friedman: Tell me something about your youth, such as grammar school and high school. Did you have any scientific interests at that time, any achievements; were you an athlete, interested in drama?

Dr. Goldzieher: My early history from my birth to coming to the United States is in those comments that I made to the convocation of the AACE (American Association of Clinical Endocrinologists). I lived my first five years in Budapest; then, at the age of five years, was brought to the United States via Naples, escaping the fascist dictatorship. We came to the United States in 1924; and, of course, I had to learn English because my native languages are German and Hungarian.

EARLY EDUCATION, FENCING, AND LACK OF SOCIAL LIFE

I went to public school in Brooklyn, New York, at PS 217 and PS 92. They were very good schools. I fell in love with my kindergarten teacher. When I went to high school,

New York City had a special school called Townsend Harris High School, which was for gifted children. It was an accelerated school, and we did the four-year curriculum, which included Latin and math, in three years. You passed your grades, or you were out of the school. There was no repeating. I managed to do that. When I was twelve years old or so, my father said that I ought to become interested in a sport [that] he had practiced when he was young, which was fencing. He introduced me to fencing, and eventually I got to fence with Georgio Santelli, who was the U.S. Olympic fencing coach. At that time, we had moved to Manhattan to be near Townsend Harris High School. We lived at Gramercy Park in Manhattan, so I went to Townsend Harris, and I went fencing. My social life was extremely limited then because there were no study periods, no sports, no nothing in high school. You went there, had classes, went home, and you did homework; that was it. There was no boy/girl interaction, no clubs--nothing. It was strictly an educational institution.

HARVARD UNIVERSITY

I applied for Harvard, and I got into Harvard and went through the four years, majoring in chemistry. Again, if you were a chemistry major at Harvard, you didn't have time for the social clubs. You went to the laboratory, went home, did your homework, and got ready for the next day; so I was fairly limited in my social life at Harvard although I had a girlfriend for the four years, and I intended to marry her at the end of the four years, which I did not do.

FAMILY BACKGROUND**Father: physician and professor of pathology**

Dr. Friedman: Tell me a little bit about your parents. I know your father was a physician.

Dr. Goldzieher: He was a professor of pathology in Budapest, and he became a pathologist in New York City when he immigrated here in about 1923. One of his early interests was adrenal pathology; and actually in the 1920's, he tried to prepare an extract of adrenal cortex using the method that had been used to isolate insulin in the pancreas. Of course, it was an aqueous extract, so by modern standards it probably had no biological action at all, but he was actively trying to prepare an extract of adrenal cortical hormones.

Mother: linguist and translator

Dr. Friedman: Did your mother have any professional training or anything?

Dr. Goldzieher: My mother was a linguist; she spoke four or five languages, and she did some translating of Molière's plays into English and things of that sort, but she did not have a profession.

Two sisters

Dr. Friedman: Did you have any siblings?

Dr. Goldzieher: I have two sisters, both older. The oldest one made her career in the art world, and she's still alive. She's about ninety years old. My second sister got a four-year scholarship at Cornell, went to Yale Medical School, and was one of the top people

in her class. She began to do some research in her fourth year of medical school, married one of the medical students, entirely abandoned the medical life, and proceeded to have five children.

MEDICAL TRAINING

World War II: 4-F with Ghon's tubercle

Dr. Friedman: That's interesting. You graduated from NYU in 1943, how come you didn't have to go into the military?

Dr. Goldzieher: Well, we became second lieutenants in the Medical Administrative Corp Reserve. They postponed me so that I could do my internship at Bellevue and my residencies in New York City Hospital. Then it came time to be on active duty, and I went for my physical examination; and you had to bring your x-ray. I had had my x-ray taken the week before, and the chief of thoracic diseases put my film up, and looked at it, and said, "Now there is the classical primary lesion of tuberculosis called Ghon's tubercle," and somebody said, "Hey, that's Goldzieher's film." When I took that x-ray to the military, they took one look at the x-ray and said, Man, you're 4-F; we don't want you in the VA for the rest of your life. Of course, in those days, we had no antibiotic for tuberculosis.

Dr. Friedman: Ghon's tubercle was supposed to have been inactive.

Dr. Goldzieher: Well, I had no signs or symptoms, and they said to me, You need to quit this, and go up in the mountains, and spend six months in the fresh air. I said, "Nonsense, I have too much to do". I ignored it, and it healed spontaneously. But that made me 4-F.

Dr. Friedman: You were lucky. I have one, and it didn't exclude me.

Dr. Goldzieher: [laughs] Oh, my, that's an injustice.

CHOOSING A RESIDENCY IN PATHOLOGY; AN ADDITIONAL RESIDENCY IN DERMATOLOGY

Father's influence

Dr. Friedman: I noticed you had residencies in pathology and dermatology. Before you got into gyne-endocrinology, was pathology your father's influence?

Dr. Goldzieher: Yes, the dermatology was an add-on because we were short-staffed during the War. I really wanted my residency in pathology because my father said, "You will never understand internal medicine until you really know pathology." I ended up doing something like one hundred and thirty autopsies myself, which you could do in those days, before my residency was up. My chief showed me how to do autopsies, and my father would come on Sundays to the autopsy room at City Hospital and show me how a "real" autopsy was done. While we were in medical school, I got extra histopathology education from him, because we went through his entire collection of slides while I was in medical school--some four thousand slides--so I had a fabulous background in histopathology.

Marriage, internship, and residency; wife's background

Dr. Friedman: When did you get married?

Dr. Goldzieher: I got married in 1943, which was at the end of medical school. My wife saw very little of me during my internship and residency because, during the wartime years, we were on for forty-eight hours, we got a night's sleep, and we were on for seventy-two hours. Actually, when she got pregnant, the guys on the house staff said, When did you get home? That's how scarce time was in those days.

Dr. Friedman: What was your wife's background?

Dr. Goldzieher: My wife was a teacher of pre-school children and worked in a settlement house in Brooklyn for impoverished kids. Her father was a bail bondsman, and her mother didn't work. Her mother was a big hefty Scandinavian-type lady, but my wife was a very tall, gorgeous blond. A small, dark Hungarian married a tall, gorgeous blond. We were married for ten years and had one daughter. Then after ten years--her leading a doctor's wife's life, which she really had no idea of when we got married--she said, "This is no life for me." And I said, "I understand perfectly; let's go our separate ways." And so we did.

**PRIVATE PRACTICE ON PARK AVENUE WITH HIS FATHER, 1947-1952
Setting up the first research laboratory at Saint Clare's Hospital, New York;
studying urinary ketosteroids; measuring vitamin C in rats**

Dr. Friedman: Between 1947 and 1953, even though you supposedly had a private practice, you did a tremendous amount of traveling. You were going from San Antonio to New York; then later--from 1972 to 1978--you were going to Texas, then to Philadelphia.

Dr. Goldzieher: Well, let me straighten that out. From 1947 to 1952, I was in private practice with my father in New York City. He had an office on Park Avenue. I set up the first research laboratory at Saint Clare's Hospital in New York City, where I was interested in the exciting field of steroids. I started a laboratory looking into urinary ketosteroids and was also doing some work on measuring the vitamin C content of the adrenal in rats. I started up my own research laboratory in addition to working with my father in his private practice. In 1952, I moved to Texas.

On being in private practice with his father

I found private practice with my father the typical father/son thing--a little constricting. He was a German-trained professor, very authoritative; and being a kid from Harvard, I had my own ideas, and I wanted a little more independence. That got to be pretty stressful for me.

MOVING TO SAN ANTONIO, TEXAS**Nick Werthessen, Tom Slick, and the Southwest Foundation**

In 1951, I went to the Laurentian Hormone Conference and met Nick Werthessen, who had moved from Gregory Pincus's laboratory in Worcester, Massachusetts. He was sent to San Antonio--because in San Antonio there was a millionaire by the name of Tom Slick, an oilman, who was a very brilliant guy. I think he was a Phi-Beta [Kappa] from Yale. He had started an institution for basic biomedical research called the Southwest Foundation [for Biomedical Research], which had been sort of dormant during World War II; now, he wanted to activate it. He went to talk to Pincus, and Pincus sent one of his people down there; and this guy, Nick, is at the Laurentian Hormone Conference and says to me, "Joe, why don't you come down to San Antonio; we have a new institution there for basic biomedical research. I said, "What do you have to offer?" He said, "Well, we have been promised an endowment; we have 1500 acres of ranch land; we have a house and hay barn; I live in the farm house." Nick Werthessen had a wife and children. He said, "You can stay at the farm house until you find a place to live, and you can use the upper story of the hay barn for your laboratory. I have the lower floor because I'll be doing atherogenesis on calf aortas, and I can't lug calves upstairs; so I have to use the downstairs, and you can have the upstairs." I said, "Nick, for a guy who has his own

laboratory and is part of a Park Avenue practice, this is not exactly an invitation to paradise.” He said, “No, but there is no hierarchy. You will have no boss; you will be on your own, and you can make of it what you will.” I said, “You’re right.” Because I had an antipathy towards the idea, always, of going into academia and fighting the hierarchy and the territoriality and the academic politics and so on--this is not my cup of tea. He said, “It may be a hay barn, but you’re on your own.” So I took him up on that, and I worked at Southwest Foundation for twenty-nine years, and I wrote about three hundred papers while I was there. Then I left in 1982.

**Leaving the Southwest Foundation after twenty-nine years
Funding issues and stress over finding resources**

Dr. Friedman: Why did you leave?

Dr. Goldzieher: The chief reason was that getting grants was becoming so difficult that I was totally stressed out worrying over finding the salaries and the grant structures for my PhDs, and I had been doing this for twenty-nine years and was simply burned out on grantsmanship.

**ACCEPTING DIRECTORSHIP OF ENDOCRINE RESEARCH IN THE OB/GYN
DEPARTMENT AT BAYLOR**

Commuting to Houston while maintaining a private practice in San Antonio

Some friends of mine who were in the OB/GYN department at Baylor said to me, Come to Houston, you’ll be a professor, and you’ll be director of endocrine research in the OB/GYN department. I said, “No committees, no executive responsibilities, no territory?” They said, No, come to Houston. I said, “I’m not going to move to Houston. I have a very nice private practice in San Antonio.” So we argued this back and forth, and we agreed that I would live in San Antonio and keep my private practice in San

Antonio two days a week, which is what I always did anyway, and I would commute to Houston on Tuesday morning. I bought a condominium, and I would work in the OB/GYN department directing the postdocs, the residents, and the research projects; and I would fly home Thursday night. I commuted to Houston for eleven years, every week.

VISITING PROFESSORSHIP AT HAHNEMANN UNIVERSITY HOSPITAL

Dr. Friedman: What about the business with Hahnemann [University Hospital] in Philadelphia?

Dr. Goldzieher: That was a visiting professorship, and I went there from time to time and did the same thing there that I was doing at Baylor. I would get together with staff, people interested in reproductive research.

Dr. Friedman: Now, I want to diverge and go to the work that you've done--rather than your personal life.

AN EARLY CHILDHOOD EXPERIENCE WITH CHEMISTRY

Dr. Goldzieher: Well, let me tell you one anecdote--because you always want to have an anecdote. When I was about seven or eight years old, I was already fascinated about chemistry. As kids, we used to get chemo-sets. You made dyes and bad smells, and my best buddy and I used to do chemical experiments on a kitchen table in my bedroom on the third floor of the house. One day I read about the stuff called thermite. Thermite is what is in World War II incendiary bombs. It's a mixture of iron oxide and magnesium powder. When it is ignited, it burns at two thousand degrees centigrade; and because the iron oxide produces the oxygen, you cannot put the flame out. I thought, This is great

stuff. So we ground up an old rusty screen door and got some magnesium powder from fireworks, mixed them up, and put them in a little Coors crucible, took a sparkler and stuck it in the mixture, lit the sparkler, and the sparkler set off the thermite, which made enormous clouds of magnesium oxide and molten iron at two thousand degrees centigrade. The only problem was the crucible cracked. The white hot iron burned through the kitchen table, through the floor of my room, through the ceiling of my parents room, through their floor, and burned itself out on the concrete floor of the basement. Why the house didn't go up in flames, nobody knows. But it was the end of my chemistry until I got to college.

Dr. Friedman: That is an interesting story.

Dr. Goldzieher: That's a true episode.

ON THE DEBATE REGARDING MEASUREMENT OF URINARY PREGNANEDIOL

Dr. Friedman: In 1962, you described a method for doing urinary pregnanediol. Did you ever hear of Henry Guterman?

Dr. Goldzieher: Oh, I knew Henry Guterman very well.

Dr. Friedman: I know that was what he was doing in 1947--when I was at Michael Reese.

Dr. Goldzieher: Yes, the Smiths [George Van S. Smith; Olive Watkins Smith] has used the method of a Canadian scientist, Eleanor Venning--a precipitation method for pregnanediol glucuronide--which is what the Smiths used for their studies on habitual and

recurrent abortion and the use of DES (diethylstilbestrol). They had this method where you gravimetrically weighed the precipitated diol glucuronide. There was a lot of argument about that because Ian Sommerville claimed that you also precipitated DES-glucuronide, and therefore this was contaminated and an unreliable assay. I took a look at whether the Smiths' work was reliable or not, and it turned out that I got into this argument. It turned out that the laboratory in England, Sommerville's, was at a much lower ambient temperature than the laboratory of the Smiths in Boston. At his low temperature, the DES-glucuronide precipitated out, also. In the Smiths' laboratory--where it was warmer--only the pregnanediol glucuronide precipitated out, and the DES did not. So in the Smiths' laboratory it was valid, but in England it was not. I was in that debate.

Developing the colorimetric method for determination of pregnanediol

Then I developed the colorimetric method for pregnanediol. That got rid of the gravimetry.

Dr. Friedman: Where was Sommerville?

Dr. Goldzieher: He was in England working with the very famous chemist, Guy Marrian, who did the work on estradiol and estriol.

Collaborators and colleagues

Dr. Friedman: Who were Axelrod, Laitin and Dan Castracane ?

Dr. Goldzieher: Lenny Axelrod was a very overweight, Brooklyn Jewish type who had studied paper chromatography with Alex Zaffaroni--who had started paper chromatography in Buffalo or Rochester. Lenny Axelrod came to San Antonio. Because he had such a difficult personality that he was a very unpopular person, I loved Lenny Axelrod. We worked together, we screamed at each other, we fought like tigers, but we

loved one another until the day he died, and I was the godfather to his son. Lenny had magic fingers in the laboratory. He did woodwork at home that was breathtaking; he was a paper chromatographer who did wonderful things. He was the guy that did all of the steroid isolations from the incubations of tissues with radioactive substrates. That was the work that we were doing together. He did all the chromatography. I helped with the design of the experiment. I got the tissues that he needed; then he would go off on something else, and I said, "Lenny, we need to write a paper," but he would never write a paper. I would lock us up in a room and say, "Today, we are going to write the paper on so-and-so, and we're not going to leave here until we do." We fought and screamed at each other, and we got the papers written. We had a very successful relationship. That was Lenny Axelrod.

Howie Laitin was a man who was stationed in the military in San Antonio. He's a mathematician. All I needed from him was the mathematical analysis to look at the results we had with fractionated 17-ketosteroids--to look at the consistencies and the trends and rubbish that meant nothing. And he had the mathematical tools to do that. That was our only relationship.

Dan Castracane came from Jim Leatham's laboratory and was very interested in primate research. He was with me until 1982, when I closed my department at Southwest Foundation. Then he went into industry for a while; then he went out to Texas Tech in Amarillo as a reproductive biologist there, and we have worked together since then, and still do. We've written a number of papers together, and he's a reproductive biologist at Texas Tech.

URINARY RADIOACTIVE STEROID METABOLITES

Early insights of his father on menopause, dry skin, and hormone deficiency; developing an estrogen cream; using radioactive estrogen to establish estradiol passage through skin

Dr. Friedman: On paper number one hundred, you wrote a study of urinary radioactive steroid metabolites after percutaneous absorption. What stimulated your interest in this?

Dr. Goldzieher: That goes way back to the days when I was working with my father, who was brilliant enough to say, “Menopausal women have dry atrophic skin probably due to hormone deficiency. Why don’t we put estrogen in a cream and stick it on the skin and see if the skin gets better.” Of course, it did; and I published a study where we did skin biopsies on very, very elderly people at City Hospital. We published the histology of the effect of estrogen applied locally to the skin. Some Canadian has rediscovered that--about ten years ago. My father actually joined with some businessmen to market a product called “Endocrine,” which went on the market as a cosmetic. It was very successful until the FDA said, “This is a drug, and you have to have an FDA license to market it.” Of course, they didn’t have the means or money to go through an FDA/NDA application, so Endocrine went off the market; but I got the introduction to estrogen and the skin way back in the 1940s. [Later, when] we had radioactive estrogen and I was at the Southwest Foundation, then I did it over to prove that, yes, in fact, estradiol does go through the skin in very substantial quantities and comes out in the urine as radioactive metabolite.

Dr. Friedman: Does this have anything to do with the hormonal patch?

Dr. Goldzieher: No, that came much later. We had creams that took the estrogen right through the skin and worked on the skin, but we had no idea that this could be a delivery system. We just used ordinary Ponds cold cream, mixed radioactive estradiol with it, and had people rub it on their skin.

PIONEERING THE DEVELOPMENT OF ORAL CONTRACEPTIVES

Myomas and progesterone

Dr. Friedman: There was another thing that I was curious about. You wrote a paper on selective injury to myomas with 6,17-dimethyl delta progesterone. What happened to this method? How come it didn't become an excellent method of getting rid of myomas?

Dr. Goldzieher: Couldn't be duplicated. What happened was this: In Mexico, we were second only to Gregory Pincus in testing oral contraceptives. We had a formulation that had 10 mg norethynodrel in it. One of our associates was a pathologist in Mexico City, by the name of Manuel Maqueo. Some of these patients who got birth control pills had hysterectomies. He looked at them and found that there was acute hemorrhagic (red) degeneration of the myomas in these people who were on the birth control pill. So we said to ourselves, We wonder if very large doses of a progestational compound can destroy myomas. We did a study, and we published it, and we got acute degeneration of myomas; but nobody else ever reproduced it, so I don't know what the story was.

EARLY EFFORTS AT DESTROYING MYOMAS WITH GNRH

Dr. Friedman: You subsequently wrote one on GnRH on myomas--GnRH, and hydroxyprogesterone.

Dr. Goldzieher: It was another effort to destroy myomas chemically; it went nowhere.

Dr. Friedman: Do you think its got potential?

Dr. Goldzieher: Well, the fact is women who have fibroids and have pregnancies do have degeneration of some of their myomas. There is something here, but whether it will affect all myomas or only myomas of a certain size in which the vasculature can be compromised or whatever, I don't know. I certainly think it's worth the salt.

ORAL CONTRACEPTIVES

Oral contraceptives and diabetics; debate over adverse effects of contraceptives on carbohydrate metabolism

Dr. Friedman: Being that I'm also an endocrinologist, I was curious about your work on the use of oral contraceptives--long and short term--on diabetics. Also, I wonder why there was an absence of the microangiopathy on the use of oral contraceptive in diabetics.

Dr. Goldzieher: Frankly, I think the whole issue of the effect of oral contraceptives on carbohydrate metabolism was grossly overstated. It was engineered chiefly by some people in England who had, for decades, a vested interest in saying bad things about oral contraceptives. Martin Vessey was the architect of much of the negative stuff that has come out about birth control pills. He had some associates; they looked at carbohydrate metabolism and found some biochemical changes in carbohydrate metabolism and, therefore, said that birth control pills create a risk in general and particularly in diabetics. We, however, found that not to be true. Nobody ever verified it, and the studies on microangiopathy failed to show any effect; and the long-term prospective studies and retrospective studies failed to show any effect. The oral contraceptives--low or high dose--have no clinically significant effect on carbohydrate metabolism. There was a period of a decade or two where this was counted as a major hazard of oral contraceptives, and it was advised that diabetics shouldn't take birth control pills, which I

believe is probably the worst medical advice of my generation. Of all the people in the world who don't want an unintended pregnancy--with all the complications of pregnancy in the diabetic--diabetics are the ones who should use the most effective contraceptive there is; and here was this British nitwit saying, "Don't use it in diabetics," and it drove us up the wall.

On the efficacy of estrogens—with and without progesterone—on carbohydrate metabolism; on choosing to do the developmental work in Mexico

Dr. Friedman: What did you learn about the effect of the estrogens, with and without progesterone, on carbohydrate metabolism?

Dr. Goldzieher: We did some work on that in Mexico--where most of the developmental work that we did on birth control pills was done because in the US it was simply too much and too difficult--and it was so much easier to do it in Mexico in collaboration with my friends there. What had happened was that Pincus's pill had a whole lot of mestranol, which is methylated ethinyl estradiol, in the pill. They took it out and put it back to control menstrual bleeding. I said to myself, I wonder what this estrogen is doing in the pill, because there are two compounds here, not just one. Everybody said, Well, we know that Premarin and estradiol have very poor pituitary inhibiting action. I said, "That's fine, but that's not ethinyl estradiol." So we got hold of some ethinyl estradiol by itself and did the studies in Mexico and found out that the ethinyl group confers a unique potency in terms of gonadotrophin inhibition on the estrogen. In fact, the 150 micrograms of mestranol Pincus had in his pill was quite enough--even without the progestin--to be a birth control pill. They had no idea about that, and they thought the estrogen was only there for cycle control. I started a series of studies in Mexico looking at how much ethinyl estradiol does it take to inhibit ovulation. We found that 20

micrograms was not enough for consistency, but 50 [micrograms] was; and we actually got together with Eli Lilly Company and designed a product, which eventually came out on the market as C-Quens--which was marketed as a sequential birth control pill--which used ethinyl estradiol as the ovulation inhibitor at 80 micrograms and a progestin at the tail end to take care of the bleeding. That worked very well until they started reducing the level of estrogen, and once you got down to 50 [micrograms], it was not one hundred percent efficacious; so that the sequential pills disappeared as the doses got lower and lower. But that was my interest in the pituitary-inhibiting action of the ethinyl estrogen.

Dr. Friedman: You wrote an article with A.B. Weingold. Is he the one who became the professor at George Washington? The article was on diagnostic evaluation of a woman prior to beginning oral contraceptives. There is an Allan B. Weingold who was graduated from NYU in 1955, who is professor of OB/GYN at George Washington University School of Medicine.

Dr. Goldzieher: I don't know. As a matter fact, I had completely forgotten that paper.

ON HYPOTHESES REGARDING THE PATHOGENESIS OF POLYCYSTIC OVARY DISEASE (PCOD): FROM STEROIDOGENIC ORIGIN TO INSULIN RESISTANCE

Dr. Friedman: You've done so much work on PCO over the years, and the last paper I think is coming out this year, which of course I haven't read, but how have your thoughts changed on the etiology and treatment of polycystic ovary disease in recent years?

Dr. Goldzieher: Of course, the recognition of the metabolic consequences of PCO has revolutionized the field. Up until a few years ago, there were people who said, This is a

primary defect in the ovary; and there were others who said, This is a primary defect in the hypothalamo-pituitary system; and people who said, This is an androgen disorder and the androgens cause all the screw ups. First of all, they began to see this in very young people and said that this is a failure of the adolescent hypothalamo-pituitary-ovarian axis to mature--that hypothesis came chiefly out of Italy. Then the latest thing that happened was the recognition that we have insulin resistance as an important component of PCO, and--just a week ago--John Nessler from Vanderbilt gave a paper, and the gist of it was that insulin resistance causes PCO, and everything else is a consequence of insulin resistance. We have gone from a steroidogenic origin of PCO to insulin resistance as the pathogenesis of PCO--and everything in between.

Insulin resistance as pathogenesis of PCO; the problem of PCO without symptoms

Dr. Friedman: They talked about insulin resistance a few years ago in reference to PCO.

Dr. Goldzieher: It started about ten years ago that more and more information began to accumulate, as people followed PCO patients over their lives. We saw more and more insulin resistant diabetes, hypertension, syndrome X, and so the--Nessler's current concept is that insulin resistance with its genetic components and other admixtures is the basic pathogenesis of PCO. Of course, the problem I had with that is that, when [Howard] Jacobs and others in England screened young girls-- who had no problems whatever but came for a routine health examination--they find a significant percentage of PCO on ultrasound with absolutely no symptomatology. So where is their abnormality? Where is their insulin resistance? What is causing their PCO? The insulin resistance hypothesis certainly does not explain this. The other thing is that we know a significant percentage of people have associated adrenal steroidogenesis disorder, so where does

insulin resistance come in to make the adrenal make more androgens than usual? So insulin resistance hypothesis has a lot of holes to fill in before I am comfortable with it.

Ultrasound as a requisite part of a PCO diagnosis

Dr. Friedman: Did they make the PCO diagnosis in these routine examinations on the ultrasound or the MRI, or did they make it on a clinical picture, or were there clinical manifestations in these people?

Dr. Goldzieher: These young girls, who were randomly ultrasounded, had no clinical manifestations. PCO has turned up with Cushing's syndrome, Leydig-cell tumors--with a whole lot of other hyperandrogenic disorders. I think today you have to say that the picture of polycystic ovary on ultrasound is a requisite part of the clinical pathological diagnosis. Does that answer your question?

Dr. Friedman: Yes, if you don't have the clinical picture, then it's not PCO.

Dr. Goldzieher: You can have hyperandrogenism without PCO, but to say you have polycystic ovary syndrome (PCOS) today, I think you have to have ultrasound proof that there is, in fact, an ovary preferably enlarged and preferably with a fibrotic capsule--preferably with a peripheral distribution of cysts of approximately the same size. That is the classic morphological definition of the polycystic ovary.

Dr. Friedman: In other words, if you have the symptoms without the ovarian picture, you won't call it PCO.

Dr. Goldzieher: Right. I will call it hyperandrogenism, or I will call it insulin resistance or syndrome X, but if there is no morphological polycystic ovary there, then this is not PCO.

OVERVIEW OF HIS WORK ON ORAL CONTRACEPTIVES

Dr. Friedman: Since you did so much work on steroid studies and determination methods--as well as your known reputation in the oral contraceptives with estrogen and various progestins--suppose you discuss [each] one of these at a time--as as much as you feel like talking about--

Dr. Goldzieher: Do you want to ask me specific questions, or how would you like to do this?

**Beginning with urinary pregnanediol and urinary 17-ketosteroids; early interest in hirsutism and hyperandrogenism
Collaborating with Axelrod; steroidogenesis in tissues; radioactive steroid tracers; deciding to look at metabolism of estrogen when the field was focused on the clinical outcomes of oral contraceptives**

Dr. Friedman: Why don't you just give me an overall?

Dr. Goldzieher: First, I started with urinary pregnanediol and urinary 17-ketosteroids, and I was interested in hirsutism and hyperandrogenism. There were a lot of people interested in that at the time. Then when Lenny Axelrod came on board and radioactive steroid tracers became available--then we added on to that--the collaboration between Axelrod and myself looking at steroidogenesis in tissues. That I think was the most fruitful collaboration of my life. My memory of Lenny Axelrod is one of the fondest memories of my career. Then, when we got into the oral contraceptives, it was clear that everybody was focusing on clinical outcomes, and nobody was looking at the metabolism

of the estrogen. Since I had fooled with urinary estrogens and estrogens on the skin, I thought we needed to look at the metabolism of ethinyl estradiol; and radioactive material was available, so I began studying the metabolism of ethinyl estradiol and mestranol.

Third World birth control controversy; agreeing to work with the USAID; administration of radioactive ethinyl estradiol to women volunteers in Nigeria, Sri Lanka, and the US yields startlingly different results

At this time--by chance--a man from USAID (United States Agency for International Development) by the name of Ray Ravenholt came by and said, "USAID wants to send lots of birth control pills to Third World countries, but if we do, we, of course, are going to be accused of using Third World women as guinea pigs--the usual stuff; i.e., it causes cancer, et cetera. So we need to set up some research in Third World countries, so that people who are indigenous say, We have tested these things on our people, and we're okay, so would you mind setting up some research projects in a couple of Third World countries?" I said, "Fine." Unfortunately they didn't pick the countries I picked, but they picked Nigeria and Sri Lanka. I went over there and helped them set up their family planning clinics and educated them about the use of oral contraceptives. We agreed that one of the things we would do would be that they would administer radioactive ethinyl estradiol to a dozen or two of their volunteer women, and they would collect the urine and would ship it to me in San Antonio. I did the same thing with US women volunteers with the radioactive ethinyl estradiol, so we had a chance to look at the metabolism of this estrogen in three different ethnic groups. It turned out to be startlingly different: In the American urine, there were oodles of metabolites, 2-hydroxylations, 6-hydroxylations, 16-hydroxylations, and all sorts of stuff; when you did the chromatogram it was full of peaks. In Nigeria, they mostly excreted ethinyl

estradiol and a conjugate and very few hydroxylated metabolites--remarkably different. In Sri Lanka, it was in between the two. So whether it was nutrition, genetic, or whatever it was, I had no way of determining; but the differences from culture to culture clearly said that we have to look at these things on a country-by-country or ethnic group by ethnic group basis because what's going on in the United States is not necessarily going on in Nigeria. Indeed, the cardiovascular hazards that the British claim were caused by the pill--and was subsequently shown to be wrong--never appeared in Thailand, Sri Lanka, in Nigeria, or anywhere else.

Dr. Friedman: Did you do it long enough?

Dr. Goldzieher: I think so, because Thailand had the pill for years and years, and Sri Lanka has had the pill until this day; and they have never reported the frequencies that were alleged by the British and claimed in the United States. In fact, with the medium and lower dose pill, this issue has essentially disappeared.

ON THE HISTORY OF ORAL CONTRACEPTIVES

Feminism and the pill

Dr. Friedman: What about your tremendous knowledge on oral contraceptives? Is there anything else to add to what you've already discussed with me?

Dr. Goldzieher: I think the oral contraceptives have a history--which has been well described in my book *Pharmacology of Contraceptive Steroids*, which I edited in 1994, Raven Press, and [in] numerous reviews since then. The gist of this is that the pill was enthusiastically accepted as the emancipation of women from reproductive slavery. In fact, that is true. Then came the naysayers--the feminists who said, This is an evil plot by

male chauvinist gynecologists and greedy money-hungry drug companies foisting off a dangerous pill on women. Why the feminist took this attitude, I will never know. But there was this backlash, and anybody who could come up with an adverse effect got published in the British journals, which were terribly anti-pill and still are. Everything good about them had to be a ten-year prospective study. So there was a tremendous backlash on the side effects and dangers of the pill. Of course, the Catholic Church had a significant role to play in this, as did some other churches, which were anti-contraception.

Dr. Friedman: In England, there weren't that many Catholics.

Dr. Goldzieher: In England, it was the vested interest of the professor of epidemiology at Oxford, Martin Vessey. Martin Vessey made a career out of saying bad things about the pill, and he actually got to be head of the department on the basis of his publications, which are seriously flawed epidemiology, as has been proven over and over again since then. He is the generator of much of the bad public press that the pill has had, and--every ten years or so--he engineered a public scare in the English newspapers, and I have publicly said that Martin Vessey is the intellectual father of more unwanted children than anybody in history.

Dr. Friedman: Is there anything else you want to talk about?

Dr. Goldzieher: No, I think we're there.

Oral contraceptives: potential hazards

Dr. Friedman: As far as the hazards are concerned, you're convinced that the only questions of hazard are the circulatory ones; and they're not questionable anymore in your judgment.

Dr. Goldzieher: The only hazard that has survived is that in heavy smokers over the age of thirty-five the pill produces an incidence of deep vein thrombosis, equivalent to that seen in normal pregnancy, and the issue of the hazard of stroke and heart attack is simply non-existent and was an epidemiological artifact, which has disappeared. The epidemiologists--to save their reputation--have said that, well, it is the reduction in the strength of the pill, which is why you don't see these hazards any more. But they have no proof for that statement whatsoever--because time has passed, not just reduction in dosage. And with the passage of time, the epidemiological methods have improved; and the critics have been paid attention, too--so they have no evidence that the reduction is the reason why we don't see the cardiovascular hazards anymore. They've also shown that people with rare genetic thrombophilic disorders like factor V Leiden thrombophilia--who have a genetic predisposition to thrombophilia--people who have a genetic thrombophilia are aggravated by oral contraceptives. The heavy smoker over thirty-five and the people with rare thrombophilic genetic disorders are, in my view, the only ones who are at risk taking the pill. Of course, that risk has to be balanced against the benefits of taking the pill.

Dr. Friedman: How about the pill and smoking in terms of hypertension?

Dr. Goldzieher: The hypertension thing has appeared only in a WHO study of Third World countries and really hasn't shown up elsewhere.

ENDOCRINE SOCIETY

Dr. Friedman: I'm going to change the subject again. Have you had any significant relationship with the Endocrine Society? Except for the numerous papers you published or presented, have you had any functional participation in the Endocrine Society?

Dr. Goldzieher: I am a person who avoids executive committees or administration responsibilities and that sort of thing, and I try never to be on the executive boards and committees of organizations. I'm allergic to this. I'm a loner; I am a maverick, a person who wants people in authority to do their thing, but I don't want to be there.

Dr. Friedman: Is there anything else you think you should tell me that I didn't ask you about or that you might think interesting to talk about? Because when this is finally finished, we'll send a copy back to you for your own files. So is there anything else you think we should put into it?

RECENT WORK

On menopause, "estrophobia," and the failures to explain the benefits and risks of hormone replacement therapy

Dr. Goldzieher: The last decade or more I have been very involved in the management of menopause. I'm particularly involved in this because I perceive a phobia about estrogens in the medical community in general; and among obstetricians, gynecologists, and oncologists in particular.

Dr. Friedman: The laity, also.

Dr. Goldzieher: Well, the laymen are bombarded with "estrogen causes cancer." Every time we have a breast cancer drive--"hormones cause cancer." So from this anti-estrogen group comes this whole thought. Back in the 1940s, the FDA said, "In treating

menopause, treat the symptoms with as little estrogen as possible, for as short a time as possible.” My answer to that is, “What are the warning symptoms of a hip fracture?” It’s ridiculous! This has gone in cycles. We had estrogens; there was enthusiasm. Then came the rat and mouse experiments; then estrogen went down the tube. Then they became popular again. Then we had the beagle dogs and the breast cancer business, and of course, the oncologists and the surgeons got into breast cancer, and they make an enormous living out of this--estrogen is an anathema. I happen to think they’re wrong. I’ve maintained all along that the role of endogenous estrogen, age of puberty, age of menopause, and number of pregnancies also influences breast cancer statistically. I am convinced that exogenous administration of estrogen in menopause has, if any at all, a trivial effect on breast cancer, even after long-term use. The rest of it--I’m convinced that there is no relationship between hormone replacement therapy and breast cancer. I have maintained that position to this day, and I have lectured extensively to medical groups and the public whenever I could that “estrophobia” is a manufacture of the oncologists, the surgeons, the epidemiologists, and these people who have this phobia about estrogens. There are thirty-five million women in this country who are menopausal--and it’s increasing at the present time at the rate of about thirty-five hundred women a day reaching the age of fifty-years old--who are being neglected by the medical profession, and who are being turned off by the media, the surgeons and the oncologists. And I think this is a devastating situation, which is affecting millions of people. I think the endocrinological community should have been involved in communication with the public far more than it has been, and that the gynecological professional has done a miserably bad job in generating the information that enables women to make an

intelligent choice. I have repeatedly shown statistics [of] how deficient the gynecological group and the medical profession in general has been in explaining the benefits and the risks of hormone replacement therapy--aside from this dogma--which at best gives a little towards hormone replacement therapy and always has in its background that estrogens are dangerous substances. Today we're seeing the pharmaceutical companies initiating a campaign of minimalism in estrogen replacement therapy and recommending doses for HRT which are slightly above placebo level. The final thrust of my years of communicating with the profession and the public is that the management of the peri- and postmenopausal woman is a huge endocrinological problem, which the endocrinological community has failed to address today--is what I'm tub-thumping about.

BELIEF THAT HISTORY WILL VINDICATE HIS ASSESSMENT ON THE VALUE OF REPLACEMENT THERAPY

Dr. Friedman: I have a personal experience. My wife comes from a family of breast cancer and--among others--was opposed to her using it.

Dr. Goldzieher: The fact is the literature fails to support any evidence that estrogen replacement therapy in people with a family history of breast cancer increases the incidence. There are papers to show the opposite. When you take that information, plus the beneficial effect on bone, cardiovascular effect, Alzheimer's, colon cancer, et cetera, there is no question that the contraindications to hormone replacement therapy in the menopausal woman are very few. Certainly the claim that you should not give estrogen to somebody who has had breast cancer is totally false. There is no such evidence. There is a 1994 paper [Cobleigh MA, Nortock FE, Oleske DM & Starr A. (1994). Estrogen replacement therapy in breast cancer survivors: a time for change. *Journal of the*

American Medical Association, (272) 540–54], which shows there are no data at all.

Currently--to me--to use raloxifene or tamoxifen is obviously a good idea. We have excellent statistics. Once those three or five years are over, estrogen replacement therapy should kick in for a lifetime. That's my current view, and I won't live long enough to see it vindicated because I'm already eighty-two, but I know I will be vindicated.

Estrogen and bisphosphonate for the treatment of osteoporosis; on the failure of the medical community to address vitamin D deficiency in osteoporosis

Dr. Friedman: That's very important documentation. Of course, the other thing is the osteoporosis is such a big factor.

Dr. Goldzieher: Here the pharmaceutical companies are going around promoting raloxifene and promoting bisphosphonates, and the fact [is] bisphosphonate and estrogen work together in an augmented fashion. So that to use bisphosphonate instead of an estrogen is stupid, and you should use both in a case of severe osteoporosis. The raloxifene business on osteoporosis is not all that great because not all fracture risks are benefited equally by raloxifene, whereas they are by estrogen. I think the interests of the pharmaceutical companies are at odds with my view of the benefits that we have available therapeutically for the treatment of osteoporosis. None of these people are addressing the fact that there are studies, in Boston and elsewhere, that show that people in general have deficient intake of vitamin D, especially in the northern part of this country, and that old people have a deficiency in the metabolism of vitamin D to 1,25-dihydroxy D [calcitriol], and that old people should get far greater doses of vitamin D than are currently recommended for the prevention of osteoporosis. The data are sitting there in the literature, and the medical community does not pay attention.

RAISING THE ALARM: THE COMING OSTEOPORITC HIP FRACTURE EPIDEMIC

Dr. Friedman: Of course, there's a lot that they don't pay attention to.

Dr. Goldzieher: But this affects thirty-five million women, which is going to grow to seventy million women by the year 2015. That's a lot of people in America alone.

Osteoporotic hip fractures kill more people than breast, ovary, and endometrial cancer combined. We are not looking at hip fractures as that deadly an epidemic. You don't see that in the media. You hear breast cancer every six months when the American Cancer Society has a fund-raiser. Hollywood stars start their own campaigns--the race for the cure, blah, blah, blah, but how about the race to stop osteoporosis? We know how to do that. So you see, [laughs] I'm really on a tub-thumping expedition at this stage of my life. [laughs]

Dr. Friedman: Well, I appreciate the time and the knowledge that you've given me, and [I am] most grateful for the interview.

Dr. Goldzieher: Well, I'm honored that the Endocrine Society should take an interest in me. I never expected this. I was surprised by the award I received from the American College of Clinical Endocrinology and was totally taken aback by that standing ovation, which I never dreamed would ever happen.

Dr. Friedman: Well, here's the reason.

Dr. Goldzieher: That may be as it may, but I'm deeply honored that the Endocrine Society has enough interest in me to send somebody like yourself to talk to me.

Dr. Friedman: Thank you.

End of Interview

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