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MELVIN M. GRUMBACH, MD

Interview conducted by
Adolph Friedman, MD
January 10, 2000

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[Tape 1, Side A]

FAMILY BACKGROUND

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

Dr. Grumbach: You are, Dr. Friedman.

Dr. Friedman: Thank you. Dr. Grumbach, I know you were born in New York, December 21, 1925. Tell me a little bit about your parents. Were they American born? To what degree were they educated? Did they have any professional positions? What did they do?

Dr. Grumbach: Both my mother and father were born in the United States. They are of French, Alsatian and Swiss descent. Both of my parents completed high school education but had not gone to college.

Dr. Friedman: Did your mother work?

Dr. Grumbach: Yes. My mother was a legal secretary and was an executive secretary in a large real estate firm in New York City, but she quit soon after I was born.

Dr. Friedman: What did your father do?

Dr. Grumbach: My father was a businessman. He was a textile merchant and ran an import and export business.

Dr. Friedman: Do you have any siblings?

Dr. Grumbach: I have a brother who joined my father's business. My father, I suspect, anticipated that as the older son I would follow in his footsteps; when I chose otherwise, he was most supportive.

EARLY EDUCATION

Dr. Friedman: Now, where did you go to high school and so forth?

Dr. Grumbach: I went to New Utrecht High School in Brooklyn and had a very good education. The school offered what would be the equivalent of advanced placement classes, today, and the pre-college preparatory program provided a very challenging education. I was involved in many extra-curricular activities including being news editor of the school paper.

An Eagle Scout

Watching polo games at Fort Hamilton with his father

Leading a forty-mile hike

An early influence towards a career in pediatrics

Dr. Friedman: Any other achievements? Were you an athlete? Were you interested in art, music, drama?

Dr. Grumbach: I was interested in drama and music, but never played an instrument. I am one of the few people in my family who does not play an instrument. I was very interested in art and had haunted museums in New York City from the time I began to ride the subways. I never made the varsity, but I made the junior varsity in baseball, and I was active in intramural sports. My big investment at the time was in the Boy Scouts, and--for a city boy--scouting provided me a chance to spend time in the outdoors. My family lived in Brooklyn, in a residential area near Shore Road and the Narrows; as a matter of fact, there were still truck farms in our neighborhood. I remember going to the army fort, Fort Hamilton, which we lived near, to watch polo games with my father. The future General George S. Patton was captain of the polo team. The Boy Scouts--I love the outdoors, and the Boy Scouts gave us who were city folks an opportunity to engage with enthusiasm in the outdoors. We went on an overnight hike about once a month or so. I spent a good part of the summer in Boy Scout camp. Eventually, I became an Eagle Scout and a scout leader. One of the high points was taking a group of twenty boy scouts on a forty-mile hike--the Ten-Mile River Scout Camp Reservation over a five-day period--and that was a great adventure. I enjoyed interacting with young people and found that I was able to communicate with them and to motivate them.

Dr. Friedman: Is that what interested you in pediatrics?

Dr. Grumbach: Yes. I think that that was one of the major reasons why I became a pediatrician.

CHOOSING COLUMBIA COLLEGE

Dr. Friedman: Did your family have any influence on your selection of a career?

Dr. Grumbach: No. They were very good about that. They let me pick where I wanted to go to college, and I decided that I wanted to go to Columbia College. They left that decision entirely to me.

Dr. Friedman: You've got your bachelor's from Columbia College?

Dr. Grumbach: No. I never finished the undergraduate requirements. It was during World War II, and I was on an accelerated program. But I went on to the College of Physicians and Surgeons of Columbia University and entering medical school in October 1944. I was 18 years old when I

started medical school. In contrast to current lore, I was accepted to P&S as a freshman college student who had just turned seventeen.

Dr. Friedman: You were a youngster.

Dr. Grumbach: I was a youngster. I had a lot to learn.

MARRIAGE AND CHILDREN

Dr. Friedman: When did you get married?

Dr. Grumbach: I was married in 1951.

Dr. Friedman: That was a while later. And you said your wife is a psychiatrist?

Dr. Grumbach: My wife, Madeleine, is a child psychiatrist and has been a very important, key part of my life, both personal and professional. She has been a great supporter and an incredibly talented, unpretentious woman. We have three sons. I take great pleasure and joy in my family. We are tight!

Dr. Friedman: Tell me about them.

Children's interests and careers

Dr. Grumbach: Our oldest son, Ethan, was a cellist, but he recognized that he was just not good enough to be a professional cellist. He eventually became a clinical psychologist in Los Angeles and is training to become a certified psychoanalyst. He does research in early infant development. Our middle son, Kevin, went to Harvard. While in college, he became very involved in drama as an actor and director. He took a year off and studied mime with Marcel Marceau's teacher, Étienne Decroux, in Paris. He came back and finished at Harvard, and then went to The Neighborhood Playhouse in New York for a year. He had met his future wife while they were classmates. They moved to New York where he spent a year studying acting at The Neighborhood Playhouse. He had been working at nights in Maria New's lab at Cornell Medical College. The next year he worked full-time in Maria New's lab and applied for medical school. He is sort of a polymath type, who was a quarterback on a championship high school football team, catcher on a baseball team, and a scholar athlete when he graduated from high school in San Francisco. He applied to medical school--obviously, he did not want his old man to know too much about this--and got accepted wherever he applied, and fortunately came to UCSF. It was quite a challenge to lecture to his class--I lectured to the first and second year class--and having your son in the audience, who was very critical about education. I remember giving back-to-back one-hour talks with an intermission where we had refreshments for this class of one hundred and twenty-five students. Kevin came up to me and sort of patted me on the back and said, "Dad, you're doing fine. Just relax." Anyway, he had gone to medical school with the

intent of going into family practice, and he did not waiver. At graduation he was a Gold-headed Cane awardee.

Dr. Friedman: That's nice.

Dr. Grumbach: He really is an outstanding young person, and he stuck to his guns, did most of his clinical training here at UCSF at the San Francisco General Hospital. When he finished his residency, he took fellowship training in health policy research as a Robert Wood Johnson Scholar. He became a member of the Institute of Health Policy Studies, here, and has become a young leader in family and community medicine. His research is in health policy, a very pertinent area of inquiry these days.

Dr. Friedman: Absolutely.

Dr. Grumbach: My third son is Anthony Havemeyer Grumbach, and he is the tallest of our three sons. Kevin is the shortest; he is about 5'8^{1/2}. Havie was a good athlete. He went on to Stanford. He was a political science major there, but became very interested in drama and went through the American Conservatory Theatre program here in San Francisco. As you see, we have this theatrical blood in our family. He spent the next nine years acting. He was in the theatre in Los Angeles and TV--had done all the advertisements he could get a piece of. He taught high school part-time, waited on tables, and did catering. He painted houses and all sorts of things to maintain his independence. He decided--when the big "three-O" was coming up--that he really wanted to settle down. He applied to law school and ended up at Harvard Law, and he did very well there. He was on the Harvard Law Review and graduated magna. He clerked in the United States Court of Appeals for the Ninth Circuit which covers a big part of the West. He met his future wife, who is also a lawyer in Seattle. Then he worked in the Civil Rights Division of the Department of Justice for three years. He returned to San Francisco and is a deputy City attorney in the City Attorney's Office in San Francisco. We have two grandsons and one granddaughter.

Family support

We are a close-knit family. We see a lot of each other. I have had incredible support from my family all these years. I never thought that these were easy, undemanding positions that I have had. It took a lot of time, and my family was very understanding about it.

COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS

Rustin McIntosh

Dr. Friedman: We tend to neglect our families, yes. Once you got into your residencies and fellowships, were you exposed to any famous people during those periods of time, besides Lawson Wilkins?

Dr. Grumbach: At Columbia there was an outstanding faculty in pediatrics. The department was headed by Rustin McIntosh, who was a preeminent academic pediatric leader. He was the first full-time head of the department at Columbia. He set very high academic standards and chaired a very talented faculty. He had a number of full-time pediatric scientists or clinical investigators who opened my eyes to the positive environment at that time at Columbia in medical science and clinical investigation. I got to know Philip Smith, Chair of the Anatomy Department, who developed the procedure for hypophysectomy in rats. I got to know a number of people in the Department of Biochemistry, for example, DeWitt Stetten, David Shemin, and David Littenberg. I puttered around a bit in the lab. During my pediatric residency, the Korean War broke out. I was in the Air Force Reserve.

Sidney Werner; Joe Jailer; Robert Loeb

Dr. Friedman: Excuse me. Before we get into that, did you have any contact with Sidney Werner while you were there?

Dr. Grumbach: Yes. I had a lot of contact, and I will come to that because--when I returned as a young faculty member to Columbia and Babies Hospital--we collaborated on several research projects. Robert Loeb was a professor in medicine when I was a medical student; he was arguably the most outstanding chairman of a medical department in the country, and he also had a great influence on me. He was a very demanding, Socratic type of teacher, and had very, very high standards.

KOREAN WAR

Presque Isle, Maine

Dr. Friedman: Why don't you talk about the Army, then?

Dr. Grumbach: No, no, I was in the *Air Force*. I was assigned as a pediatrician to an F-86 jet fighter base in Presque Isle, Maine, and a B-36 bomber base in Caribou.

Dr. Friedman: You weren't there in the winter, were you?

Dr. Grumbach: I was there at the beginning of winter. And the snow was up to the second story of the bachelor officers' quarters; the snow was half way up to the lower window. You talk about wind chill factor! It was incredibly cold. But it was beautiful when I first arrived in July. Then, for reasons which are really hard to understand--I had mentioned that I was interested in research--the next thing I knew I was assigned to the Oak Ridge Institute of Nuclear Studies in Oak Ridge, Tennessee. I eventually was trained in atomic, biological, or chemical warfare defense.

Oak Ridge Institute of Nuclear Studies; studying nuclear physics with Jim Black

Dr. Friedman: With the advancement of the climate.

Dr. Grumbach: [laughs] It was really that going to Oak Ridge had a special connotation. I had to go through all sorts of clearance. I ended up with a Q clearance, which was above top secret. I had an incredible experience at Oak Ridge. Through the DRIP course--that was the isotope course--learned a lot about nuclear physics. One of the really coincidental and fortunate things that happened to me was that my lab partner was a man by the name of Jim Black, who was a chemist at the Exxon Laboratories in New Jersey and a Princeton PhD. I was recently married, but my wife was interning in New York City, so there was leisure time and Jim was single. He took it upon himself to drum calculus and physical chemistry into me. As his lab partner I was the person in the lab who did all the experiments and wrote them up under Jim's watchful eye. He did the critiques. It was an incredible experience; Jim was an exceedingly talented teacher and good friend.

Dr. Friedman: At the same time he was tutoring you?

Dr. Grumbach: He was a superb tutor. This experience taught me what mentoring was all about. We took a shine to each other; he was determined to fill in gaps in my science education. So, all in all, this turned out to be a really unusual experience.

Atomic, biological, and chemical warfare defense at Fort Detrick

Writing a manual on infectious disease

An outbreak of anthrax

After I finished at Oak Ridge, I was sent to Fort Detrick in Frederick, Maryland. I was assigned to the Surgeon General's office, but I was involved in atomic, biological, and chemical warfare defense. Fort Detrick was the biological warfare center where they prepared a host of biological weapons. I was taking care of scientists that were involved in laboratory accidents. I had been immunized against everything that you could imagine, including anthrax, various encephalidites, and so forth and so on--all of these exotic agents. It was another very valuable experience. While there I wrote a manual on many of these agents, in terms of how to manage lab accidents. We had an accident involving anthrax; I really don't want to go through that experience again.

Medical ethics: putting the breaks on a planned experiment with soldiers

Dr. Friedman: Any antibiotics at that time?

Dr. Grumbach: Well, we had penicillin, and we had some broad-spectrum antibiotics, Achromycin, streptomycin, sulfa drugs; Achromycin, Gentamycin, Terramycin, Chloromycetin were broad spectrum antibiotics and had only recently become available. The valuable lesson for a young man was the respect I developed for the people I came in contact with. My senior officer locally was a colonel, a veterinarian who was a gifted and very humane person. A group of us

went out to meet with microbiologists from the universities in this city--that will be nameless. An experiment was planned that involved human subjects. There is no need to go into details. We were quite amazed to see how enthusiastic the university consultants were to this. A couple of us, including the Colonel, said, "Would you want to read this in the newspaper, ten years from now?" That really put the brakes on it. These are the kind of people you met. I mean, here's somebody dealing with the most involved and destructive agents. This entails a very broad philosophy about what is right and what is wrong. I was at two of the A-bomb tests at Camp Mercury, Nevada. I was supposed to go to Eniwetak, when my grandmother died, and I was excused to go to her funeral. Otherwise, I would have ended up in the South Pacific at the H-bomb test. Those were very different days, and it is very hard to look back through the perspective of the year 2000.

Dr. Friedman: It seems like so long ago.

Dr. Grumbach: Considering what people were thinking and what we were all concerned about in those days.

Dr. Friedman: We were concerned about it last month.

Dr. Grumbach: Yes. I just remembered when I was at the fighter base--an alert involved Soviet bombers testing the DEW line, Distant Early Warning line, up north--this was obviously a dangerous game. This was not sport; this was serious business. Virtually nothing got into the newspapers, but these encounters were going on all the time.

Dr. Friedman: Were there any casualties during this study that you did at the university?

Dr. Grumbach: They didn't do the study. But later a study was done in the Bay Area where *Serratia marcescens*--supposedly a nonpathogenic bacteria--was sprayed to see what the diffusion pattern was.

Dr. Friedman: Could you spell that name please?

Dr. Grumbach: Capital S-e-r-r-a-t-i-a; m-a-r-c-e-s-c-e-n-s.

Dr. Friedman: What was this bacteria?

Dr. Grumbach: It's a pigmented bacteria, and it was considered non-pathogenic, but some people, in retrospect, did get ill who had compromised or immature immune systems.

Dr. Friedman: Who is allergic to it?

Dr. Grumbach: Well, people who had low or impaired immune systems. This is long before AIDS. There were some children and adults who became ill from exposure to this supposedly nonpathogenic organism. But again, in the Air Force I just met an extraordinarily talented and committed group of people who I had a lot of respect for. It wasn't the usual Air Force. There

wasn't a lot of spit-n'-polish. We were all working together in a dangerous, challenging arena, and rank did not come up except for duty schedules.

Dr. Friedman: I think the only spit-n'-polish and show-off aspect of the Air Force were the pilots in combat. I mean, they were the gung ho, and they wore the white scarves.

Dr. Grumbach: This was interesting. At Fort Detrick, the Army, Navy, and Air Forces, all three services were represented. This was not an Air Force or Army or Navy independently-run operation. The Chemical Warfare Center at Edgewood Arsenal, MD, was primarily Army. During the A-bomb tests, all three services participated. And again, there were a spectrum of biomedical scientists, physicians, and veterinarians.

FELLOWSHIP WITH LAWSON WILKINS AT JOHNS HOPKINS

Early interest in congenital adrenal hyperplasia; choosing Johns Hopkins

Dr. Friedman: Two questions: first, when you were at Hopkins, were you aware of where you would go next?

Dr. Grumbach: Yes.

Dr. Friedman: Were Blizzard, Migeon, and Al Bongiovanni there?

Dr. Grumbach: Before I went in the service, I had talked with Rustin McIntosh, the chairman of pediatrics at Columbia, and physician-in-chief of Babies Hospital. I had become interested during my residency--here is where I first met Joe Jailer over an infant with congenital adrenal hyperplasia, the salt-losing form at Babies Hospital/Columbia. I was really distressed at how little we could actually do. When I first saw these patients, we didn't have cortisone; we just had DOCA. We did not have glucocorticoids available. Then we did. Joe Jailer, who was in the Department of Medicine, Obstetrics, and Gynecology, and I became very interested in these patients. I remember sitting by the bedside of an infant with the salt-losing form of congenital adrenal hyperplasia. In those days, methods for determining serum electrolytes were not what they are now. Monitoring this infant through the night, I really became aware that I had a lot to learn about pediatric endocrinology. So I talked to Rusty McIntosh about this, and he was very supportive. I was called up by the Air Force, and while in the Air Force, I applied to be a fellow in Lawson Wilkins's laboratory. There were really only two places for pediatric endocrine fellowship training. One was with Nate Talbot and Allen Butler at the Massachusetts General Hospital and the other was with Lawson Wilkins at Hopkins. Lawson's interests really very much overlapped my growing interest in this field. At that time in Lawson's group there was Al Bongiovanni.

On being awarded a fellowship from the March of Dimes

Dr. Grumbach: Alfred Bongiovanni became an important leader and imaginative, productive clinical investigator in pediatric endocrinology, and we will talk more about him and Walt Eberlein. Claude Migeon had left Hopkins before Al Bongiovanni arrived from the Rockefeller Institute and was studying and working in Leo Samuels' steroid chemistry laboratory in Salt Lake City. When I went to Hopkins, I was joined by Jud Van Wyk. And interestingly in those days, Lawson had funds for less than one full-time position, so he urged the two of us to apply--I had applied to the National Foundation for Infantile Paralysis and to the National Research Council, and I was fortunate to have gotten both of these fellowships in the same week. While at the time the National Research Council was prestigious, it only paid something like \$4,700; whereas, the March of Dimes National Foundation [for Infantile Paralysis] was paying \$5,500. Obviously, there was no question about which one you took, especially when you are expecting your firstborn child. It just so happened that Jud Van Wyk also got one of these very coveted National Foundation fellowships. So we both had fellowship support. Jud and I became litter mates and uncommonly loyal friends for five decades.

Lab makeup and culture; an exciting period of improved specificity and technology

When we arrived at Hopkins, Al Bongiovanni was running Lawson's laboratory, and Walt Eberlein, who was an associate of Al, was helping out in the lab. They became a very important research team. George Clayton was a second-year fellow at the time. Jud and I were joined by Tom Shepherd, who later became a leader in teratology and human developmental research. He developed one of the first fetal tissue banks at the University of Washington. Tom became an important figure in human teratology. So, it was quite a group.

Al Bongiovanni was a great laboratory mentor for Jud Van Wyk and myself. He was really superb in his devotion to making us into academic pediatric endocrinologists capable of doing original research. I feel that Al was really critical in this. He left--after we had been there a year and a half--to head up the pediatric endocrine division at the University of Pennsylvania and at the Children's Hospital of Philadelphia; Walt Eberlein left with him. Al Bongiovanni--while he was there--had developed a very practical method for determining urinary pregnanetriol: a metabolite of 17-hydroxyprogesterone excreted as a glucuronide conjugate. This was a very exciting period because we were going from crude, chemical tests, such as the measurement of 17-ketosteroids by the Zimmerman Reaction and the measurement of glucocorticoids by the blue tetrazolium reaction--both of which had problems with specificity--to much more specific methods including the advent of separation of steroids by paper chromatography, so that we could be much more sure about what we were measuring. In any case, we were a group that was bonded: I would say incredibly bonded. We all worked together. We all learned together. We all went out and had fun together. Our first son was born in Baltimore.

Lawson Wilkins as leader and mentor

We really thrived in this clinic and laboratory of Lawson Wilkins, who is--in my mind--the father of pediatric endocrinology. His motto, of course, was meticulous observation. His clinical intuition

was incredible, and he had a knack for getting to the heart of crucial questions--what is the question--and whether they could be addressed by methods that were available at the time. While he was not a laboratory person, he really had picked people who could advance his interest in clinical problems. He had gradually built up an extraordinary, diverse clinic with patients with all sorts of disorders.

Lawson liked to take time off in the summer. When Jud and I arrived, Lawson was around for about two weeks to sort of make sure that he could trust us, and then he went off sailing on the Severn River, which is in Maryland. Here we were, taking care of these complex patients. George Clayton would come down to the clinic to check us out. Obviously, when Lawson came back he reviewed all the charts, but this was really a great responsibility for young fellows. I think this taught us a lot about clinical endocrinology, but also about developing confidence in trusting our judgment, and we became very aware of what we knew and what we didn't know. This was an invaluable experience. Lawson was an incredible mentor and leader who--once you are a part of the family, you were part of it forever.

Early interest in genetics: collaborating with Victor McKusick and Barton Childs; setting up a Galton-Garrod Society

While I was at Hopkins, I became very interested in congenital adrenal hyperplasia, including the genetics of this fascinating, challenging disorder. I had the good fortune to link up with Victor McKusick, a fellow in the Department of Medicine. One of his interests was Hurler syndrome. And we had some interesting patients with Hurler syndrome in the Pediatric Endocrine Clinic. We became colleagues and friends. Later, Barton Childs, a young member of the pediatric faculty, returned to the Department of Pediatrics from England, where he had been studying genetics at the Penrose Laboratory in London. Under Victor and Barton's leadership, a Galton-Garrod Society was established, and we met about once a month at the Hopkins Faculty Club on the main campus. Sir Archibald Garrod proposed "inborn errors of metabolism" and fostered the development of the concept of inherited disease, and Sir Francis Galton, the Victorian polymath, progeneticist conceived the statistical approach to the study of human genetics. We met once a month to talk about human genetics. This was invaluable and led to a study that Barton Childs and I did along with Jud Van Wyk.

Dr. Friedman: Excuse me. Spell Barton Childs.

Dr. Grumbach: B-a-r-t-o-n; C-h-i-l-d-s. The study with Barton Childs and Jud Van Wyk involved carrying out a genetic analysis and a biochemical analysis of patients with various clinical forms of congenital adrenal hyperplasia and their families. This work was eventually published in the *Journal of Clinical Investigation* in 1956. Now, Al Bongiovanni left in the fall or the winter of 1954. Claude Migeon came to replace him as head of the laboratory. Jud and I left Hopkins in June of 1955. Claude Migeon arrived in January 1955, or about that time.

[Tape 1, Side B]

RETURN TO COLUMBIA UNIVERSITY (1955-1965)

Dr. Grumbach: Clause Migeon arrived about January 1955 to head up the pediatric endocrine laboratory in Wilkins's unit. When Jud and I left at the end of June or early July of 1955, Bob Blizzard and H. David Mosier came in to replace us as fellows. Jud developed the pediatric endocrine unit at the University of North Carolina in the Department of Pediatrics and has been there ever since. He has put that unit on the map internationally and was a superb mentor and investigator. I went to Columbia to set up an academic pediatric endocrine program and pediatric endocrine services and to establish a fellowship program. It was at that time that I interacted with Joe Jailer in the Department of Medicine. Nick Christy was a fellow with Joe in the Department of Medicine. He later became secretary of the Endocrine Society and an important adult endocrinologist.

Learning basic steroid chemistry, technology, and how to interact with PhDs in Seymour Lieberman's lab

Before my lab was set up, I worked in Seymour Lieberman's laboratory and learned a lot of basic steroid chemistry, how to use the infrared spectroscope, as well as learning how to interact with basic scientists. His labs had a number of PhDs and, later, some MDs in it. Seymour was a great synthesizer. He was absolutely a brilliant man, who later became president of the Endocrine Society. He was a pioneer in the application of steroid chemistry to human biology.

Dr. Friedman: Do you know what he is doing now?

Dr. Grumbach: He is semi-retired but still at the bench.

Forming a journal club; a growing network

Dr. Grumbach: We formed a joint journal club with Nick Christy, Fred Hoffman, Seymour Lieberman, and a number of others: a combination of people from both basic science departments and from pediatrics and medicine. This became an exceedingly successful journal club. We met every other week; eventually folk came down from Yale, from Rutgers, from labs all over the city to attend these interactive exercises. It was a very critical review of the literature. We all learned about radiochemical purity. It was an incredibly interesting and exciting time. Again, this led to a growing network of the people who became friends--more than just acquaintances--and led to interactions at many levels. This was a very exciting time in endocrinology at Columbia.

The genetics of intersexuality: working on Barr bodies and collaborating with Murray Barr

When I was in Lawson Wilkins's laboratory, I had become very interested in intersexuality. I

came across a paper by Murray Barr who described with Burton a sexual dimorphism in interphase nuclei, originally of the cat and later the human being. I contacted Murray Barr, who was professor of neuroanatomy at the University of Western Ontario in London, Ontario. We became friends over time. I was able to obtain--initially--skin biopsies, which we processed for microscopy in our laboratory, and sent sections or tissue blocks to his laboratory. We were able to compare the results of Barr body studies. At that time they were known as sex chromatin bodies. As you know, these chromatin bodies, lying in opposition to the inner surface of the plasma membrane of the nucleus, are present in a significant proportion of nuclei from XX individuals and are absent from XY individuals. Lawson and Alfred Jost had speculated about whether patients with a syndrome of gonadal dysgenesis or Turner syndrome--who were phenotypic females, whether they might not be XY individuals. While Lawson was in England on sabbatical, we collected material from patients with Turner syndrome. We had Murray Barr check our interpretations. We found that these patients were chromatin negative. At the time we didn't know that a negative sex chromatin pattern could mean they were XO as well as XY. This fit with Jost's study on castrated fetal rabbit fetuses. If you castrate rabbit fetuses early in gestation, they are born as phenotypic females--in terms of the development of their internal genital tract and external genitalia. So we put this together as a manuscript with Al Bongiovanni's help. He insisted on taking his name off the resulting paper, but we put Lawson Wilkins's name first because we felt that he had really stimulated us in the notion that these patients might be XY individuals. We sent it to the *Journal of Clinical Endocrinology and Metabolism*. It was published virtually simultaneously with a paper in the *Lancet* from Guy's Hospital, London, by Paul Polani, who came about it from a very different point of view. The skewed male to female sex ratio of coarctation of the aorta in individuals with classic gonadal dysgenesis syndrome or Turner syndrome--he had speculated that some of these individuals might be XY individuals. Well, we now know that they have a single X in the classic form and forty-five instead of forty-six chromosomes and only a single sex chromosome, the X. I had become very interested in the syndrome of gonadal dysgenesis, an old interest of Lawson Wilkins. He had described this disorder as ovarian agenesis and had done some very definitive work on identifying hypergonadotropic hypogonadism and, by laparoscopy, the gonadal lesion.

So the studies with Barton Childs and the studies in gonadal dysgenesis really got me interested in the genetic aspects of endocrine disorders, which were initially focused on the pathogenesis of intersex disorders. I devoted a great deal of time to thinking about the origin of the Barr body. We had set up, as part of our pediatric endocrine laboratory, a cytogenetic laboratory where we were able to do karyotypes. It wasn't until 1956 that it was discovered that human beings had forty-six chromosomes instead of forty-eight. The sex chromosomes in the female were XX and in the male XY, as had been suspected. In any case, we carried out a number of collaborative studies with Murray Barr over the years in which we were doing the karyotype and chromosome studies, and he was doing studies on interesting and informative cytologic studies on patients with a variety of sex chromosome abnormalities.

Seeking the origin of Barr bodies; collaborating with Herbert Taylor

One of the aspects that became a thorn in my saddle was, what was the origin of the sex-chromatin body? It had been speculated--because it had a bipartite configuration--that it was made up of two X chromosomes. We had an opportunity--I came across a paper in the PNAS by Herbert Taylor, who was a faculty member in the Department of Botany and Zoology at Columbia--this was about 1958 and Herbert Taylor had been studying thymidine uptake by the chromosomes in the seedling roots of vicia, and he later carried out a seminal study in a Chinese hamster cell of asynchronous replication of chromosomes in a paper published in 1960 in the *Journal of Biophysical and Biochemical Cytology*.

Dr. Friedman: Is this v-i-c-i-a?

Dr. Grumbach: I believe that's the way the bean is spelled. He was way ahead of his time and had devised a method using tritium-labeled thymidine and autoradiography to study mitosis and DNA synthesis in vicia and later in a hamster cell line. This was very exciting to me because I thought if this could be applied to the human complement, we could look at DNA replication and maybe gain some insight into the origin of the sex-chromatin body. We collaborated with Herbert Taylor--this was with one of my first fellows, Akira Morishima, who to my great sorrow died this past year. The reprint I gave you is dedicated to his memory. He worked on sex chromosome disorders. He was a friend and colleague for over forty years. He left Columbia to come with me to San Francisco. He later returned to Babies Hospital to head up the pediatric endocrine unit at Columbia. In any case, this approach turned out to be extraordinarily successful. And using Herb Taylor's technique--learning autoradiography in his laboratory--it was possible to show that one of the two X chromosomes in the normal female somatic nucleus completed DNA replication later than any other chromosome in the complement, including its homologue, the other X. And by studying triple-X and four-X and five-X individuals and XXY individuals, we were able to show that the number of sex-chromatin bodies was always one less than the number of X's in the sex chromosome constitution, and not only that, but that any X in excess of one was always late replicating. So if there were five X's in the complement, four X's were late replicating, or completed their replication late. They were almost completely silenced and heterochromatized.

The X-activation hypothesis

Dr. Friedman: If you analyze it before the forty-six were completed, would you get forty-five and a blank?

Dr. Grumbach: If they had only forty-five chromosomes, they always had one active X, just as in the male. It was always active. We'll talk a little about a particular cell line that we came across in which it turned out there may have been only a single-X in a certain proportion of cells, in which it was late-replicating, but that was a cultural anomaly, although very informative. In any case, we were able to show--using radioautography--that the sex chromatin bodies represented the late-replicating X's. In a karyotype with 5X chromosomes, there was a maximum of four sex chromatin hot bodies; whereas, in a XY karyotype you didn't see a hot body that resembled the sex-chromatin body. We are able to show using radioautography that

the hot spots were actually sex-chromatin bodies. This led us to look at an X-linked gene encoding erythrocyte glucose-6-phosphate dehydrogenase (G6PD). In this study with Paul Marks, who later became dean of Columbia P&S and, later, president of Sloan-Kettering, we studied individuals who had X, XX, XXX, XXXX, XXY sex chromosomes, and so forth. And we found that they all had virtually the same amount of erythrocyte glucose-6-phosphate dehydrogenase activity. The point was this gene located on the X chromosome that coded for glucose-6-phosphate dehydrogenase, was turned off in all but one X. This was about the time Mary Lyon had come up with what we called the X-activation hypothesis--that has become known as the Lyon hypothesis. She was working on the genetics and expression of sex-linked coat color loci in the mouse and found that only one X chromosome was active in the female mouse. The point is that this is a very interesting, challenging observation that led to the hypothesis that early in gestation--really at the blastocyst stage--a decision was made in each cell in the female, in which one of the two X's--either the maternally derived or the paternally derived X--is inactivated. Females who have double dose X-linked genes have virtually the same amount of expression of X-linked gene activity as the male. Now, one of the interesting things that came out of this--and the mouse people all felt that the entire second X in the female was turned off; we could never buy that because of the fact that in syndromes of gonadal dysgenesis, or Turner syndrome--there were all these physical, somatic abnormalities; whereas, in the mouse they had normal ovarian differentiation (although these mouse ovaries regress after maturity) and they did not exhibit any of the anomalies found in 45,X individuals. It turns out that some of the genes that are on the human X chromosome are on autosomes in the mouse--but in any case, those of us interested in human developmental biology held the view that the X was not entirely inactivated in the human female; whereas, those interested in the mouse thought it was. It has been resolved now that it has been established that the human X chromosome has a number of genes that are active on the so-called "inactive X," and this is all being worked out very carefully with molecular biologic techniques.

Working in Seymour Lieberman's lab on steroids; working on growth hormone; collaborating with Maury Raben and setting up a pituitary collecting network; studying growth hormone in children with hypopituitarism

I had been working in Seymour Lieberman's lab initially on steroid metabolites in the urine of infants, children, and adolescents. After that we became very interested in growth hormone. Maury Raben had purified human growth hormone and offered to provide us with highly purified growth hormone if we were able to supply him with pituitary glands. So Dr. Kaplan and I set up this elaborate collection system in the greater New York area, where we contacted pathologists, then visited them, and told them why it was important to collect pituitary glands. Almost all of the pathologists were very cooperative and collected pituitaries for us, which we sent to Maury Raben; he sent us back highly purified human growth hormone. Now, this enabled us--very early in the game, after the initial studies of Maury Raben and of John Beck (Montreal group)--to study the effect of growth hormone in children with hypopituitarism.

Collaborating with Berson and Yalow, and Glick and Roth on the development of a

radioimmunoassay for growth hormone

About that time Sol Berson at the Bronx VA Hospital, and working in his laboratory, Roz Yalow, a biophysicist, had developed a radioimmunoassay for insulin. I don't know if it is recorded anywhere, but I went to see him--we knew each other from the "Young Turks" and other encounters--and I talked to him about developing a radioimmunoassay for growth hormone.

Dr. Friedman: When was that?

Dr. Grumbach: That was in the early sixties. He said, "Yes." We had a super guinea pig and rabbit antiserum to human growth hormone. The antibody titer was one to a couple million with a high affinity for hGH. We were darn lucky. We had used the guinea pig and rabbit footpad for the site of injection and hGH in Freund's adjuvant. We just hit. By luck, we got it--a couple of animals in which we obtained very high antibody titer. As you know, one in a million, or one in two million titer goes a very long way. It turned out these anti-hGH and antibodies had a very high binding affinity and were highly specific, which was a great boon. We gave some of this to Sol, and he said, "Well, two very bright fellows, Seymour Glick and Jessie Roth, will be arriving in a few months to work in my lab, and I'm going to put them to work on this." Sol was very protective of his staff regarding attribution of credit for their work. When they had perfected the radioimmunoassay and actually had submitted their paper, he taught Selna and me how to do this assay, which used radioautography to separate the bound and the free hormone. This was a radioimmunoassay with labeled human growth hormone; and, of course, it was a real trick to label it without damaging the hGH. Initially, when we imported it into our laboratory, we were getting the labeled growth hormone from Sol. Eventually a chloramine-T method was devised by Fred Greenwood in London, which led to much better radioactive iodine-labeled preparations and much better separation of the damage from the undamaged I-131 labeled growth hormone. In any case, this led us to develop one of the first radioimmunoassays for studying serum hGH in children with growth disorders, a long term interest of our group over the years.

Alfred Jost; developmental endocrinology; studying hormonal patterns in the fetus and in childhood

Also, we became very interested in developmental endocrinology. This is, I think, partly the influence of Alfred Jost of the Collège de France in Paris, who I came to know very well personally and visited his laboratory in France on many occasions. Eventually he invited me to give a professorial lecture at the Collège de France, which was a special honor.

Dr. Friedman: Who was this again?

Dr. Grumbach: This was Alfred Jost, one of the very early, especially distinguished and highly productive fetal endocrinologists. He is regarded by many as the father of developmental endocrinology. In any case, we became interested in the ontogeny, the development of the endocrine system in the human, particularly in relation to the hypothalamic-pituitary axis. This

led us to look at the ontogeny of human growth hormone. Dr. Selna Kaplan and I had access to hypothalamic tissue, pituitary glands, and blood obtained from abortions that were carried out by obstetricians, and who contributed the fetal tissues to us. We had nothing to do with who got an abortion and who didn't, but they were able to inform us when an abortion was scheduled so that we could obtain the samples from the pathologist soon after the abortion took place. The cooperation of the obstetricians and pathologists from multiple sites was incredible and greatly appreciated. This enabled our group to look at growth hormone-prolactin, FSH and LH in their developmental patterns, and to look at--in the hypothalamus--the development of somatostatin, thyrotropin-releasing factor (TRF), and LHRH. It really enabled us to work on the ontogeny of growth hormone-prolactin and FSH and LH in fundamental observations.

UNIVERSITY OF CALIFORNIA SAN FRANCISCO (1966-present)

Working with the sheep model at the University of California; Freisen isolates human prolactin

Dr. Grumbach: We then extended these studies to work here at UCSF on the chronically catheterized sheep fetus. We were no longer restricted to *static* data--the measurement of a single sample of blood and the pituitary content of these hormones and hypothalamic neuroendocrine hormones.

Dr. Friedman: Is this where Henry Friesen came into this?

Dr. Grumbach: Friesen was the first to purify human prolactin and to characterize its amino acid composition. Before that it had been known that growth hormone had both growth-promoting activity and prolactin activity unlike the sheep or pig growth hormone, for example. There was a lot of discussion at this time about whether there was a separate prolactin. Henry isolated and characterized a separate human prolactin, and developed a radioimmunoassay for it. He was the first one to study circulating prolactin in the human, and was an enormous contributor to our understanding of human prolactin and pituitary peptide hormones.

Discovering human chorionic growth hormone-prolactin, developing a radioimmunoassay for it, and studying its effects with Selna Kaplan

Dr. Friedman: Did I break your train of thought?

Dr. Grumbach: No, no. John Josinovich at the Boston-Lying in Hospital had reported a human placental hormone, which he called placental lactogen. We were also very interested in this protein that we independently discovered in our laboratory, which we came to call human chorionic growth hormone-prolactin which we found had not only prolactin activity, but growth hormone activity as well. This was a placental hormone that was found in a very high concentration in the maternal circulation, much lower concentration in the fetal circulation. Selna and I had developed a radioimmunoassay for this so we could measure it in the serum of pregnant women and follow the normal pattern of secretion throughout pregnancy. It correlated with the size and the weight of the placenta: if there were triplets, there would be about three

times as much in the maternal circulation, and we had one case of quadruplets in which it was even higher. We studied the physiology and biology of this hormone. We gave it to humans and showed that it did increase free fatty acids. It had growth hormone-like activities but very much less than the specific activity of hGH. Indeed, in one study it increased growth in hypopituitary-growth hormone deficient children. Still today, we don't really understand all of the actions of this hormone, which is produced in enormous amounts by the placenta.

Dr. Friedman: But it's still different from growth hormone.

Dr. Grumbach: Yes, it is still different from growth hormone. We now know that the placenta also synthesizes relatively small amounts of a human placental growth hormone as well as a chorionic growth hormone production, which is now called human chorionic somatomammotropin (hCS), or human placental lactogen. Interestingly, the human placenta secretes hCS as well as a separate growth hormone identical to that secreted by the pituitary gland. There is uncertainty about the role of each relative in human pregnancy.

Dr. Friedman: So you now have three hormones? You have pituitary and placental growth hormone--

Dr. Grumbach: And pituitary prolactin.

Dr. Friedman: Okay, and a true chorionic growth hormone-prolactin.

Dr. Grumbach: And then this other hormone, which is on the same chromosome--these genes are in tandem: chorionic somatomammotropin [placental lactogen] and growth hormone.

Studying hypothalamic influence on pituitary secretion: discovering causes and effects of "idiopathic" hypopituitarism

Well, we were very interested in the hypothalamic influences on pituitary secretion and the pathogenesis of so-called idiopathic hypopituitarism in infancy and childhood. We were able to show that the vast majority of patients with so-called idiopathic hypopituitarism had primary *hypothalamic* rather than primary *pituitary* lesions. In the course of our studies, we came across a group of children who had profound hypoglycemia in the newborn period--and they were full-term infants, so this was rather unusual--and they did not have elevated circulating insulin. We found that they had growth hormone deficiency, and, usually, ACTH deficiency as well. The males, who had micropallus or micropenis due to fetal pituitary gonadotropin deficiency, all had, primarily, hypothalamic defects. This turned out to be a useful contribution, that is, the detection of the syndrome in the male with micropenis and at risk for hypoglycemia as very early manifestations, and as a signal to look for hypopituitarism. Many of these infants--my friends in neonatal nursery have told me--died due to cortisol deficiency or severe hypoglycemia that was unrecognized. If you have both growth hormone and ACTH deficiency in an infant, you have a serious clinical problem. So these patients were dying or were brain damaged from prolonged

hypoglycemia. We were able to call the neonatologists' attention to this syndrome. Of course, the counterpart occurred in the female, but the female did not have external genitalia abnormalities as a physical marker. In full-term infants with hypoglycemia--one of the things you must think about is neonatal hypopituitarism as a cause, and one that is treatable. These infants do not have hyperinsulinism, which is another cause of severe hypoglycemia in the newborn.

More on hormonal patterns from infancy to puberty; chairing the Airlie House Conference on control of the onset of puberty; discovering the juvenile pause and hypothalamic restraint of puberty

In any case, we focused a good deal of attention on the hypothalamus and developed radioimmunoassays for FSH and LH, testosterone, estradiol--very critically carried out to reduce nonspecific reactions--and went on and attacked the pattern of development of these hormones from infancy through puberty. And we worked out the normal patterns for FSH/LH in the male and the female--and testosterone in the male and estradiol in girls. And our group had shown, for example, that using a method for steroid analysis, which first involved solvent extraction of serum followed by thin-layer or column chromatography and then radioimmunoassay, had very satisfactory specificity, precision, sensitivity, and reproducibility. The method was sufficiently sensitive to detect with precision less than four or five picograms per milliliter of plasma estradiol, recognizing the limitations on the amount of the blooddraw in children. In some reports at the time, all sorts of values for plasma estradiol in the pre-pubertal child were described, but they were really measuring junk. The values we obtained have been recently reconfirmed by a highly specific, sensitive estradiol assay. In any case, the hormone values we obtained enabled us to define the hormone changes during sexual maturation. I was asked to chair a conference on the Control of the Onset of Puberty supported and sponsored by the NIH in 1972 at Airlie House, Virginia. We brought together all the people doing animal research, basic research, and clinical investigation on puberty.

We had made an interesting observation in our patients with Turner syndrome. We found that, early in infancy and for the first couple of years of life, they had high gonadotropins, which you might expect since they are virtually gonadal, and then--despite the lack of gonads--at the age of three years, the concentration of FSH and LH fell into a normal or high normal level for a child. Then, at about nine years of age, FSH and LH rose and eventually again reached castrate levels. Here you had elevated levels in infancy--this is shortly after birth--and then a drop at three to four years of age when gonadotropins fell very strikingly in gonadal children. We called this fall in gonadotropins "the juvenile pause"--that there was the maturation of an inhibitory central nervous system mechanism for suppression of hypothalamic LHRH release, independent of sex steroids. So we were saying that in the normal course of development not only is there sex steroid negative feedback, but a CNS inhibitory mechanism, which lasts for about a decade--the juvenile pause--from three to four years to nine to ten years of age--in which the hypothalamic LHRH secreting cells (the LHRH pulse generator) were inhibited. Two mechanisms lead to this suppression: largely CNS inhibition, but there is as well an element of sex steroid negative feedback. So these

two mechanisms restrained puberty by restraining the secretion of gonadotropins. This was borne out later by studies in the primate by Tony Plant in which it was shown that there was the same type of juvenile pause in the Rhesus monkey. Normally, if you castrated a Rhesus monkey as an infant, gonadotropins were elevated, and then they dropped off--just the way they did in the human--and remained low until the rise in FSH and LH began at what would be the normal age of puberty in the Rhesus monkey. So this is a mechanism of hypothalamic restraint. We still don't understand all of the components of this mechanism, but through the work of basic scientists, particularly those working on the monkey--Tony Plant's group in Pittsburgh, Ei Terasawa at the University of Wisconsin, and Sergio Ojeda at the Oregon Primate Center--we are gaining ground.

Dr. Friedman: Please spell that last name.

Dr. Grumbach: Capital T-e-r-a-s-a-w-a. The hypothalamic GnRH restraint mechanisms have begun to be better understood, at least components of them. We recognize, for example, gamma-amino butyric acid, GABA, as a very major restraining neurohumor factor in this CNS inhibition. In other words, GABA is inhibiting the LHRH neurons from secreting LHRH, and therefore there is very little pituitary gonadotropin secretion.

[Tape 2, Side A]

On a lifetime collaboration and friendship with Selna Kaplan; the importance of team science

Dr. Grumbach: None of this work could have been carried out without the complete collaboration--and we worked as an absolute team--of Selna Kaplan, who has been my colleague and friend since she joined me as a fellow in 1958. This has been an exceedingly rich relationship and a very fruitful collaboration. Selna is my severest critic, and we have been blessed with a very large number of exceedingly talented, hard working, imaginative fellows. The important thing is to understand that this work comes out of a multifaceted laboratory; all these contributions couldn't be done without people working well together. One of the most gratifying experiences is one's role as a mentor of fellows, residents, and students.

Parallel studies: comparing human hormonal patterns with those of sheep; implications for the prenatal onset of adult degenerative disease

Now, as I mentioned to you, we were carrying on parallel studies in the chronically instrumented sheep fetus, which means that you could put catheters into a maternal circulation and into the sheep fetal circulation and sample the fetus periodically over a period of time. We did a lot of dynamic experiments--which you can find in the bibliography--in which we were working on the ontogeny of the hypothalamic-pituitary regulation in the sheep fetus, and they had a lot of connotations for the human. We had the human pattern from the studies that we had done on human fetal tissue, and we were able to compare this pattern with what we found in the sheep fetus. These studies are challenging and really may have some practical significance. There has

been increasing focus on the prenatal onset of adult degenerative diseases, that is, adverse events affecting the fetus, particularly the low birth weight infants and the development in adult life of hypertension, hyperlipidemia, obesity, and insulin resistance. This is all new, and David Barker in England has reported these epidemiologic studies, but the point is that a lot of people are becoming interested in what's going on in the fetus that predisposes--years later—to certain common diseases in the adult. So you never know where interests that might seem rather far removed from clinical practice may provide significant new insights.

More on collaborating with former fellows

Dr. Friedman: That's true of many things. You think about it when it's too late.

Dr. Grumbach: Yes, and the other thing regarding collaborations with former fellows, for example with Felix Conte, who is a longstanding colleague of mine and who was co-author for the chapters in *Williams Textbook of Endocrinology* on abnormalities of sex determination, and with Dennis Styne who co-authored the chapter on puberty, physiology and abnormalities, and endocrinology--you will find that in the bibliography--those have been exceedingly fruitful, long lasting collaborations.

The Endocrine Society: a unique forum

I really want to point out that endocrinology has been a real leader for decades in providing a meeting ground--through the Endocrine Society--for researchers in basic endocrinology and researchers who are working in various aspects of clinical endocrinology--whether patient-oriented or bench-oriented research--but involving patients. In any case, this is a most unique forum, which provided, I think, the impetus for a large number of the advances in clinical endocrinology and the other way around. Observations that were made in the human being were then investigated by those interested in basic endocrinology and animal research in an attempt to clarify it; so it went from bedside to bench, and then from bench back to bedside. There is an incredible combination of talent and good fellowship that provided a unique forum so that people with a common interest in endocrinology--no matter what aspect--could meet, discuss, learn from each other, and gain respect for each other. This did not happen in disciplines that wall themselves off--as clinical gastroenterologists or so forth--but endocrinology really has set the tone and provided a unique paradigm. The Endocrine Society has fostered meaningful interactions and collaborations. And I think, as a consequence of this, the Society has grown and has nurtured many fine, basic endocrinologists and people with various skills in basic science, who were attracted to endocrinology because of the rich models. Look at what is happening in the field, for example, new insights into the biosynthesis and mechanism of action of steroids. We are now in the era of molecular genetics and genetic analysis and that's going to, again, initiate feedback--both ways: bedside to bench and bench back to the bedside. Translational biomedical research has been fostered for decades by the Endocrine Society. This kind of unique interactional relationship has now been adopted by other disciplines, particularly the human geneticists.

Estrogen in the male: an example of clinical observation, collaborations, and biomedical science advancing clinical insight

I would like to conclude this--as kind of a long and I hope not too meandering discussion--and talk a little bit about the fact that clinical observations are not yet dead. And that's come up with regard to two important clinical observations in regard to estrogen in the male that have been made recently. One was the description by Eric Smith and his colleagues in Cincinnati of a 28-year-old male who had a mutation in the estrogen-alpha receptor--that means he did not express in any cell, one of the two estrogen receptors, the estrogen alpha receptor. He was a very tall adult and had severe osteopenia. In our group, Dr. Conte had come across a patient with what turned out to be aromatase deficiency: a female that was born with ambiguous genitalia, and then at puberty had developed progressive virilization and continued to grow. Despite the fact that she had elevated circulating androgens, her bone age was delayed. Dr. Karry Morishima, who was one of my early fellows, called me about a patient that he had seen who was a female pseudohermaphrodite. We, in collaboration with Evan Simpson, a world authority on aromatase and its molecular genetics and his group at the University of Texas Southwestern Medical School, had identified a mutation in the gene encoding aromatase, called CYP19--the enzyme that converts androgens to estrogens, for example, testosterone to estradiol. Karry presented the clinical findings. We talked about what studies needed to be obtained. I said, "Does this patient have any brothers or sisters?" He said, "I will ask." As it turned out, she had a brother. And the brother walks in and is two hundred and four centimeters tall; he has a bone age of 14, and he has severe osteoporosis. We worked with Karry in studying this patient. The genetic studies were carried out by Evan Simpson and his group within three weeks of the time we sent him tissue samples and blood from this patient. He called and said, "I found a mutation; I will let you know exactly what it is." Now, it would have taken us two years to set up this method. This is what I am really trying to say about the pace of biomedical science: You can go to somebody like Evan, who has been working on the P450 gene encoding aromatase--including the human gene--for years; he has a whole laboratory set up to do this, and he can answer that question in no time at all. So the male--like the estrogen receptor-alpha-deficient male--had tall stature and delayed skeletal maturation at age 24. Our patient had macroorchidism and high testosterone levels and hyperlipidemia and insulin resistance.

A paradigm shift

So the point about this is that in the male, estrogen, not testosterone, is critical for the pubertal growth spurt and epiphyseal fusion. It is also important for bone accretion and the prevention of osteopenia. This had not been the party line. In the female, of course, estrogen was important for the pubertal growth spurt--we had known that for decades--and for advancing skeletal maturation although there were some people who thought that adrenal androgens and ovarian androgens were the key factor.

Dr. Friedman: What do you think now? Is it the adrenal androgen?

Dr. Grumbach: No, we don't think the adrenal androgen is a major factor.

Dr. Friedman: What stimulates axillary hair?

Dr. Grumbach: It's mainly testosterone, but adrenal androgens or androgen precursors are also important in the female. The ovary secretes androgens, which are converted to testosterone locally and bring about growth of sexual hair. There is some pubic hair growth, for example, in patients with Turner syndrome, which is due to the action of adrenal androgens and androgen precursors that converted locally to androgens. But the important thing here is that this represents a whole paradigm shift in terms of estrogen action in the male. And we have other evidence from studies that we have carried on in carbohydrate-lipid metabolism. Estrogens are important in the male. The testis only contributes a small proportion, roughly twenty percent or so, to the circulating estradiol levels in the male, but the peripheral conversion is by many tissues not only adipose tissue of testosterone to estradiol. Not only are the circulating levels important; we have come to learn what's really important is what happens locally, at the tissue-level, the conversion of androgen precursors to estrogen.

Dr. Friedman: Pre-receptor or post-receptor?

Dr. Grumbach: Pre-receptor. And then the estrogens act on the receptor in the cell. You will see it in that little paper. I have a diagram, which I think you will be amused at looking at. In any case, Adolph, what I really mean to say is that all these advances were important. And this is in parallel with the concurrent and independent development of knockout mice for the estrogen receptor alpha and the later discovery of a second estrogen receptor, the estrogen receptor beta, and the knockout of that receptor in developing mice. So now we have mice with a double receptor knockout of both the alpha and the beta. My point in all these developments is that biomedical science contributes a great deal to new clinical insights.

I don't want to leave you with the impression that androgens aren't important in the male; obviously, they are very important. Even in terms of bone, it may be that androgens play a role in the maintenance of bone remodeling, especially cortical bone and in the maintenance of bone mass, but an awful lot is due to conversion to estrogen.

Dr. Friedman: That's terrific.

Therapeutic implications

Dr. Grumbach: This, of course, has all sorts of possible therapeutic things. For example, there are now several generations of aromatase inhibitors and of anti-androgens, and there are now a variety of anti-estrogens, and estrogen agonists that work at the cellular level, primarily through these estrogen receptors. In terms of growth disorders, the potential usefulness--as you will see--is of aromatase inhibitors in preventing bone maturation while the child continues to grow. This

may be useful in the treatment of congenital adrenal hyperplasia and of various forms of sexual precocity in the male. We look forward to future advances in the tailoring of new pharmacologic agents, either synthetic or biosynthetic, that will be highly specific and, of course, the long-term clinical studies required to determine efficacy and safety.

On building the Department of Pediatrics at the University of California San Francisco

One of the special privileges that I have had when I left Columbia at the end of 1965 was to be invited to come to the University of California San Francisco, as chairman of the Department of Pediatrics. It was a very productive and--I hope--useful, and indeed gratifying experience to build an outstanding Department of Pediatrics, sort of from scratch, and to take part in the tremendous change at the University of California, San Francisco during a transformative period--where it went from a largely geographically localized institution, with good clinical skill, good clinical practice, to become one of the major biomedical powerhouses in the world. It has really been a privilege to have taken part in this transition. Obviously, this was a very exciting time in the history of this medical school and this health science campus, and it was really a privilege to be able to build and direct a department. Fortunately, the department--in terms of our clinical and teaching responsibilities, while they were great--did permit time for research and scholarship on the part of the chairman; whereas, if I had been chairman at a very large pediatric hospital, I would not have been able to devote time and effort to do other things aside from running the administrative end of the department, building the department, and fostering scholarship and collegiality, and developing and making sure the teaching program for medical studies and house staff were really top drawer. So after twenty years, I was of the view that it was time for me to step down. It was a very fruitful, challenging, and demanding time. I treasure having had the good luck to participate in this incredible venture.

Stepping down as chairman after twenty years; working part-time

Dr. Friedman: When did you finally retire?

Dr. Grumbach: I stepped down as chairman of the department in 1986, and that was after twenty and a half years, starting in January of 1966, and I finished up in July of 1986. I thought the time had come that I would rather--I had turned sixty in December 1985, and I thought as did my lifelong partner--for a lot of reasons--that it was time for taking a fresh look at things. Second of all, you don't get resources when you stay in a job too long. The school was going to get some additional space--which actually was held up for awhile--and I thought that a new chairman ought to plan the use of that space and the recruitment of faculty to fill that space. I thought that recruiting new people at the end of your term is not fair or necessarily beneficial. The university had a special arrangement back in 1994, in which you could retire and get recalled. It was a very, very nice system, and I was asked to come back half time. I work full-time, but I got sort of reimbursed for part-time work. It has been a wonderful part. They had given me--in 1983, I became the first Edward B. Shaw Professor of Pediatrics, which is an endowed professorship, and it gave me great freedom to be very inner-directed, after being both

inner and outer-directed. This really gave me a great feeling--to be inner-directed. I have enjoyed this time very much. I had been playing an active role in the department, not politically, but in teaching and serving as a mentor. And had been, for example, chairman of the advisory committee for the Pediatric Clinical Research Center. I have been called upon to chair committees dealing with very difficult personnel issues in the medical school, in the department, or to be a member of committees seeking unprejudiced views. In addition, I was asked by the dean to be his representative to the Children's Health Initiative, which was a Lucille and David Packard Foundation initiative, which we hope is going to continue. This is a commitment for about twenty to thirty million dollars a year for pediatrics--to improve children's health in Northern California and for pediatrics at Stanford and UCSF. I found this is a real challenge to be able to participate in the planning for this. The hope is that over the next ten years anywhere from three hundred to six hundred million dollars will go into child health services, teaching, and research in Northern California.

Dr. Friedman: Do you still have a sure professorship?

Dr. Grumbach: Yes, I do. It would be for professor emeritus now, but recalled.

[Tape 2, Side B]

PARTICIPATION ON PEDIATRIC REVIEW COMMITTEES

Dr. Friedman: How did you get on all these pediatric review committees in so many different colleges: Yale, Michigan, Colorado, Toronto, Mount Sinai in New York? Here you are in California.

Dr. Grumbach: These were the committees which carried out reviews of departments, or they were advisory committees providing extramural advice to a medical school. To my mind, it's part of your duties as a citizen of the biomedical community to serve when called upon. These are not waste-of-time efforts; you and your colleagues on the committee can help to examine old and formulate new policies, adjudicate different approaches to problem solving, and so forth.

THE ENDOCRINE SOCIETY

President-elect 1980-1981; President 1981-1982

Dr. Friedman: It is not only a citizenship. I think it's a compliment and an honor that they catch you from all over the country.

Now, you held many, many positions in the Endocrine Society. Which do you feel gave you the most gratification, and in what work did you feel you were most productive to this society?

Dr. Grumbach: As president, but I'd like to give a few other responses. The obvious thing, I think, as president you have a real responsibility to keep the ship on an even keel and to begin

some innovative programs. One of the things, Adolph, you may want to do is--I wrote these newsletters--you may want to look at them if they are still in the file somewhere. The *President's Letter*--I don't have copies of them unfortunately.

Dr. Friedman: I am trying to get the presidential addresses.

Dr. Grumbach: I have one. Do you want it? I will get it for you.

Dr. Friedman: Yes, and all your papers related to the Endocrine Society if you are willing to part with them.

Dr. Grumbach: That would be--you see those books up there?

Dr. Friedman: Yes, but look at all the house cleaning you could accomplish.

Dr. Grumbach: Certainly, I will; it will eventually come to you folk. I will have to move this out, but I can get you the presidential address for the--

Dr. Friedman: Do you know what else I would like?

Dr. Grumbach: Let me write these things down.

Dr. Friedman: When you were active in the Society, did you enjoy your presidential year, or do you think you did more effective work on the council? What did you enjoy the most? What did you think was the most productive for your time? After all, your time is valuable.

Dr. Grumbach: I think it was a very productive time. I think it is very hard in a one-year period to be able to--particularly in those days--to do much in the way of redirecting the Society.

Dr. Friedman: A year in advance.

Inklings of dissension in the clinical group

Dr. Grumbach: Elwood Jensen was president--a year in advance--and I worked very closely with him on clinical investigation and clinical problems. I can tell you that the first inklings of some dissension in the clinical group were at the business meeting when I was president. Now, these business meetings are very rushed, but people got up and said, "Well, the program is fine, but we are finding that there isn't enough clinical material for us. What are you going to do about it?" That's when things built up. I don't mean that--

Dr. Friedman: I was one of them.

Dr. Grumbach: Yes. And they really questioned me about it. I mean, come on guys; give us a

break. You know the Council is made up of basic endocrinologists or neuroendocrinologists, and academics. Some people in practice associated, essentially, in geographic full-time and academic departments. An important segment of the Society were full-time clinical endocrinologists. It took a while to really steer a course through that because, Adolph, we didn't want to lose the basic science and physician science contingency. The basic endocrinologists did not know how to deal with some of the issues that were coming up in our clinical practice community. And there were people around the table who were very concerned about upsetting the apple cart and leading to disaffection of the basic endocrinology group.

Fostering positive interaction between basic scientists and clinical endocrinologists

I can tell you that as this emerged it was done very well. It just took time, and I think, Adolph, it took too long. I was president in 1981-1982, and it really didn't get going until 1987 during John Potts' presidency. Jean Wilson had real reservations about change. He was very conservative in his views about this matter. Jean was concerned about the impact it would have on the gestalt of the Society. As it turned out, it was a very constructive change but we understood and appreciate his concerns. What we need to do is keep a balance of all of these constituents. The constituents in our Society all have specific aims, aspirations, and needs. It is very important to be responsive, but at the same time it is very important to balance all of these aspects and concerns so that we don't lose very important constituencies that have made our Society what it is and what it will become in the next century, certainly in the next decade. So I am very sensitive to this, and I think that it's really important to continue to be mindful to this issue. I don't think the Society is really in a position to satisfy all of the clinical crises that are going on with managed care now. I don't think anybody can. I think we need to figure out ways to be as helpful as we possibly can to the clinicians, who are really in a state of depression and concern about their future. I am not talking about adult endocrinology. We are lucky as pediatric endocrinologists. I mean reproductive endocrinology in the adult is really being preempted--in part by the gynecologist, and the medical treatment of prostate cancer by the urologists, and so forth. So I think there are still a host of areas where endocrinology will be able to make a contribution of its own, but it is a discipline that has changed. It changed enormously over the last sixty years, and I don't think it is in a box yet.

On providing support to young endocrinologists and pushing along *Endocrine Reviews*

Dr. Friedman: You didn't tell me enough about the parts of the work that you really enjoyed.

Dr. Grumbach: I will tell you what I really enjoyed; I enjoyed the ability to provide support that we had started for young endocrinologists, for example, travel funds so that they were able to attend our meetings. I enjoyed having played a role during the presidency. And in 1976, 1977, I was a part of establishing, for example, *Endocrine Reviews*. Mort Lipsett and I were on this subcommittee with Gene Yates. There were lots of questions around the table, and finally we formulated a plan to establish *Endocrine Reviews*. I helped to push that along. And I think that

the service on the publications committee was a useful contribution. While on the Council, a group of us felt strongly about strengthening the breadth and depth of the program for our annual meeting to provide and highlight important and exciting developments in broad aspects of endocrinology and related fields from new paradigms to new technologies, to highlighting clinical advances and novel therapeutic approaches. We had as a goal to make the annual meeting a must meeting for endocrinologists around the world--a large goal and ambition.

Dr. Friedman: Yes, that was a good contribution.

Dr. Grumbach: Norm Geschwind was chairman of the Publications Committee for a good part of that period. The presidency--I would say--trying to foster good interactions between the basic scientist and clinical endocrinologist was one of my challenges.

Concerns about fractionation of the field; establishing symposia

Dr. Friedman: That was your biggest challenge?

Dr. Grumbach: Yes. The other thing was--remember these were the years when a real concern of mine was the fracturing of endocrinology--the American Society of Bone and Mineral Metabolism was established. It turned out to be a very fruitful group. We were all worried about the thyroid group, and obviously, the American Thyroid Association had been going for years, but we were worried about fractionation. The neuroendocrinologists formed their own group, and so forth. And we really felt that it was terribly important for people to return to the delta. I mean to come up to the delta, to the main stream, once a year for a kind of renewal. I think one of the things that I helped to accomplish had to do with the programs at the Endocrine Society meetings--the movement to symposia. You could have many state-of-the-art symposia, so that people who are not working in the field could get an idea of what was exciting in that particular field.

Dr. Friedman: So there were many postgraduate posts.

Dr. Grumbach: Yes, at the annual meeting. Those are the kind of things that I was--let me just say this; there weren't many controversial issues. I remember there was this question about election of the secretary and--that really very difficult, difficult scene to deal with--for both the president and the council. We did not have much of that. So I would say that, in many ways, it was an era of relative stability.

And remember that the molecular biology field was exploding at that time. We were concerned about losing our Bert O'Malleys, Ron Evans, Ernie Knobils, Kate Horowitzs, and other folk from the Endocrine Society. I would say cohesiveness was one of our major themes during my presidency: to keep these diverse groups coming together and represented in governance, sharing their experience, and getting something out of it, so they felt it was worthwhile. The young people are the ones that are terribly important. Because the old people come to see their buddies,

no matter what field they're in, but the question--look at the Society and you see how many young people are coming.

Dr. Friedman: Well, they are making a bit of an effort to subsidize their attendance at the meetings with all these grants.

Dr. Grumbach: It is vital to continue to move on this challenge. It is especially important to have these young people attend and get caught up in the spirit of what these meetings represent.

Regarding the association of nuclear medicine and endocrinology

Dr. Friedman: Another thing that surprised me [was that] after your four years at Oak Ridge in the Air Force, you didn't have more of an interest in the association of nuclear medicine and endocrinology.

Dr. Grumbach: When I was at Hopkins, we did our own RAI thyroid scans; we scanned the anterior neck and the thigh. One of the problems I worked on was looking for a salt-losing factor in urinary extracts. We infused radioactive sodium into adrenalectomized animals prepared with subcutaneously administered DOCA in search of a salt-losing factor. We looked for an antagonist to mineralocorticoid. Aldosterone was identified by the Taits and its structure determined by Reichstein during my fellowship.

At the start of my fellowship, I found while browsing in the library the paper by Murray Barr in *Nature* in 1949 and in the SGO (Surgery, Gynecology, Obstetrics) in 1953. This strikingly stimulated my interest in genetics. One of the things that I have learned is how important environment is, and how important not being rigid in your thinking about problems, and always looking for what other disciplines may be able to teach you in terms of advancing work on your problem. The other aspect is knowing when to stop or pause on a problem, knowing when the methodology or even the hypothesis isn't there that can be tested.

Dr. Friedman: I always have said to my kids--and I try to teach them something--I said, "When I know it all, when I think I know it all, I think it's time for me to die."

CURRENT VIEWS OF THE FIELD

Dr. Grumbach: It has been an exciting period in endocrinology, in pediatrics and medicine, imaging technology. As we look to the future, I firmly believe that endocrinology will continue to play a major role. I think that metabolic and hormone pathways, hormone action--all this is going to open up a whole new pharmacology. One aspect that is important is the massive amount of information--how do we deal with that? Here bioinformatics and the web are becoming increasingly important. We can't retain all this in our minds. We have to teach our young--and I really stress this with our fellows--how to find stuff on the web and mastering bioinformatics. We have a California digital library that the University of California sponsors.

Hundreds of journals are available electronically. How do you ask questions in a form that you can get ready and rapid answers? I am not talking about chat rooms. I am referring to the critical advances in bioinformatics and its impact on our thinking and approaches.

Dr. Friedman: I think it's a good thing.

On evidence-based medicine, bedside intuitiveness, and the gratification of working with patients

Dr. Grumbach: Evidenced-based medicine promises to contribute importantly to testing clinical and therapeutic approaches to how we care for patients and in preventive medicine. I am very concerned, though, about the loss of the bedside round and what I call bedside intuitiveness.

Dr. Friedman: That's what the patients complain about today. They go to the doctor and they say the doctor said, "What's bothering you?" He takes out a blood pressure cuff and a thermometer--no history, no background, and may or may not listen to the heart after taking the blood pressure or feeling the belly if it's an abdominal thing--and orders twenty tests.

Dr. Grumbach: Well, one of the things that I have really enjoyed in my own career, I must say, is my involvement with patients and patient care, both on the outpatient and inpatient service. This has given me tremendous satisfaction and solace. If things don't go right in the lab or administration--you see patients, and it is another world. You feel a sense of accomplishment in interacting with children and adolescents and their parents. It has its gratifications. I am concerned at the way our approach to patient care is becoming more impersonal, more remote. I don't know how it's going to play out in the long term.

Dr. Friedman: I am afraid it is not going to be for the better.

Dr. Grumbach: It is going to be different. We can't yet say whether it is better or worse, but it is going to be different. The electronic medical record with the patients' record stored on a chip: When the patients visit their physician, the whole history, and so forth appears.

Dr. Friedman: That would be good. A lot of them don't even pay attention to the history, today.

Dr. Grumbach: Well, I appreciate your concerns.

Dr. Friedman: I do appreciate all the time you have given me.

Dr. Grumbach: You are a very thorough, active interviewer.

Dr. Friedman: I thank you very much.

End of Interview

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