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A conversation with Jean Wilson

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Conversations with Giants in Medicine

We are joined by a JCI favorite, Dr. Jean Wilson from the University of Texas Southwestern Medical School, who was the editor in chief of the JCI between 1972 and 1977 (Figure 1). Dr. Wilson's research centered on cholesterol metabolism and steroid hormone action, laid the groundwork for understanding male/female genital development, and led to the first medical therapy for benign prostatic hyperplasia (BPH). The full interview can be seen at http://www.jci.org/kiosk/cgm. JCI: Can you tell us about what drove you to seek a career as a physician? Wilson: I don't remember when I decided to become a physician. My parents were the first generation in their families to attend college, and they were both teachers. When I was 11, I was given a chemistry set for Christmas; chemistry sets in those days were both more fun and more dangerous than they are now. My mother was afraid that I would set the house on fire, so my father built a small laboratory in our backyard where I had marvelous fun with my chemistry set; so I became interested in chemistry very early. Also, one of my elementary school courses had a nature appreciation element, and I set out to make a complete collection of all the wildflowers in Cottle County, Texas. Through this, I became interested in nature studies […]

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JCI: Can you tell us about what drove you to seek a career as a physician?

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JCI: How did you land at UT Southwestern?

Wilson: Financially, the choice was between two schools: the venerable UT Medical Branch at Galveston and the new school – UT Southwestern. I chose Southwestern because its chairman of medicine was Tinsley Harrison. He was one of the most famous physicians in America and had established a phenomenal training program in Dallas. However, between the time I accepted the appointment in February 1955 and the start of classes that September, Harrison resigned to go to the University of Alabama. Fortunately, Donald Seldin was appointed his successor. Seldin did a phenomenal job of creating an exciting learning environment and scientific environment. And I worked in his lab the summer after my junior year in medical school, and there I chose the problem that I worked on for the rest of my life: how hormones act. So in the end I lucked out by going to Southwestern.

JCI: So what was your path from there to choosing testosterone as the main focus of your lab?

Wilson: Seldin had weekly student conferences, and a patient with pseudohypoparathyroidism was presented to him one Wednesday. Pseudohypoparathyroidism was a condition in which parathyroid hormone is secreted normally by the parathyroid glands but cannot act in the tissues. Patients develop symptoms of hypoparathyroidism even though blood parathyroid levels are high — there is something wrong with the way the hormone acts. I realized that studying hormone-resistant states would be a good way to investigate how hormones act.

At the time there was still a doctor's draft, and I was fortunate enough to serve my military obligation at NIH. Two years later, I accepted an appointment to come back to Dallas, and I needed to write a grant request. I read about various hormones and I discovered that in the 1930s, Charles Kochakian had shown that castration of male dogs causes excretion of nitrogen in urine and administration of testosterone to these dogs caused nitrogen retention in the body. It was subsequently shown that nitrogen is retained in two places: the muscle and the male urogenital tract. I decided that studying testosterone and the nitrogen-retaining effects of testosterone would be a good way to investigate hormone action.

Within a couple of years, I was able to show that the reason that nitrogen excretion goes up in the castrated state is that protein synthesis goes down and that testosterone administration causes an increased rate of protein synthesis in target tissues. With trying to figure out what happened to the androgenic hormone inside the nucleus, we found that in target tissues testosterone is converted to dihydrotestosterone, which is a much more active androgen than testosterone itself. That was a eureka moment, because I knew that androgen action was necessary during embryogenesis to convert what is fundamentally the default female anatomy into the male phenotype. We hypothesized that deficient dihydrotestosterone formation would impair male sexual development.

My colleague Joe Goldstein had read about a rare disorder of male sexual development termed pseudovaginal perineoscrotal hypospadias. Though rare, we came across a family in Dallas with the same disorder, and were able to show that the loss-of-function mutation in the 5α-reductase gene causes dihydrotestosterone deficiency in which genetic males fail to differentiate and are raised as phenotypic females.

JCI: So, how many patients are there with defects in 5α-reductase?

Wilson: Our laboratory characterized the first 50 or so families with such mutations. Subsequently, laboratories around the world have added many additional families.

JCI: As part of your studies of the action of testosterone and dihydrotestosterone, you studied many different animal species. How many different animals did you look at?

Wilson: More than nine, because of a unique phenomenon: namely, prostatic hyperplasia, a common disorder in aging men and aging male dogs, does not occur in any other species. It was a logical extension from my standpoint to ask, What is the difference between the prostates that develop prostatic hyperplasia and those that do not?

A student, Robert Gloyna, showed that 5α-reductase activity is essential in all species for the prostate to form during embryogenesis. In most species, the enzyme remains active up until the completion of puberty, and then it disappears from the prostate; but in man and dog, there is no downregulation of the enzyme. The prostates of these two species continue making dihydrotestosterone throughout life, so we did further studies that suggested that unregulated dihydrotestosterone formation was the key cause of prostatic hyperplasia in those two species.

JCI: Merck, among other pharmaceutical companies, developed a 5α-reductase inhibitor (finasteride), which was the first real medical treatment for BPH. That must have been a tremendously rewarding to watch.

Wilson: It was. The interest of pharmaceutical companies was reinforced by the

finding that men with 5α-reductase deficiency do not develop a prostate. Several companies set out to develop 5α-reductase inhibitors, but Merck hit the jackpot with finasteride. It had been on their shelves for many years but was thought to be a physiologically inactive steroid because it has a nitrogen substitution for carbon 4 in the A-ring of the steroid. It turns out that this change causes it to fit tightly into the active site of the enzyme and inhibit it.

JCI: It was during this time, at the peak of your research career, that you took on the editorship of the *JCI*.

Wilson: That was one of the wisest decisions I've ever made and was a big and interesting responsibility. But for two reasons, it actually aided my research: I got agreement from the dean at UT Southwestern to remove me from all medical school committees, and I stopped traveling. Travel is one of the vices for academics, and so for five years, I limited my travel to a two-week vacation a year. As a consequence, I was in the lab more and always accessible to the fellows. And, not being distracted by committee assignments, I had a great deal of exciting time being at the epicenter of American medical research.

JCI: You also acted as editor for both Harrison's and the *Williams Textbook of Endocrinology*.

Wilson: Seldin, who was very enthusiastic about my being editor to the *JCI*, tried to talk me out of being editor of Harrison's textbook of medicine [*Harrison's Principles of Internal Medicine*]. He felt that textbooks were obsolete and there were better ways to learn; he didn't teach from textbooks and didn't use textbooks. He thought it was a waste of time and that I would not like reducing volumes of data to the essence, which is the challenge in deciding what's good for students and what could be left out. But just as I was mulling the offer, I was a visiting professor at the Institute of Nutrition in Mexico City, which was the premier internal medicine hospital in Mexico. I was astonished at the quality of the house staff. Their presentations were so good and so scholarly. I couldn't understand how they could be that good because I knew what medical education in Mexico City was like — medical students were just turned loose into large public hospitals to teach themselves medicine. I asked the house staff how they learned medicine, and they told me that they carried Harrison's textbook with them, went back and forth from the patient to the textbook, and taught themselves medicine in this way. I decided on the spot that if Harrison's textbook of medicine was having that sort of effect in underdeveloped countries, it was worth trying to make it as good as possible. I thoroughly enjoyed my work as a textbook editor and never regretted the decision.

Figure 1
Jean Wilson on May 9, 2012. Image credit: Ushma Neill.

JCI: What did you feel were the most critical components to being a good mentor to trainees?

Wilson: I ran a Medical Scientist Training Program for more than 15 years, and I have a lot of experience advising students and fellows. And I have a reputation for doing this very well among my colleagues, who frequently send their problem students to me. My general approach to students is to find out what they want to do, to try to encourage them to do it, and to work out pathways that will fulfill what they want in life. I never try to get them to do what I or other faculty or their parents want them to do. The vast majority of student problems have nothing to do with intellect or scientific issues. They have to do with personal issues, frequently problems of immaturity and issues of social interactions with friends and lovers that are not going well. Students with personal problems need to be supported and advised on how to get through. Not infrequently, the most difficult students to counsel turn out to be late bloomers who really are worth all the trouble.

JCI: Did you learn any important lessons about mentoring from your own mentors?

Wilson: I had three mentors: Seldin, Marvin Siperstein, an MD/PhD who had come to our school to run the metabolism unit, and then Sidney Udenfriend of the NIH. Each one of them taught me something different. Udenfriend taught me that you can never do enough controls. It was exhausting, but he was a man who never made mistakes. And you wanted to be a scientist who never made mistakes. And I've tried to teach my fellows and trainees about controls. I believe, from my experience as editor of the *JCI*, that medical fraud is very rare and that the vast majority of it starts off as mistakes; people don't do the right controls and don't design the experiments correctly, and then they're trapped into believing what they want to believe. It's not that they're crooks, they're just sloppy.

Marvin Siperstein taught me that if you had a good idea you should just try it out; the vast majority of them don't work and have to be dropped, but you should always try out every idea. And Seldin taught me that it's critical to choose important problems. In brief, each of my mentors taught me different lessons that stuck with and became a part of me.

JCI: Did you ever consider doing anything other than pursuing a career in medicine?

Wilson: I think there are two types of people in the world: one is like Saul on the road to Damascus, who gets a specific call and then focuses their life on that specific call. Then there are other people who are not so focused who could be happy doing a lot of different things. And I am in the latter category. I'm basically a happy person. I have a good time wherever I go, and I enjoy a lot of different things in life; and I considered becoming an old-fashioned English teacher, doing a broad humanities course in American studies. I even considered archaeology as a possibility. As my life turned out, I would like to have been better, but once I landed in Seldin's laboratory I never wanted to be anything else than I became. I have enjoyed every day with its different challenges and am never bored.

JCI: I think I speak for legions of patients and fellow scientists who are delighted you chose this path with the discoveries that you made.

Ushma S. Neill