



Sharron Francis:

WKU graduate, world-renowned expert on erectile dysfunction drugs

BY KATH PENNAVARIA

IF ACADEMIC INSTITUTIONS KEPT GUINNESS-STYLE RECORD BOOKS, THEY WOULD SHOW THAT 1965 WKU GRADUATE SHARRON FRANCIS HAS A COUPLE OF FIRSTS TO HER CREDIT — AMONG THEM BEING THE FIRST FEMALE STUDENT TO RECEIVE A PH.D. IN THE DEPARTMENT OF MEDICAL PHYSIOLOGY AT VANDERBILT UNIVERSITY.

Raised on a working farm near Bowling Green, Francis attended Warren Central High School, and planned to become a high school biology and chemistry teacher. Those plans changed when she became an undergraduate at WKU. Today, Francis teaches at a major American university and is a world-renowned expert on drugs that are used to treat erectile dysfunction and pulmonary hypertension. She could not have imagined this career for herself when she enrolled at WKU in the early 1960s as a biology major and chemistry minor.

For a female college student at that time, becoming a research scientist was almost an impossible dream. Fortunately for Francis, two exceptional and inspiring WKU faculty members, Dr. Don Bailey and Dr. Bill Norris, recognized the young lady's potential and gave her not only encouragement and advice, but also employment as a laboratory instructor in Biology. As for her class work in the sciences, said Francis, "I just loved it. The more I found out, the more I wanted to know, and the more I realized I didn't know."

She finished her WKU degree in a lightning-fast three years. Bailey and Norris helped her find graduate

programs that offered scholarships, a new possibility in academia stemming from the government's decision to devote money to science education after the Sputnik news broke in the late 1950s. Immediately following graduation from WKU, she entered the graduate program at Vanderbilt to seek a Ph.D. There she had her first opportunity to do original laboratory research. The results of that research formed the basis for her thesis, and she earned her Ph.D. in Medical Physiology in 1970, the first female to do so at Vanderbilt. She finished her doctoral degree in five years, published five manuscripts in high-profile scientific journals, and then launched her post-doctoral career, which took her first to Washington University in St. Louis, then to the National Institutes of Health to the Heart and Lung Institute in Bethesda, Maryland, and finally back to Vanderbilt as a faculty member, where she remains today.

"So I came back to the same department where I earned my doctoral degree and began my career as a scientist and teacher," said Francis. She credits WKU with preparing her for the competitive environment at a major research institution. "WKU gave me a very strong and solid foundation in biology and chemistry," she said. "You have to have that as your bedrock. I came out of WKU well-armed and prepared." As a newly hired scientist at Vanderbilt, Francis began to focus on the ways that hormones regulate cell function. "At the time we knew a little about how some hormones worked, but the research was in its infancy," she said.

Much of her training had been on determining how cell proteins carry out their functions, such as allowing cells to metabolize. She eventually became a specialist in this area, and particularly on the interaction of small molecules with proteins. She and her research group studied a process called “second-messenger signaling,” a new scientific concept at the time which won its creator, Earl Sutherland, a Vanderbilt faculty member in Medical Physiology, the Nobel prize in Physiology or Medicine in 1971. “First-messenger signaling,” she explains, “is when a hormone travels from one cell type to another where it binds to a “receptor” protein typically on the surface of the target cell.” This “first messenger molecule” then causes production of another chemical, or a “second messenger,” inside the cell, she said. Cyclic GMP is one such “second messenger,” and Francis began to work on developing an understanding of the actions of cyclic GMP to change cellular functions.

During the research, Francis and her colleagues found a heretofore

unknown protein that interacted with cyclic GMP differently than other known proteins. The new protein proved difficult to isolate and characterize. She decided to focus first on purifying this protein in order to determine its function. Further lab work helped them determine that the mystery protein was a phosphodiesterase, a particular

the clinical testing soon shifted to test this medication as a treatment for impotence. Sildenafil is now marketed as Viagra for treatment of erectile dysfunction and as Revatio for treatment of pulmonary hypertension in adults and neonates.

The process of erectile dysfunction was poorly understood at this time, but based on their

“WKU gave me a very strong and solid foundation in biology and chemistry,” she said. “You have to have that as your bedrock. I came out of WKU well-armed and prepared.”

kind of cellular enzyme that breaks down cyclic GMP and terminates its action in cells. The newly discovered protein, labeled PDE5, is involved in the relaxation of smooth muscles in blood vessels, airways, and the gastrointestinal tract. Other labs were working in the same area, but the unique approach taken by Francis and her colleagues demonstrated that the “second messenger” known as cyclic GMP and its signaling pathway were critical for relaxing muscles.

Based on this research and that of others, scientists in academia and pharmaceutical companies began efforts to develop new drugs that would block PDE5 action and have potential use in treating hypertension, a disease in which the smooth muscles encircling the blood vessels are excessively contracted, thereby compromising blood flow to organs. Indeed, a new drug (sildenafil) that blocked PDE5 action was developed by Pfizer and tested. Its efficacy for controlling high blood pressure was not as optimal as desired, but male patients reported marked improvement in erectile function, which depends on adequate blood flow to penile tissues. The focus of

research, Francis and her colleague, Jackie Corbin, had earlier proposed that inhibitors of PDE5 would be useful in treatment of impotence. When a man is sexually aroused, his brain sends a signal to nerves in the penis to release a compound (nitric oxide) near the smooth muscles surrounding penile arteries and specialized vascular structures in the penis. This nitric oxide increases production of cyclic GMP in these tissues. At the same time that cyclic GMP production is increased, it is also being broken down by PDE5 in these same cells. With normal erectile function, enough cyclic GMP accumulates so that the muscles in the blood vessels relax, blood rapidly flows into penile tissues, and erection occurs. However, for many men suffering from diabetes, hypertension, depression, vascular maladies, or spinal cord injuries, cyclic GMP does not accumulate sufficiently to effectively bring about the process. One reason for this is that PDE5 may break down the cyclic GMP faster than it can be made. Insufficient hormone signaling can also occur with aging, and it is estimated that erectile dysfunction affects more





than 50% of males over forty years of age. The active compound in Viagra (sildenafil) blocks PDE5 action so that when a patient takes a Viagra pill (or related medications such as Cialis or Levitra), cyclic GMP can accumulate to a level that relaxes the blood vessels. "It may take a bit more time," said Francis, "but they can get a normal erection."

Francis believes that her work has improved the lives of both men and women by improving their sexual lives as well as helping countless young men who have spinal cord injuries or Type 1 diabetes and are still starting their families.

"This subject is not commonly discussed," she acknowledges. Even writing about erectile dysfunction was unusual until the late 1990s. Malfunctions of other systems do not cause the embarrassment that erectile dysfunction does, which bothers Francis. "We take medication to relieve heart disease, headaches, diabetes, and other conditions, and everyone talks freely about it. With erectile dysfunction, it's different." Prior to the advent of Viagra, reliable data on the incidence of erectile dysfunction was hard to come by, and doctors often did not ask patients about it because little could be done

to relieve the problem. Impotence was once thought to be largely a psychological problem, she said, "but today we know it's primarily biological, and these drugs have worked miracles in people's lives — serious miracles." She notes, "Work on possible use of PDE5 inhibitors in treatment of a number of other maladies is currently a vibrant and exciting area of biomedical research."

Knowing she has contributed to the physical and psychological health of so many people helps Francis shrug off the jokes about her research. "This is biology," she said firmly, "and it's a normal bodily function." ■