Although he never focused on practical applications of the basic science he pursued, Ernst Knobil laid the groundwork for revolutionary treatments for dwarfism, infertility, and prostate cancer. He's shown here with his wife, scientist Julane Hotchkiss, during their years in Pittsburgh. (c. 1981)

ERNST KNOBIL UNRAVELED THE SECRET LIFE OF HORMONES | BY SHARON TREGASKIS

IN THE TIMING

Ernst Knobil adored fast cars, and he drove them enthusiastically, if not well. Over the years, newer models replaced their mangled predecessors in the family garage—Karmann-Ghias, Fiats, and finally, in the late '90s, a black BMW. Paternal goading earned son Nick his first speeding ticket while driving an Alfa Romeo through West Virginia. When a state trooper finally nabbed the pair, the teenage driver nearly burst into tears. Knobil leaned across the front seat to explain. "It's all right," he said. "I'm the boy's father." "He took my dad out of the car, and they sat in his cruiser for a long time," says Nick, now in his mid-40s. "My dad came back, got in the driver's seat, and we drove quietly for a while. Then he said, 'Let's not tell your mother about this.'"

Julane Hotchkiss would hardly have been surprised. "He got tickets all the time," she says, recalling a stop in upstate New York when the officer informed her husband he'd been clocked at 92 miles per hour.

"He almost said, 'Hell no, I was going 120,' but he clapped his hand over his mouth."

Knobil had a "need for speed," says son Nick, seen here with his dad.

PHOTOGRAPHY | COURTESY JULANE HOTCHKISS

Such episodes of reckless abandon form a stark contrast to the reputation for meticulous research the reproductive endocrinologist earned in the course of five decades in laboratories at Harvard University, the University of Pittsburgh, and the University of Texas at Houston. During those years, Knobil's lab discovered why a cow's growth hormone is useless when injected in a human (the idea of species specificity**)** and documented the mechanisms of the primate menstrual cycle. He laid the groundwork for revolutionary treatments for dwarfism, infertility, and prostate cancer.

If not for his April 2000 death at age 73, and the medical establishment's late 20th-century preoccupation with molecular—rather than organismal—biology, say colleagues, Knobil (pronounced *no-beel*) might have warranted a Nobel.

"He did whole-animal physiology in the context of a complex, controlled problem," says former Harvard and UCLA physiologist F. Eugene Yates.

Knobil began his academic career in 1952, in Harvard Medical School, as a postdoctoral fellow in endocrinologist Roy Greep's lab studying the adrenal gland and growth hormone in primates. And while the research yielded impressive results, Knobil became increasingly frustrated with a personal failing—he couldn't understand the human menstrual cycle well enough to give a lecture on the topic as part of his duties.

"I could never understand it because it was completely based on beautiful work that had been done on rats and guinea pigs," the scientist recalled in a 1995 interview.

"I had all these monkeys hanging around, left over from the growth hormone stuff, and I said, 'Dammit, I'm going to find out how it works, starting from scratch.' And that's exactly what I did."

As chair of physiology at Pitt from 1961 through 1981, he required his entire faculty to attend every first lecture medical students heard from a department newcomer.

"To this day, the most horrifying, terrifying day of my life was the day I gave my first lecture," says Jimmy Neill, who completed a postdoctoral fellowship with Knobil in 1967, spent four years as a physiology instructor at Pitt, and eventually retired as a Distinguished Professor from the University of Alabama at Birmingham.

Tony Plant's first lecture was on the endocrine basis of human sexual behavior.

"I spent several weeks getting the lecture ready, to impress Ernie and everyone else," says Plant, a postdoctoral fellow in "Knobilab" in the '70s and now a professor of cell biology and physiology and of obstetrics, gynecology, and reproductive sciences at Pitt.

"There was a student in the front row with his feet up on my desk, reading the paper. He raised his hand and asked if the lecture had a lab."

Plant froze, mortified by the student's insouciance. Like all who had preceded him, Plant later got a call from Knobil's secretary, inviting him to come by and discuss the lecture.

"Ernie told me I should have answered that student with, 'Yes, but only with wax models.'"

Knobil always began his own lectures by giving the history of the topic, says Neill, who later collaborated with Knobil on two editions of the textbook, *The Physiology of Reproduction*. "The medical students hated it. But he felt that you must always know where the ideas you are currently studying came from." Knobil's tough exams and tougher grading didn't boost his popularity, and his pass rates frequently lagged the rest of the school. "Some years we flunked more than were acceptable to the dean," says Plant, "and that caused major friction."

Even after decades in the classroom, Knobil never managed to avoid intense prelecture jitters himself. Clouds of blue smoke outside his office were a dead giveaway, says Neill.

"He was pacing up and down the hallway, smoking one cigarette after another, terrified that he had to give a lecture."

Knobil was born in Berlin in September 1926 to Jewish parents. His family fled Hitler's Germany for Paris when the boy was 6. In 1940, they boarded a boat to New York from Genoa, Italy. Fluent in German and French, Knobil began his study of English at 13. As an adult, he took great pride in his accent-free pronunciation.

Neill—raised on a hardscrabble, West Texas ranch—remembers being so intimidated by his mentor's extensive vocabulary, he bought a notebook in which to record unfamiliar utterances. "As soon as he left the room, I'd look up the words," says Neill, "then memorize them." In the Knobil household, only one book was allowed at the table—the dictionary.

A few weeks shy of his 16th birthday, Knobil entered Cornell University, and in December 1944, at 18, married classmate Nancy Berckmans. He took a two-year hiatus from his studies to join the army, and son Erich was born in 1947. The trio remained in Ithaca, N.Y., while Knobil earned his PhD with zoologist Sam Leonard. Leonard recalls his tall, blond protégé: "Smooth to talk to, smart as hell—never smart acting." In fact, says Leonard, Knobil could be paralyzed with self-doubt—when anticipating the oral exam for his 1951 doctoral degree, for example. "I told him, 'You don't have to be nervous. Don't forget you know more than anyone on your committee.'"

In 1951, the family moved to Cambridge, Mass., for Knobil's postdoctoral fellowship where son Mark, now a cinematographer in Pittsburgh, was born. When the marriage dissolved, Nancy and the boys moved to New Hampshire; their father remained in Cambridge.

In Greep's laboratory, Knobil examined why growth hormone isolated from the pituitary glands of cattle failed to affect human physiology. The problem was not, he speculated, lingering impurities in the hormone collected from slaughterhouses—as conventional wisdom then maintained. He instead hypothesized, and demonstrated, that the way the hormone evolved was different for each species, rendering, for example, a cow's hormone useless to you or me. He presented his findings—uninvited—at an international symposium in Detroit in October 1954.

Greeted with hostility by senior academics whose own reputations were on the line, Knobil's data ultimately led to the founding of the National Pituitary Agency, the development of synthetic human growth hormone, and the treatment of thousands of children afflicted with what's known as hypopituitary dwarfism.

"Ernie's original idea of species specificity not only produced a new and effective therapy but also had a unique role ushering in the new era of recombinant biology and the birth of the biotechnology industry," says retired chair of physiology at the University of Massachusetts H. Maurice Goodman, who enrolled at Harvard in 1956 as Knobil's first graduate student.

Goodman also served as a chaperone of sorts, as Knobil nurtured a budding romance with Julane Hotchkiss, another protégé of Sam Leonard. When afternoon turned to evening, Knobil would frequently visit the grad students' lab to check on their data. "He'd ask if I'd like to go out and have a drink," says Goodman, "and 'By the way, ask Miss Hotchkiss if she'd like to join us.'" Hotchkiss soon found a new adviser for her PhD, and the couple married in 1959. Eugene Yates, who headed the lab across the hall, served as best man. Nick and Kate Knobil were born in the next few years.

In 1961, Knobil was appointed the Richard Beatty Mellon Professor of Physiology and founding chair of Pitt's Department of Physiology. Benjamin Spock was in child psychiatry, Niels

Jerne in immunology. "Pitt was a powerhouse," says Neill. "The one big hole they had was in physiology, and Dr. Knobil was the one they brought in to fill it."

It was at Pitt that Knobil's investigations of the primate menstrual cycle really took off.

But first, his lab needed monkeys—so Knobil founded Pitt's Center for Research in Primate Reproduction, a venture he headed from 1974 until 1981, and built the Pittsburgh Primate Center. He also began developing radioimmunoassays (radioactive techniques) to measure the composition of minute hormone samples. He wanted to be able to detect the hormones released by the pituitary that stimulate the ovaries and testes.

On Knobil's wish list: Understanding how the ovaries work; gleaning how the pea-sized pituitary, (the endocrine system's master) and the brain (specifically, a region known as the hypothalamus) interact with the reproductive cycle; unraveling what causes the various organs to switch on and off during the menstrual cycle and throughout the life course (at puberty, during lactation, and at menopause).

He coined the phrase "pelvic clock" to describe the role the ovaries play in the menstrual cycle. In primates, Knobil's team found, a pulsing secretion of hormone from the hypothalamus, directly above the pituitary, permits the stage to be set with pituitary hormones for ovulation. However, the ovaries are the menstrual cycle's timer—its *zeitgeber*, as Knobil put it. (In the rat, the brain, not the ovary, is the timer.)

Knobil delved further into the pituitary's effect on the ovaries, investigating the concentration of the various reproductive hormones in the bloodstream. The data seemed to be all over the place. The group began increasing the frequency with which they collected blood samples. Eventually, they measured the hormone levels at 5-minute intervals, a strategy that revealed the oscillation of the gonadotropins (hormones released by the pituitary that target the gonads) on a schedule of just 60 minutes.

"It's something I wish I'd discovered," says Yates, now a science adviser to the John Douglas French Alzheimer's Foundation.

What mattered, Knobil learned, was not the average levels of the pituitary hormones in the bloodstream, but the fact that their presence was intermittent or discontinuous. The pulsatile secretion of gonadotropins is caused by a pulsatile secretion of hormones from the hypothalamus. That secretion, in turn, is set off by sporadic electrical activity—which can itself be affected by other hormones, stress, sleep, food, light, and other biological inputs. In fact, the normal functioning of the overall reproductive system relies on the timing and intermittency of such electrical activity in the hypothalamus. These findings led to new strategies for correcting the inability to enter puberty, for stalling precocious puberty, and for female contraception and assisted reproduction. They also pointed to a way to treat prostate cancer. Clinicians already knew that halting testosterone production slowed the growth of the disease—but surgical castration wasn't exactly a popular treatment.

LEFT: By 1960, Knobil's work had attracted international attention. Here, he's greeted by Jawaharlal Nehru. RIGHT: The Department of Physiology in 1962, shortly after Knobil (front row, fifth from left) arrived.

"Using Ernie's research, they realized they could do chemical castration," says Yates.

Crafting a manuscript for publication in Knobilab was an art, and for myriad postdocs, pure agony.

Neill recalls the process: "I was really quite proud of my first manuscript. Dr. Knobil said, 'Let's go in my office.' He read through it quickly, said, 'This is pretty good,' and sets it aside. He lit a cigarette and got another cup of coffee, pulls his pen and pad out, and starts right from the beginning, including a new title. He completely rewrote the thing."

"He really couldn't tolerate irrationality or sloppy thinking," says Plant. "If you wrote something stupid," says Plant, "he would tell you it was stupid, and why."

It was a side of their father the four Knobil children rarely saw; they are more likely to recall how he could be reduced to tears of laughter when reading aloud James Thurber. But Nick Knobil does remember volunteering at Presbyterian University Hospital as a teenager. That's when he ran into one of his father's former students in an elevator while wearing an "E. Knobil" nametag:

"He was this doctor in his 40s, in a white coat, and he says, 'Are you related to Ernst Knobil?' I said, 'Yeah, he's my father.' He looked at me with venom, and he said, 'He failed me. I didn't deserve it.' I think I grumbled under my breath something about, 'I get him every semester.'"

Knobil left Pitt in 1981 for the deanship of the University of Texas Medical School at Houston. The gig lasted only a few years, but it was long enough to impose administrative changes felt to this day. He recruited a host of new department chairs in his first year and then overhauled the tenure system.

He soon sparked conflict with the health science center's president, and in 1984 Knobil returned to his laboratory, delving into the electrical mechanisms by which the brain releases hormones into the bloodstream.

Later, he led a panel convened by the National Research Council to investigate the effects on the environment of such endocrine disrupters as dioxins and PCBs. Knobil took heat for the panel's cautious 1999 conclusion that the extent of harm caused by exposure to such compounds was debatable. But Knobil, always a stickler for adequate data, wouldn't back down. "This field is rife with uncertainty," he told *The New York Times*, pointing to questions of how DDT triggered fragility in an eagle's egg. "What is the endocrinologic basis of eggshell thinning?" he asked. "No one has come up with one yet. If you don't know the mechanism, you can't ascribe the effect to endocrine disruption."

Without data, Knobil wouldn't be convinced. But given time, he would devote decades to understanding a whole system, creating the tools to collect the data he craved. Ultimately, says Hotchkiss, her husband had a clarity of thought, and a basic intuition about how systems worked, that she's not seen rivaled in her five decades in the field. In the late 1970s, she recalls, Knobil had a hunch about a hormonal mechanism that launched puberty. Fellows in the lab disagreed, and soon the debate had escalated to a challenge, with Knobil crafting an experiment and his fellows waging bets—a bottle of wine here, a case of beer there.

"He said, 'If I'm right, my name will be first on that paper,'" recalls Hotchkiss, noting that ordinarily, the fellows' names appeared first on a paper. *Science* published the resulting Knobil et al. paper in 1980. ■