Before Klaus Hofmann came along, most hormone chemistry was hypothesis.

KLAUS HOFMANN GAVE HIS STUDENTS AND SCIENCE AN ADRENALINE RUSH

BY LEAH KAUFFMAN

THE KING OF PEPTIDES

It's a graduate student's anxiety dream come to life. You're working in the department chair's lab, where it's standing room only: Every spot at every bench hosts a colleague hard at work. Then your chemistry experiment with a known explosive—the one that's so dangerous that a postdoc must closely supervise your work—detonates in a shower of glass.

It happened to Robert Wells (PhD '64) the summer after his first year of grad school, though he'd followed all the protocols, done nothing wrong. The explosion knocked Wells to the floor, stunned. By the time he realized what had happened, the room was filled with smoke. Wells made for the door on hands and knees, but just as he was about to clear the threshold, he was stopped by a pair of immaculately polished Bally shoes. Wells' eyes tracked up the sharp crease of a trouser leg, up a well-cut suit jacket and stylish tie, to the eyes of the chair of the biochemistry department, Klaus Hofmann,

DRAWING BY HENRY KOERNER

standing resolute at more than 6 feet. Loud noises didn't alarm Hofmann. As a boy, he'd gleefully exploded nitroglycerin-soaked bits of paper; as a young man, he'd commanded a corps of heavy artillery in the Swiss militia.

Hofmann looked down at Wells, whose face seeped blood from dozens of small cuts. "Bobs," Hofmann counseled, "I think you better take the rest of the day off." Although Hofmann had a nickname for everybody—Noboru Yanaihara, the postdoc supervising Wells' work, was called "Nobby"—no one in the lab dared reciprocate.

Hofmann knew the chemistry at work within Wells' body during those fearful moments: He was one of the world's experts on the molecular structure of hormones. Hormones, secreted by one set of tissues and circulated to another, tell cells what to do, when. Hormones are what guide our bodies to make the myriad small adjustments that keep us functioning within our changing environment, adjusting our metabolism to respond to hot, cold, night, day, hunger, and satiety. And when things get tough, hormones guide the mechanisms of self-preservation. Hurting? The hormone endorphin will secrete from your pituitary gland and circulate through the brain, reducing the perception of pain. Just explode something in front of your department chair? Your body will let loose epinephrine, also known as adrenaline, and norepinephrine, which will circulate to the heart, causing it to pump faster. These two hormones open the passages of the lungs to increase respiration and direct blood toward the brain and muscles—all to help fuel the ability to flee, or in the direst situations, to keep the brain oxygenated enough to survive.

Sixty years ago, most hormone chemistry was hypothesis. It was understood that there were two main classes of hormones: steroid hormones, which are derived from cholesterol, and peptide hormones, which are composed of amino acids. But their molecular structures were just beginning to be teased out. In long-drawn, step-by-step experiments, hormones were purified from animal extracts to analyze their structure, then synthesized to understand their function.

These days, the job of peptide hormone synthesis is automated. For the price of a faculty member's salary, your lab can have a peptide-making machine of its own, or you can call up and have your made-to-order peptide hormone delivered. But in the early days of hormone biochemistry, peptide synthesis was a laborious, meticulous process of stringing molecular beads, all within a set of narrow conditions that encouraged new chemical bonds without breaking the extant ones. It required quiet hands, patience, discipline, and rigor. It required someone like Klaus Hofmann, who spent 51 years at Pitt investigating peptide hormones and other proteins, chaired the biochemistry department from 1952 to 1964, and helped a generation of first-year medical students, when faced with his notoriously demanding biochemistry course, master their epinephrine-fueled urge to flee.

Hofmann was recruited to the University of Pittsburgh's College of Arts and Sciences in 1944 to help elevate its research program. His reputation as a chemist was already well established. His postdoctoral work with Leopold Ruzicka and Vincent du Vigneaud, who would both become Nobel laureates, placed him in a fine pedigree. After his tightly run laboratories and courses established his reputation as a leader, Hofmann was invited to chair the new biochemistry department in the School of Medicine.

It was about this time that Hofmann became an American citizen (though he would later serve as an honorary Swiss consul) and fell in with European expatriate Patrick Laing, a British orthopaedist at Pitt. Laing got to know Hofmann because of the biochemist's precise scale, the only one like it in the medical school. Laing had sought out such a scale to further his studies on the degradation of metal implants. Their friendship, in which they shared a world of ideas outside science, would span the next 40 years (and a dozen-and-a-half metal implants—all of them, unfortunately, in Hofmann).

First-year medical students expecting Hofmann's course to be a breezy refresher of their undergraduate labs blanched at its demands, for it detailed the whole of biochemistry. Hofmann took his teaching obligations seriously and expected his faculty to do the same. To keep his perspective and the material fresh, he reinvented the course each year. His blackboard notes were no incidental asides, but carefully storyboarded in advance. His destruction of each lecture's preparatory notes ensured that he never delivered the same talk twice. Once a month, he observed surgery, to better understand how basic science affected clinical practice. In the company of Hofmann and his similarly precise colleagues—Jack Myers (chair of medicine), Frank Dixon (chair of pathology), and Hank Bahnson (chair of surgery)—Pitt's star rose.

Hofmann took delight in his fearsome reputation, yet he was equally and secretly pleased with the accomplishments of his trainees, many of whom now lead biomedical research. Barry Brenner (MD '62) of Harvard University rewrote the book on kidneys. Robert Wells of Texas A&M has challenged paradigmatic notions of DNA. Bert O'Malley (MD '63) of Baylor College of Medicine earned a special place in Hofmann's heart by remaining in the hormone field and by bringing good scotch to conferences. According to O'Malley, Hofmann "didn't mix in a lot of polite tact. But, on the other hand, he loved his students, and he wanted them to do well, and he wanted them to learn."

He loved the finer things. (He played violin in string quartets and with critical care medicine giant Peter Safar on piano. And he'd often take a midday repast at the Pittsburgh Athletic Association.) That appreciation came at the knee of his grandfather, who amassed an early fortune manufacturing silk ribbons, then treated himself to retirement and a castle at the age of 36. Yet whatever sense of entitlement Hofmann had was lost along with the family fortune, squandered on a bad business deal when he was a teenager. He would have to make his own way.

At the Swiss Federal Institute of Technology Zurich, he trained as a chemical engineer, then spent several years working on the structure and synthesis of steroid hormones. His success is archived in a set of 13 papers, astounding prolificacy for a trainee, but he'd had enough of the crowded steroid field. Knowing that steroids' cousin molecules, peptide hormones, were relatively unexplored, he arranged a fellowship with protein chemist Max Bergman at the Rockefeller Institute and, later, with Vincent du Vigneaud at Cornell University. There, Hofmann purified and revealed the structure of biotin, also known as vitamin H. His training was then complete, but it was wartime, and universities were reluctant to hire foreigners, so Hofmann accepted refuge as a guest scientist in industry, at what's now Ciba Pharmaceutical Products in New Jersey. Eventually, Arts and Sciences Dean Herbert Longenecker invited him to the University of Pittsburgh. News soon came that du Vigneaud had isolated and synthesized the posterior pituitary peptide hormones vasopressin and oxytocin. Seeking undeveloped real estate, Hofmann decided to go after adrenocorticotrophic hormone (ACTH), an anterior pituitary hormone.

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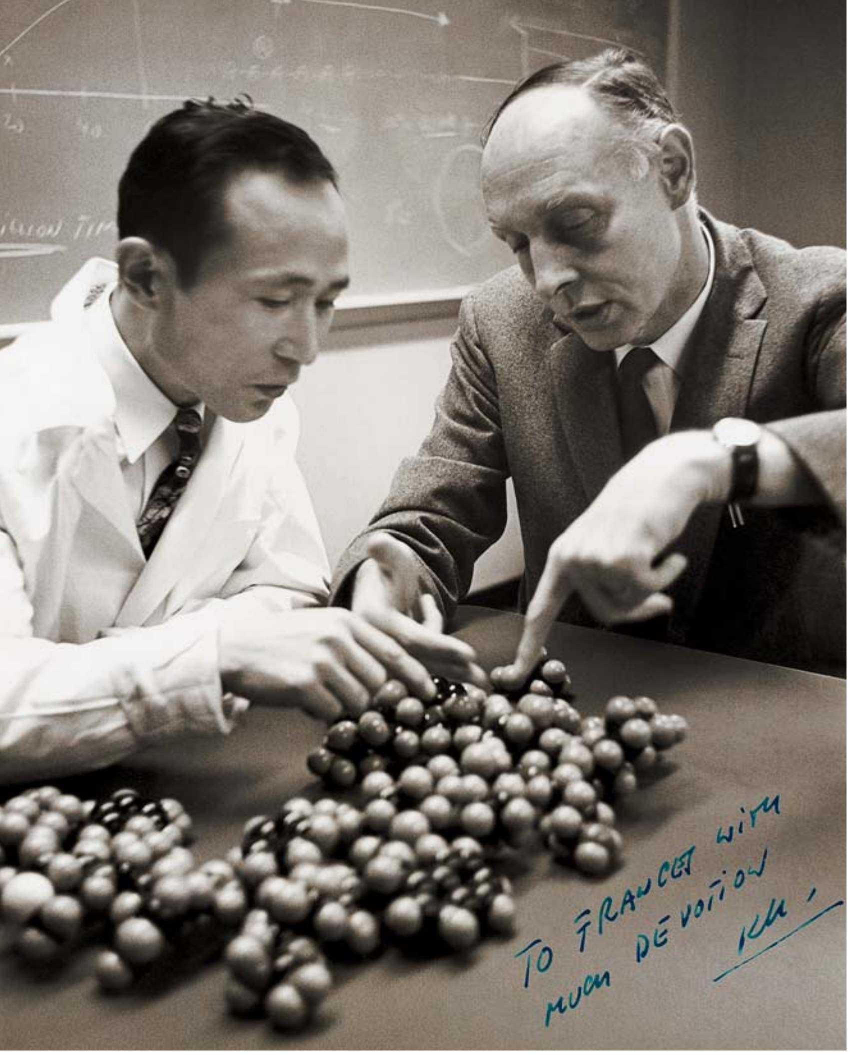

In 1960, Hofmann discusses ACTH synthesis with Haruaki Yajima, a fellow investigator in his lab. The hormone helps preserve crucial brain function during difficult times.

ACTH is an intermediary in a complex cascade caused by physiological stresses like infection or trauma. The hormone helps preserve crucial brain function in difficult times.

Early work by Armour & Company in Chicago showed that ACTH was rich in the amino acid arginine, but no one had yet developed a way of inserting arginine into synthesized peptides. Looking ahead, Hofmann developed a new method. When another group finally purified ACTH and determined its structure, Hofmann was ready to synthesize it, the gold standard experiment for proving that its biological effect was attributable to the hormone alone and not something unrecognized in the mix of animal brains from which the natural purified form was derived.

No one had synthesized a molecule as large as ACTH, which is 39 amino acids long. The task was made less onerous when another group showed that when purified ACTH was limited to just the first two-thirds of its length, it was still biologically active. Hofmann synthesized a sequence corresponding to the first 23 amino acids and showed that the molecule had biologic activity. But now he had new questions to answer. For instance, how does the hormone influence its target cells? What do those other 16 amino acids do?

And who is that new graduate student? Frances Finn arrived in the Hofmann lab in 1961. It's hard to believe that Finn was, like everybody else, terrified of Hofmann, at first. Later, cooking for guests in their home, the two would raucously compete for top chef honors, poking fun at each other and everybody else, their pet parrot joining in, sometimes cursing a blue streak. (Hofmann tried to blame that on Finn, but the parrot's Swiss accent gave him away.) Finn jokes that Hofmann married her as an anchor for the lab, a counter to the students who cycled through every few years.

"I certainly stayed there for 30 years," says Finn (now Frances Finn Reichl). "That worked."

It was a heady time for Hofmann. He was a newlywed in his 50s. He had recently been elected to the National Academy of Sciences—the first Pitt medical school faculty member to be so honored. He received the first Chancellor's Medal, and was the first—and last—Jonas Salk Professor named by the Commonwealth of Pennsylvania (renamed the Commonwealth Professorship). While the accolades, lecture invitations, and faculty position offers poured in, Hofmann maintained that in science, "you're wrong if you go after prizes; the only real way to do science is for the fun of it." By then, he craved more time for his studies. Chancellor Edward Litchfield obliged, accepting Hofmann's resignation as chair and granting him space on the 12th floor of Scaife Hall. Hofmann took delight in applying his engineering education to the design of his new Protein Research Laboratory, then devoted himself full-time to answering the remaining ACTH questions. Finn, an adept protein chemist, had a place at the lab bench and co-authorship on all of Hofmann's papers. (In addition, Finn, now faculty emeritus in the Department of Medicine, taught biochemistry for three decades.)

Those extra amino acids? Scientists still are unclear as to what they do, says Finn. But Hofmann was able to zero in on how ACTH influences its target cells.

His studies led him to believe that some of the molecule's first 23 amino acids represented sites that were recognized by a receptor on the target cell. They allowed the hormone to "dock" at the right place on the cell surface. This was an important process to understand, for if a synthetic hormone was going to be of any practical use, it had to be able to initiate a response after binding to target cells, and only the correct target cells. (You don't want your ACTH docking in your thyroid gland, after all.) But measuring such minutiae in animal models was too uncertain. Hofmann, who insisted his work be correct rather than first, needed a new model.

An enzyme called ribonuclease, a string of 124 amino acids, showed promise. By swapping out amino acids, Hofmann determined how a peptide binds to a protein—a fundamental discovery. He reasoned that this must be the way a peptide hormone binds to a protein receptor on a target cell. Hofmann considered this breakthrough, rather than the synthesis of ACTH, his most important contribution to science.

In 1977, while hosting a party in his role as Swiss consul, Hofmann tripped on the dance floor and refractured a hip he'd broken some 20 years before. As party goers rushed to his assistance, he called out, "Get me two things: a bourbon and Patrick Laing!" Laing put Hofmann's hip back together with 18 screws. Once the hip was knit, and Laing removed the screws, Hofmann weighed himself to see if their absence made a difference. It didn't, but then he wasn't using the very precise scale over which he and Laing met.

Hofmann isolated the receptor for insulin in 1984. He'd hoped to use the same method for ACTH, but identifying that receptor would have to wait. At the time, it was too difficult to purify enough of the target cells from the adrenal glands.

By the time the rest of the ACTH field caught up to Hofmann, he had inoperable liver cancer. As Hofmann's world contracted to home and hospital, Laing helped Finn keep him company. In their 40 years of companionship, the two men had always been able to talk about anything at all. Hofmann died in 1995.

Remembering him, Laing says quietly, "He was my friend." ■