Thomas Hastings Wilson

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Thomas Hastings Wilson, M.D., Ph.D., Professor Emeritus at Harvard Medical School, died on the 27th of December in 2015. Tom was a widely respected educator and noted intestinal and microbial physiologist, biochemist, and molecular biologist with a decades-long interest in discovering how small molecules are transported through cell membranes. Dr. Wilson was born on January 31, 1925, in Philadelphia, Pennsylvania. His parents were Dr. David Wright Wilson and Helene Connet Wilson. David, a member of the National Academy of Sciences, was head of the Department of Physiological Chemistry at the University of Pennsylvania. In that position, David played an important role in hiring Otto Meyerhof as a research professor in the department in 1940, thereby permitting him to escape Nazi Germany. Helene worked at Johns Hopkins in the lab of Drs. Banting and Best, the duo who discovered insulin. Tom had an older brother, John Ewing Wilson, who sadly passed away when he was eleven years old, and a younger sister, Juliet Wilson Welch. Julie worked for many years at UC Berkeley as a staff researcher in the Department of Plant and Microbial Biology. Tom attended Oberlin College as an undergraduate and then received his M.D. in 1948 from the University of Pennsylvania. Tom's Ph.D. was awarded in 1953 at the University of Sheffield, England, under the guidance of Nobel laureate Sir Hans Adolf Krebs.

While in England, Tom met his future wife, Dorothy Blanchard. Although Dorothy was born in the U.S., her family moved to England when she was two years old. Dorothy and her family survived the bombing raids during World War II by spending many nights in a bomb shelter in their backyard. She attended Cambridge University and then went on to receive her master's degree at Sheffield University. While at Sheffield, Dorothy and Tom were married on December 27, 1952. After Tom and Dorothy moved back to the U.S., Dorothy earned her Ph.D. in microbiology at George Washington University. She took a long hiatus from research to raise their four active children, Katherine, Peter, Susan, and Elizabeth, and then returned to microbiology research in collaboration with Tom.

In 1960, Tom moved to Harvard Medical School as an assistant professor of physiology. By 1969, he was a full professor and chair of the Department of Physiology. As departments merged and evolved over the years, he continued his research first in the Department of Cellular and Molecular Physiology and, until his retirement, in the Department of Cell Biology.

Tom's first scientific studies, conducted in 1946 while still a medical student, involved osmotic hemolysis of human red blood cells by tannic acid in solutions containing chloride. The work led to studies of osmotic resistance in patients with carcinoma and sickle cell anemia. The osmotic characteristics of red blood cells would later figure significantly in Tom's medical science lectures as a physiology professor at Harvard. After graduating from medical school, Dr. Wilson became an instructor of physiology at the University of Pennsylvania. Tom, however, was already making plans to pursue a Ph.D., and he wrote to Hans Krebs at the University of Sheffield in England to see if he could study under him for his degree. Krebs was eager to have him in the department, and Tom made his way to Sheffield with a fellowship sponsored by the American Cancer Society. Tom told Krebs that he was interested in studying the intestinal absorption of purines, but Krebs was reported to have replied that he knew next to nothing about absorption and purines. Krebs, however, directed Tom to walk across the hallway and work with a bright fellow there named Gerald Wiseman, who did know something about amino acids. Professor Krebs had given Tom profound advice.

Though Wiseman also replied that he knew nothing about absorption and purines, he was eager to collaborate. Tom and Gerald developed the everted intestinal sac, a groundbreaking method for studying intestinal physiology. They examined many laboratory animals, such as rats, mice, pigeons, and hamsters, before finding suitable intestinal tissue from the gut of the golden hamster, *Mesocricetus auratus*. After excising a piece of hamster gut and washing it with buffer, they used a piece of piano wire to evert the gut manually and tied both ends of it shut. The method produced an inside-out intestinal sac, which had the appearance of a tiny sausage link. In the months and years that were to come, their novel preparation method of intestinal tissue was used for a new generation of solute transport studies, including amino acid transport. Their original method also permitted Tom and Gerald to measure respiration and glycolysis during solute transport because the gut's biologically active mucosal side was directly exposed to oxygen in the buffer suspension. Their studies demonstrated that the absorption of glucose by the gastrointestinal tract involved converting glucose to lactate. The methodology of a sealed, everted gut sac was an ingenious invention relevant to the study of intestinal solute transport across many taxa and remains relevant to the intestine's physiological studies today, over sixty years later.

After earning his Ph.D., Tom returned to the U.S. and continued studying small-molecule absorption by the intestine. Collaborating with his father, David Wright Wilson, Tom studied the metabolism and absorption of pyrimidine nucleic acids across the intestine, publishing the work in a series of papers in the mid-1950s. Much of this and other work would be elegantly described in a pioneering monograph, *Intestinal Absorption*, written by Tom and published in 1962. The now-classic book outlined the history of intestinal physiology starting in the mid-19th century and ended with the state of affairs in the mid-20th century.

In the 1960s, not long after Francois Jacob and Jacques Monod at the Pasteur Institute in Paris had studied the lac operon regulation, Tom Wilson's laboratory at Harvard began to study lactose permease from the bacterium *Escherichia coli*. Tom garnered an interest in bacterial sugar transport thanks mainly to his colleague, Eugene P. Kennedy, in the nearby Department of Biological Chemistry. Tom's early work on lactose permease focused on its physiological properties. His research indicated that the uphill transport of lactose is coupled to energy. In particular, lactose transport is coupled to the transport of H^+. Tom's group showed transport could occur in the absence of an H^+ electrochemical gradient, and surprisingly, lactose permease could carry out what became known as counterflow—the exchange of a lactose molecule on the outside of the cell with one on the inside. The study of counterflow became an essential tool in elucidating the mechanism of lactose transport. In the 1980s and 1990s, Tom's work on lactose permease embarked on a molecular understanding of the transport process. This research involved various biochemical and genetic approaches to study the relationship between the protein structure and its ability to move H+ and lactose across the membrane. His laboratory became the first to solubilize and functionally reconstitute lactose permease into membrane vesicles. This discovery paved the way for studying lactose permease in a purified state. Another critical approach pioneered in Tom's lab was the isolation and the DNA sequencing of mutants with specific transporter function changes. An exciting finding was that mutant forms of lactose permease could be energy uncoupled. Such mutants could still transport lactose across the membrane, but they lost the ability to transport lactose against a gradient. He identified key amino acid residues involved in sugar transport energetics. Tom discovered the salt bridges formed by ionic interactions between charged amino acids. He found mutants that transported sugar without concomitant translocation of protons and mutants that transported protons but not sugar. His research identified many mutants that were altered in the sugar recognition process. Much to everyone's surprise, single mutations in lactose permease resulted in dramatic changes in sugar specificity. This work led to early models for the structure of lactose permease within the membrane. Tom's work spanned several decades and provided foundational knowledge regarding transporter structure and function. To this day, the lactose permease remains a paradigm of how the transport of solutes across biological membranes is coupled to energy.

Starting in his early years in the Department of Physiology, another primary avenue of transporter research involved melibiose permease. These studies were overseen mainly by his wife, Dorothy Wilson. They would work together for over 24 years studying how this sugar is transported across the bacterial membrane via the MelB cotransporter. Their first collaboration identified the energetic nature of the proton motive force in cells depleted of ATP. Their studies supported the then-controversial (but ultimately shown to be correct) chemiosmotic theory proposed by Peter Mitchell. As with the lactose permease, Tom and Dorothy's collaboration on melibiose permease led to several exciting discoveries. In particular, their work revealed that melibiose permease can recognize different cations (H+, Li+, and Na+) and that its cation specificity depended on the sugar that was being transported. They also identified many mutants that were altered in their sugar recognition and cation recognition. As scientific techniques advanced, Tom and his colleagues exploited them to identify the many structure-function relationships within the *melB*-encoded transporter.

Looking back on Wilson's research, his achievements were instrumental in providing crucial insights into the structure and function of cotransporters. Since Tom's early work, thousands of cotransporters have been studied by hundreds of research labs. Many of these transport systems are important from a medical or biotechnological perspective. Tom Wilson's research over several decades has provided a foundation for understanding how all of them work. Each of his discoveries constitutes significant contributions to the physiology of sugar transport across the biological membrane.

Tom carried on his father's tradition of educating the next generation of medical students by teaching physiology to the first-year medical students at Harvard. He believed in the power of demonstration and participation to make lessons meaningful and memorable. For example, he conducted hemolytic experiments with student participation. In the amphitheater at Harvard Medical School, Tom prepared a series of large glass chromatography chambers filled with a red blood cell suspension in hypotonic, hypertonic, or isotonic solutions. A flood lamp was placed behind each chamber so that each solution's turbidity could be readily seen throughout the amphitheater. Tom would hand out stopwatches to student volunteers. Turbidity changes allowed the timekeepers to measure the various blood lysing rates. Tom would construct a table of hemolytic timing data on the chalkboard, and the students made the necessary calculations. Toward the end of the process, Tom would walk over to a particular chamber, remark on its lytic tardiness, and return to writing numbers on the board. The chamber, now to Tom's back, would suddenly clarify, causing an audible gasp in the auditorium. And Tom, with his back still to the experiment, would remove a stopwatch from his pocket, click it with a flourish, and write down the final piece of data. Theatre! It's been said, "Good teaching is one-fourth preparation and three-fourths pure theatre." Tom could put on a show. Even his now geriatric students recall with fondness what it was like to sit as privileged witnesses to the Tom Wilson Show, which was by all accounts a surprising joy to see for the first time. Former students recall with contentment and admiration how a rumble would overtake the main Harvard Medical School amphitheater to mark the giddy anticipation and camaraderie that filled the air as students recognized one by one, and in pairs, and groups, that Dr. Wilson was about to do it again!

Humor was also on the agenda of his lectures. For example, Tom, you need to know, was a notorious flasher. During each of his physiology lectures, Tom would appear in a fully buttoned-up lab coat. When key concepts were explained, he invariably mentioned the investigators who made the discoveries and their groundbreaking experiments. Then Tom would slyly unbutton his coat to reveal a shirt with a photograph of the investigators who had made the key contributions. It was not long before the mere mention of a scientific deity would cause the room to buzz with anticipation. It was fun. During some lectures, he was also known to present television commercials that emphasized bellies and abdomens to illustrate concepts about the gut and glands. To demonstrate the small intestine's topology, he even showed a model of the intestinal epithelia constructed from a six-pack of beer cans with latex microvilli glued to their tops. Tom had great enthusiasm for learning and knew how to pass this on to his students.

Tom was also a profoundly caring mentor to graduate students and postdocs alike, many of whom went on to productive scientific careers. Many of these grateful mentees named their children after him, and others wrote endearing tributes on his behalf. One group of grateful students, postdocs, and colleagues bestowed an inscribed Paul Revere Bowl to Thomas Hastings Wilson in 2001 on the occasion of his retirement from Harvard. The silver bowl was presented to him by Dan Lowenstein, Dean of Medical Education, in the Benjamin Waterhouse Room of the Gordon Hall of Medicine. Dr. Lowenstein's fitting tribute summed up the thoughts of all in this statement: "for his exemplary and outstanding record of mentorship, excellent research guidance and profound influence on the professional development and careers of many postdoctoral and graduate students over the many years at Harvard Medical School."

Tom was, foremost, an amiable human being and treated all his colleagues as family members. Close associates noted that for many years Tom was a first-rate grower of tomatoes in the backyard of his home in Belmont, MA. Tom's tomato yields were legendary, and he routinely brought bags full of the delicious, fragrant fruits to the laboratory for any tomato-lovers to take home. On occasion, Tom would take his entire laboratory crew and their families to the Isabella Stewart Gardner Museum or to the Museum of Fine Arts for a tour followed by a meal at one of Boston's many fine restaurants. Scientific discoveries and social connections were both valued by him.

Outside of his laboratory, Tom had a passion for gardening, flute playing, summering in Woods Hole, Massachusetts, Cape Cod, and Indian cooking. At the Cape, he loved playing tennis with friends, swimming, and fishing on his skiff. His passion bordering on obsession with Indian food began in 1965 when Tom traveled to India and Ceylon to participate in a task force that developed cholera treatments. While there, he fell in love with the local cuisine and made many lifelong friends. Over the next several decades, he mastered the art of Indian cooking aided by his new friends, who regularly sent him various types of authentic curry powder. They jokingly bestowed upon him an honorary "Doctorate of Curry." Though typically quite humble, he once quipped that there was no food that he could not curry. He was famous for his biannual curry parties held at the cozy family cottage in Woods Hole, typically filled with friends and family. Later in life, he developed partial loss of smell and taste, after which his curry became noticeably spicier.

Tom's gracious spirit, curiosity, and enthusiasm for the scientific inquiry were evident to all who met him. Tom welcomed everyone with a smile and a twinkle in his eye. Colleagues, fellows, international scholars, students, summer interns, and office assistants were all accorded his genial manner. Tom hosted weekly discussion meetings that were held in the comfortable surroundings of his office. These gatherings gave attendees a chance to delve into new and exciting journal articles or the laboratory's latest experimental findings. Excitement over discoveries was fueled by a box of donut holes and his well-placed comments and questions. These meetings' happy collegiality opened the door to fresh insights and renewed eagerness for subsequent discovery. During the week, his wanderings about the laboratory resulted in suggestions that would help investigations move forward more quickly and with renewed energy. Whether having known Tom for a week, a month, a year, or a scientific lifetime, everyone carried the memories of his courtesy and inquisitiveness forever after.

Respectfully submitted,

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