On July 18, 2019, Kurt J. Isselbacher, M.D., passed away at the age of 93, the final curtain on his six-decade reign as a renowned physician-scientist and the premier academic gastroenterologist/hepatologist of his generation. His family lost a devoted, loving patriarch; his former patients lost an empathetic, selfless, master clinician, and advocate; his trainees and colleagues lost the ultimate teacher, mentor, career-and-life guide, and role model; and the academic community lost one of the leading physician-scientists and most influential giants of his generation in American medicine. Indeed, the world is a poorer place without him. While he earned many plaudits and tributes and led many distinguished academic societies, we honor his memory in *Hepatology* as the 18th president, in 1967, of the American Association for the Study of Liver Diseases (AASLD) and mourn the loss of a great man.

How do you capture the essence of the person whose imprint on the field of gastroenterology and hepatology was so dominant and whose career spanned the transformation of these fields from observational to science-based disciplines? We can begin with his origin and the shadow that the events of his childhood cast over his life and career. Kurt, an only child, was born on September 12, 1925, in the German Rhineland town of Wirges. While he witnessed and experienced antisemitic taunts and scarring beatings as a young child, the escalating horror of growing up in Germany erupted on a very personal level for him in 1933, when at the age of 7, he and his family were subjected to the Easter-morning storming of their home by Nazi SS troopers, who lined them up against a wall and threatened their lives by training rifles at their heads, burned their belongings, and looted Kurt’s father’s clothing store (above which they lived). Following the Nazi roadside unprovoked beating to death of his paternal grandfather and the spiraling of Nazi Germany into an abyss of brutal antisemitic atrocities, Kurt (at age 10), his parents, and his paternal grandfather, sponsored by an aunt living in Texas, fled to America in 1936, settling in Portsmouth, New Hampshire. Of his extended family who stayed behind, all perished in the Holocaust. His survival amidst such decimation motivated and propelled him throughout his life to work hard and to succeed. As he recounted in his memoir, *Don’t Call Me Cookie*, “I believe medicine became my calling in order to justify my survival,” and this dedication colored all of his life’s activities and accomplishments, transforming his life and career in a way that no one could have predicted and few have matched. Perhaps just as remarkable, the terrors he experienced, observed, and then escaped during his early childhood in Germany did not prevent him from approaching the world with a sense of optimism.
Excelling in his studies, Kurt graduated with honors from a wartime-accelerated, 2-year A.B. program at Harvard College (1946), received his M.D. (included within the then-prevailing Jewish quota) from Harvard Medical School [HMS] (1950), and trained as a medical resident at the Massachusetts General Hospital [MGH] (1950-1953). Even as a resident, he published papers on the relation between asbestos and mesothelioma and on the constellation that would come to be called Bartter’s syndrome. Between 1953 and 1956, Kurt decamped to the National Institutes of Health (NIH), where he trained in biochemistry under Danish scientist Herman Kalckar. There, his ground-breaking discovery of the enzymatic defect underlying galactosemia—the first hereditary disease for which a specific enzymatic defect was identified—catapulted him to the attention of the scientific community. As important as this period of research immersion was to the launching of his academic career, he had the good fortune, while at the NIH, of meeting and marrying (in 1955) Rhoda Solin, a descendant of the Soloveitchik rabbinic dynasty and Kurt’s intellectual match. In addition to distinguishing herself in a highly successful legal career and to raising a wonderful family with Kurt, Rhoda became Kurt’s strategist, coach, cheerleader, promoter, and advocate. Her wisdom, guidance, support, and encouragement to embrace opportunities and challenges—to stretch beyond his comfort zone—were instrumental to the success of Kurt’s academic career, and their propitious partnership endured for six decades, until she passed away in 2015.

Shortly after his 1956 return to the MGH, Kurt succeeded in his first NIH grant application, the foundation for a half-century record of continuous NIH funding, as well as the prelude to his durable service on NIH study sections and councils. A year later, in 1957, when Kurt was 31 years old and only 7 years out of medical school, Walter Bauer, MGH chief of medicine, offered Kurt the opportunity to fill a vacancy in the leadership of either the Endocrine Unit or Gastrointestinal Unit. Even though endocrinology, by then a well-established scientific discipline, aligned more closely with his biochemistry background, Kurt felt that he could make a larger contribution to and impact upon gastroenterology, a field that, at the time, was based on descriptive observation, rather than on rigorous scientific investigation (i.e., that gastroenterology was more of a new scientific frontier). He dismissed the obvious, straight-forward route for the more challenging, uncharted path, and the rest is history. In a word, Kurt Isselbacher brought biochemistry to the study of gastroenterology and became the principal architect of its transformation into a field anchored in scientific investigation and the scientific method.

As would become his signature again and again, he never shied away from, but rather embraced, challenge and reinvention. In addition to retooling as a de novo gastroenterologist to assume leadership of a GI Unit, Kurt pursued new investigative directions in 1970, when he embarked on a sabbatical to study membrane transport in normal and neoplastic cells, and in 1984, when he took a second sabbatical to study molecular biology. During his first sabbatical with M.G.P. Stoker at the Imperial Cancer Research Fund Laboratories in London (as an American Cancer Society Eleanor Roosevelt Fellow), his studies on the difference in membrane transport between normal and malignant cells revealed increased sugar and amino acid transport in tumor cells, resulting from an increase in the number of cell-surface carrier proteins. Not only did this experience in cell-membrane biology change the trajectory of his research back in Boston for the next 15 years, but this new focus also impressed upon him the importance of cell-surface protein expression in cancer and ignited his interest in the pathogenesis of cancer. Emanating from his interest in malignantly transformed cells, he challenged himself again for a second sabbatical experience, this time as a Fogarty Scholar-in-Residence at the NIH, during which he recast himself as a molecular biologist in the laboratory of his former student George Khoury. His studies of how tumor cells rely on surface membrane changes to evade immune recognition, targeting, and destruction motivated him to tackle in a new direction, by applying the tools of molecular biology to the study of cancer.

Not long thereafter, in 1987, after three decades of acclaimed success as leader of the MGH GI Unit, he accepted the call to assume the new position of director of the MGH Cancer Center. For his highly effective response to this challenge, Kurt was remembered, in the announcement to the MGH community of his passing, as “a changemaker who understood what was needed to achieve a vision and then could effectively navigate the course to get there, no matter how complex, no matter how many obstacles.”
In this vein, the success and national prominence of the MGH Cancer Center was attributed to Kurt’s visionary leadership. “He grew the center from the ground up—successfully advocating for new, modern research facilities, raising funds and recruiting the most talented and highly motivated clinicians and scientists—and built it into one of the premier cancer research institutes in the nation.” Once again, he listened to the siren song of challenge and change, just as he had initially to head the GI Unit, to transform cancer research and care at the MGH—both leadership positions that he took on without formal training in either discipline. Inventing and reinventing himself, intellectually restless, he was always looking for innovative approaches to unsolved clinical and research problems.

His prodigious scientific achievements were captured in a research bibliography of more than 400 publications. As his colleague and friend Eugene Braunwald remarked, Kurt was imaginative for five decades in combining the tools of biochemistry, cell biology, immunology, and molecular biology to make observations of both fundamental and clinical importance. His research focus included the elucidation of biochemical, metabolic, cellular, and immunologic derangements underlying a broad range of gastrointestinal, hepatic, and malignant disorders. Hepatologists remember him for his studies of the enzymatic mechanism of glucuronide conjugation by the liver, hepatic metabolism of corticosteroids and alcohol, the metabolic defects in alcohol-induced fatty liver, bilirubin metabolic pathways, benign intrahepatic cholestasis, the prehepatic-intrahepatic-posthepatic divide among causes of postoperative jaundice, and the extrahepatic manifestations of acute and chronic viral hepatitis, to name several of the most impactful.

His stature as a distinguished leader in American medicine was reflected as well by his three-decade (1967-1998) tenure as an editor of the 6th through 14th editions (editor-in-chief of the 9th and 13th editions) of the leading medicine textbook, *Harrison’s Principles of Internal Medicine*. Similarly, he exercised the same keen skills and judgment on the editorial boards of such high-impact publications as the *Journal of Clinical Investigation* (1962-1972) and *Gastroenterology* (1963-1968).

The impact of his investigative accomplishments was amplified further by the cadre of gastrointestinal and cancer-center physicians and scientists he led. Over his 31 years (1957-1987) as chief of GI and 16 years (1987-2003) as director of the Cancer Center, Kurt trained 115 clinical and research fellows in gastroenterology and approximately another 35 in oncology (almost 150 in total). The record of his trainees is remarkable for their achievements and leadership positions as clinicians, investigators, and educators. Two-thirds of Kurt’s trainees became full-time academic faculty; an extraordinary number became full professors, department chairs, division chiefs, center directors, research laboratory directors, medical school deans, university presidents, leading clinicians, and one became an academic health center president. For a snapshot of Kurt’s impact, over the last 60 years, at least 31 (27%) of his 115 GI trainees served as chiefs of GI divisions. During the first two decades of the 21st century alone, his trainees were GI division chiefs at Beth Israel Deaconess Medical Center, Boston Children’s Hospital, Brown, Columbia, Cornell, Massachusetts General Hospital, Mount Sinai, and the University of Pennsylvania. Five of his former trainees have served as presidents of the American Gastroenterological Association (AGA), three have served as presidents of the AASLD, not to mention the many others who held leadership roles in other important academic professional societies.

Arguably, Kurt selected the most talented future stars who would have succeeded in any environment and under anyone’s tutelage. Probably not! To thrive, talent requires nurturing. Kurt took these promising embryonic leaders, and as their mentor, molded them through periodic course correction, provided motivational encouragement, promoted them to positions of leadership, held them to high expectations, advocated for them, and served as a role model for their professional ideals and activities and even their personal comportment.

Kurt’s achievements and accomplishments brought him academic honors and national recognition. He was promoted to professor of medicine at Harvard in 1966 (at the age of 41—atypically young for HMS promotion), served as chairman of the HMS Executive Committee of the Departments of Medicine (“chief of the chiefs” at Beth Israel, Brigham, and MGH) for 30 years (1968-1997), and was honored with an endowed chair in 1972 as the HMS Mallinckrodt Professor of Medicine. In his honor, his name adorns
an HMS humanitarian award, two HMS endowed chairs, an MGH GI library/conference room, and an MGH Cancer Center auditorium. He was president of the AASLD (1967), the AGA (1974), and the Association of American Physicians [AAP] (1977). From the AGA, he received both the Distinguished Achievement Award (1983) and its highest honor, the Friedenwald Medal (1985); from the AAP, he received its highest honor, the Kober Medal (2001). Among his many other honors, he was elected to prestigious societies and positions as a fellow of the American Academy of Arts and Sciences, vice president of the American Society for Clinical Investigation, and as a member of both the National Academy of Sciences and the Institute of Medicine (now called the National Academy of Medicine).

In addition to his greatness as a physician leader, perhaps more so, Kurt was a loving and devoted husband and father, raising his family in Newton, Massachusetts and their summer retreat in Woods Hole. His dedication to the lab and the GI Unit might have distracted a lesser man from attention to his family, but not Kurt. He lavished undivided care, warmth, compassion, and love on his wonderful family, and all of his trainees and colleagues always appreciated how important his family was to him and how his loving family sustained him.

As his son, Eric, observed during Kurt’s eulogy, the family “marveled at the near perfect symmetry between the qualities he displayed as a physician and scientist and those he displayed as a parent and grandparent.” In a sense, Kurt had two families, one personal and the other professional, and he skimped on neither. His “roles as physician and family man were inseparably intertwined. His keen interest and dedication as a mentor, his intensive listening, his gentle advising, and his compassionate care—were as evident at home as they were at work. When he was talking with you, it was as if you were the only one in the room ... the only one who mattered to him.”

Indeed, to those of us in the GI Unit, Kurt was a father figure and a role model, with high standards and expectations not only for clinical and scientific excellence, but also for character and integrity—the humanistic qualities befitting members of his family. Rhoda and Kurt treated us all as family and helped us navigate the ups and downs, the celebrations and challenges, of our personal lives and our families. While Kurt’s academic legacy is extraordinary, so, too, is his legacy of devoted children (Lisa [who predeceased him], Kate, Jody, and Eric) and their spouses, his eight grandchildren, and his two great granddaughters. So many of the Isselbacher offspring bear the expression of Kurt’s countenance; the resemblances are striking. He lives on in their hearts, faces, notable career accomplishments, and noble bearing!

Intellectually curious, never satisfied with simplistic explanations, Kurt approached science and medicine with methodical rigor. While his standards were high, and while he could be as tough and demanding as needed, he was the epitome of compassion and empathy in his interactions with his adoring patients. As wrapped up as any of us were in the laboratory, we learned early, from Kurt’s example, that we dropped everything when our patients needed us. We learned from the example he set in his humanism; as much as we revere him for his intellect, stature, pursuit of excellence, and accomplishments, we remember Kurt for inspiring us with his decency, humanity, humor, guidance, support, positivity, humility, and kindness. He taught us important lessons—large and small, profound and prosaic—and set a very high standard to which we all have aspired but never quite attained. Those who knew him appreciated and came to expect the parsimony and precision of his words. After he listened and questioned socratically, after he weighed carefully both sides of an argument, an experimental finding, or a clinical conundrum, all he needed to convey his thinking was a shrug, a few well-chosen phrases, or a subtle change in facial expression.

What many may not know, Kurt also extended his unique kind of nurturing, devotion, and friendship to physicians and scientists from institutions beyond his own. As Eugene Braunwald articulated, Kurt shared his “substantial experience and eminent good sense” with anyone who wished to draw on his “wisdom and enormous good judgement”—an unheralded generosity of time and spirit not captured in his CV or in his many award citations. With sincerity and genuineness, Kurt intuited and encouraged what others aspired to and dreamed of. He embodied kindness, generosity, trust, and respect; he lacked pomposity; he maintained a keen ability to identify young people and to invest in them; and he took joy in the success of others. That is Kurt’s immortality—well beyond his scientific advances, his professional positions, his honors—the creation of a like spirit that endures in his trainees, mentees, and advisees.
In his presentation of the AAP Kober Medal to Kurt in 2001, Eugene Braunwald concluded that Kurt Isselbacher "exemplifies the highest values of academic medicine. With contributions as a caring, empathetic clinician; as a devoted, inspiring teacher; as a creative and productive scientist; and as a talented, rigorous editor, Kurt has advanced the care of patients with gastrointestinal disorders and cancer while educating generations of gastroenterologists and other physicians."

The MGH death announcement concluded with this lyrical paragraph: "The legacy Kurt Isselbacher leaves at the MGH reaches beyond the Cancer Center he helped create, beyond the GI Division he led and shaped, beyond the many papers and books he authored and edited. We remember Kurt for the great kindness, compassion and respect he had for all those around him, whether patients, families, colleagues, staff or students. And we will remember his enthusiasm, his spirit, and that sparkle in his eye."

Kurt concluded the prelude to his memoir with the following: "At the end, I hope it can be said that I succeeded, to some extent, in justifying my survival and existence." Succeed he did! He lived a life as rich in what it represented as in what he accomplished.

Acknowledgment: In this obituary, I relied heavily on eulogies spoken at Kurt’s funeral by his son, Eric Isselbacher, and his successor as chief of the MGH GI Unit, Daniel Podolsky; Kurt’s own memoir, Don’t Call Me Cookie; award presentations to Kurt by Norton Greenberger (Friedenwald Medal presentation) and Eugene Braunwald (Kober Medal presentation); Dan Podolsky’s reflections about mentorship on the occasion of Kurt’s 90th birthday; tributes and obituaries by others; and personal remembrances from his trainees and colleagues.

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