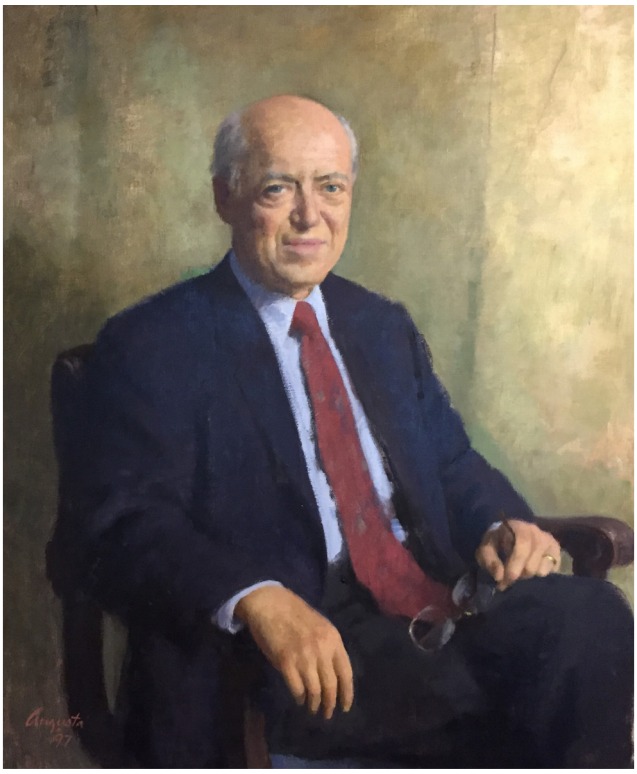
THE FACULTY OF MEDICINE
Harvard University

Kurt J. Isselbacher



A portrait that hangs in the Kurt J. Isselbacher Library, Massachusetts General Hospital

On July 18, 2019, Kurt J. Isselbacher, M.D. passed away at the age of 93, the final curtain after his six-decade career as a renowned physician-scientist and the premier academic gastroenterologist/hepatologist of his generation. The world is a poorer place without him. 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. While he earned many plaudits and tributes and led many distinguished academic societies, we honor his memory as the HMS Mallinckrodt Professor of Medicine and mourn the loss of a great man.

How do you capture the essence of the person whose imprint on a field—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 age 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 maternal 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 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 his life's

In tribute to their dedicated efforts to science and medicine, deceased members of the Harvard Faculty of Medicine (those at the rank of full or emeritus professor) receive a review of their life and contributions with a complete reflection, ***a Memorial Minute****.*

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 genuine optimism.

Excelling in his studies, Kurt graduated with honors from a wartime-accelerated, two-year A.B. program at Harvard College (1946), received his M.D. 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 relationship between asbestos and mesothelioma as well as the constellation that would come to be called Bartter's syndrome. Between 1953 and 1956, Kurt decamped to the 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, his good fortune, while at the NIH, in meeting and marrying Rhoda Solin in 1955 was an even more formative event. Rhoda was 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 return to the MGH in 1956, 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 seven years out of medical school, Walter Bauer, legendary MGH chief of medicine, offered Kurt the opportunity to fill a vacancy in the leadership of either the Endocrine Unit or Gastrointestinal Unit. Although endocrinology, by then a well-established scientific discipline, aligned more closely with his biochemistry background, Kurt felt that he could made a larger contribution to and impact upon gastroenterology, i.e., that gastroenterology was more of an uncharted scientific frontier. Still, Kurt expressed the concern that he had not trained formally in gastroenterology, to which Bauer replied, "Don't worry. People aren't born gastroenterologists; you'll just learn to become one." Thus, Kurt dismissed the obvious, straightforward 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 a 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 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 of 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. This experience in cell-membrane biology not only changed the trajectory of his research for the next 15 years, but also ignited his interest in the pathogenesis of cancer as a focus of research in the ensuing

years. 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, 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 tack in a new direction, 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 by MGH leadership to assume the position of director of the new 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." The success and now national prominence of the MGH Cancer Center reflect Kurt's visionary leadership. "He grew the center from the ground up—successfully advocating for new, modern research facilities, raising funds and recruiting 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 heretofore unsolved clinical and research problems.

His prodigious scientific achievements were captured in more than 400 research publications. As Eugene Braunwald remarked in introducing Kurt for one of his many awards, Kurt was imaginative in combining the tools of biochemistry, cell biology, immunology, and molecular biology for almost five decades to make observations of both fundamental and clinical importance.

In his research, Kurt incorporated cutting-edge advances in these basic sciences to focus on elucidating the derangements underlying a broad range of gastrointestinal, hepatic, and malignant disorders. In addition to his discovery of the enzymatic defect underlying galactosemia, gastroenterologists remember him for his studies of fat and sugar absorption by the intestine, the metabolic abnormalities of abetalipoproteinemia, elucidation of the genetic disorder isovaleric acidemia (discovered after encountering a 10-year-old boy who emanated an odor described as "smelly feet"), the role of hypoglycin A in unripe ackee fruit as the cause of Jamaica vomiting sickness, and the link between high triglycerides and acute pancreatitis. 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. Oncologists remember him for his basic studies of increased sugar intake by cancer cells, the basis for the development of positron emission tomography; foundational work on the way cancer cell surface changes evade immune recognition and containment, now timely in the context of checkpoint inhibitor therapies; and BRCA1 gene mutations associated with the risk of breast cancer, to name some 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 the 14th editions (editor-in-chief of the 9th an 13th editions) of one of the leading textbooks, *Harrison's Principles of Internal Medicine*. He exercised the same keen skills and judgement 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 by the cadre of gastrointestinal and cancer-center physicians and scientists he trained and 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. Over the last 60 years, at least 31 (27%) of his 115 GI trainees have 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 University, Brown, Columbia, Cornell, Massachusetts General Hospital, the University of Massachusetts, 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 American Association for the Study of Liver Diseases (AASLD), two have served as Editors-in-Chief of *Gastroenterology*, 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 for 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 leading gastrointestinal societies, the AASLD in 1967 and the AGA in 1974 as well as the most prestigious society in academic medicine, the Association of American Physicians (AAP) in 1977. From the AGA, he received both the Distinguished Achievement Award (1983) and its highest honor, the Friedenwald Medal (1985), and, from the AAP, he received its highest honor, the Kober Medal (2001). Among his many other honors, he was elected 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 even 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 person 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 dignified bearing!

Curiosity-driven, never satisfied with simplistic explanations, Kurt approached science and medicine with methodical rigor. While his standards were high, and he could be as tough and demanding as needed, he was the epitome of compassion and empathy in his interactions with his patients, many of whom, in turn, adored him. As wrapped up as many 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, not least, the importance and power of touch in conveying a bond as healer. Those who knew him appreciated and came to expect the parsimony and precision of his words. After he listened and questioned in a socratic fashion, 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.

So far, we have captured many of Kurt's multiple and formidable characteristics and accomplishments. Another facet of the Kurt Isselbacher gemstone was his pride in and loyalty to Harvard and HMS. Of course, he was dedicated fiercely to the MGH—his "state" in the great "nation" of Harvard University. When he wore his HMS hat, however, the perspective of the university dominated. In countless meetings of the HMS Department of Medicine Executive Committee, he set the academic bar very high for all ranks, irrespective of hospital. In his quiet way, he treated all the medicine department chiefs at the MGH, Brigham, and Beth Israel with the same level of toughness and, expecting the most from them, elevated the department to the highest academic standards.

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 expressive 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. We celebrate his legacy.

Respectfully submitted,
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Eugene Braunwald, M.D.
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Acknowledgments: A version of this Memorial Minute was published as an obituary by one of us [Dienstag JL. Kurt J. Isselbacher, M.D. Remembered (1925-2019). Hepatology 2020;71:1135-9] and is reproduced with permission. In addition, this Memorial Minute contains elements first captured in

an obituary authored by two of us [Friedman LS, Podolsky DK. In Memoriam: Kurt J. Isselbacher, MD (1925-2019). Gastroenterology 2019;157:1173-4]. Several quotations attributed to one of us are derived from Dr. Isselbacher's introduction as he received the Kober Medal [Braunwald E. Presentation of the Kober Medal of the Association of American Physicians to Kurt J. Isselbacher, M.D. J Clin Invest 2001;108:S15-9].