BIOGRAPHICAL MEMOIRS

Kurt Julius Isselbacher

September 12, 1925–July 18, 2019
Elected to the NAS, 1973

A Biographical Memoir by Daniel K. Podolsky

This past summer marked the fifth anniversary since the passing of renowned physician and researcher Kurt Julius Isselbacher. He was a towering figure in medicine whose long shadow continues to be cast through his seminal contributions and the legions of former fellows who project this legacy through their achievements. Many tributes were published in the immediate aftermath of his death, but this one is especially notable because KJI—as he was referred to by generations of trainees who revered him—had the distinction of being the first gastroenterologist elected to the National Academy of Sciences. As someone who was fortunate enough to know him for more than fifty years and having had the privilege of being able to call myself over the course of time, his student, trainee, colleague, physician, and, most meaningfully, friend, it is my privilege to reflect on his many accomplishments and the impact of his work as an investigator, clinician, and mentor.

Kurt Julius Isselbacher was born on September 12, 1925, in Wirges, Germany, the only child of Flori and Albert, who were from the village of Isselbach in Westphalia. The family fled the Nazi regime in 1936, when Kurt was eleven. Many members of the extended family ultimately perished at the hands of the Nazis, and Kurt was forever grateful for the opportunities that he and his family found upon arriving in the United States. The family began life anew in Portsmouth, New Hampshire, where his father ultimately owned a haberdashery, as he had in his native Germany, and Kurt attended public schools. Notwithstanding his need to learn English, his natural intellect soon placed him at the top of many of his classes. He enrolled in Harvard College in 1944, and with the accelerated schedule typical of many colleges during World War II, completed his degree in 1946. Notably, in 1945, he and his parents became naturalized U.S. citizens.

Kurt subsequently matriculated in Harvard Medical School and received his medical degree *cum laude* in 1950. After completing his medical studies, he pursued residency training in internal medicine at Massachusetts General Hospital (MGH). This was the beginning of an association with MGH that continued for sixty-eight years, interrupted only by three years after his residency spent at the National Institutes of Health (NIH) as a clinical investigator.

Kurt returned to MGH from NIH at the behest of Walter Bauer, the charismatic chair of the Department of Medicine who was transforming the organization of the department to the construct familiar today, comprising subspecialty divisions that brought together both clinical expertise and research focus. Bauer clearly had both an eye for talent and a willingness to break conventions. Young Isselbacher was barely out of residency and his subsequent research fellowship when Bauer approached him to suggest that he succeed the long-serving clinical chief Chester Jones as head of the MGH GI Unit—despite the fact that until then, Kurt had no special training in gastroenterology!

Bauer was prescient. Kurt went on to serve as GI Unit Chief for thirty-two years and left an indelible imprint on the field of gastroenterology through the discoveries detailed below and through the clinical and research fellows who trained under him.

Early Research and Studies of Inherited Disorders of Metabolism

Following an initial high school experience in science that sparked his interest and research experience in both college and medical school, Kurt began in-depth research training at NIH following the completion of his residency training. While at the NIH, Isselbacher made his first major research contribution, which was delineation of key facets of corticosteroid metabolism in the liver. This included demonstration of the formation of steroid glucuronides in the liver, and he continued this line of research when he returned to the MGH, where he purified glucuronyltransferase, the enzyme responsible for this transformation.

In the course of his training at the NIH under the tutelage of Herman Kalckar and working with E. P. Anderson, he demonstrated that the hereditary disease galactosemia was caused by the absence of the enzyme galactose-one-phosphate transferase. This was the first time someone demonstrated that a specific enzyme defect could cause a hereditary disease. The discovery made it possible to devise a neonatal test, which soon became commonly used for diagnosis at birth and enabled parents to institute appropriate dietary modifications to prevent the devastating clinical manifestations of this disorder.

Studies of galactosemia set a precedent for the study of other inherited metabolic disorders. Kurt and his colleagues, most notably Kay Tanaka, were the first to describe isovaleric acidemia, an hereditary congenital disorder of amino acid and lipid metabolism. They found that the distinctive odor associated with this rare disorder results from an accumulation of isovaleric acid, a metabolite of leucine. Isselbacher and Tanaka demonstrated that the accumulation was the result of a deficiency in the enzyme that normally converts isovaleric acid to beta-methyl-crotonic acid. His laboratory went on to elucidate other genetic defects in short-chain fatty acid metabolism, all of which manifest in depressed central nervous system function. An interesting outgrowth of this interest in inherited disorders of metabolism were studies that demonstrated that Jamaican vomiting sickness, an illness caused by eating unripe ackee fruit, resulted from disruption of branched chain amino acid metabolism by the compound hypoglycin found within the unripe fruit. Later, in the context of his studies of many and varied inherited disorders of metabolism, the Isselbacher laboratory demonstrated that abetalipoproteinemia, an uncommon condition that results in the accumulation of lipids in intestinal epithelial cells, was caused by the absence of apoprotein B.

Studies of Nutrient Transport and Absorption

Another early and enduring focus of Isselbacher's research was the study of mechanisms of absorption and transport of lipids and other nutrients across the intestinal epithelium. His group demonstrated that fatty acids transported across the intestinal mucosa were first activated and subsequently esterified and converted to lipoprotein for exit from the cell. His studies were the first to demonstrate the mechanisms of absorption of medium chain triglycerides (MCT), which differed markedly from the processes regulating conventional lipids comprised of long chain fatty acids. These observations formed the basis for the therapeutic use of MCT in disease states where transport of lipids was impeded, typically owing to failure in esterification mechanisms or lymphatic obstruction as in intestinal lymphangiectasia. Studies on the basic mechanisms of sugar amino acid transport and on the various digestive enzymes found on the intestinal epithelial microvillus, including disaccharidases and peptidases, led to an understanding of rare disorders resulting from deficiencies in these various enzymes.

In related observations, he paved the way for subsequent early advances in mucosal immunology by observing that macromolecules, such as ribonuclease and albumin and horseradish peroxidase, can be absorbed intact in the adult intestine—an unanticipated finding. This observation was the first insight into the possibility of antigen absorption through the gut as a basis for systemic hypersensitization.

Later studies built on these findings. Working closely with his former trainee and colleague Dr. W. Allan Walker, he demonstrated that the phenomenon of immune exclusion at the GI tract mucosal surface was attributable to secretory IgA present on the surface coat of intestinal microvilli, thereby protecting the intestine from attachment and potentially injurious uptake by agents such as bacterial toxins. Deficiencies in these mechanisms conversely were found to play a role in systemic hypersensitization.

Studies of Liver Disease

Isselbacher's span of research also included the study of liver function and the pathophysiology of liver disease. Perhaps most notable in this arena was delineation of the mechanism of alcohol-induced fatty liver, with his laboratory defining alcohol-induced effects on hepatic lipid metabolism and also the basis for alcohol-induced hypertriglyceridemia. Working with David Shafritz on hepatic protein synthesis, he demonstrated that synthesis of proteins produced for export, such as albumin, are different from those synthesized for proteins destined for intracellular use, such as ferritin.

These studies were accompanied by a broad interest in the pathogenesis of many hepatic disorders. These included demonstration of the mechanistic basis for the extrahepatic manifestations found in acute and chronic viral hepatitis, that is, immune complexes that become deposited in various tissues, including the kidney and joints. As another example in which he seized the opportunity to pivot from basic observation to clinical applications, he worked with Elliot Alpert to develop an improved assay for alpha fetoprotein as a means to diagnose hepatocellular carcinoma after devising improved methods for purification and characterization of the protein tumor marker.

Isselbacher's contributions included the development of many improved methodologies that became widely used. In addition to methods for purification of fetoprotein, he and his collaborators devised techniques for selective isolation of basolateral and apical membranes from intestinal epithelial cells. These substantially accelerated progress on the study of basic mechanisms of absorption. Working with Ulrich Hopfer, he further developed methods to prepare membrane vesicles that could be used to study sugar and amino acid transport in vitro. Similarly, he developed methods to isolate microsomes from hepatocytes that facilitated the study of hepatic metabolism.

Studies of Gastrointestinal Malignancy

Beginning in the 1970s, Kurt increasingly turned to the challenge of gastrointestinal malignancy as a dominant focus of his research. Following a sabbatical at the Imperial Cancer Research Fund laboratory in the early 1970s, he carried out detailed studies of the nutrient transport properties of human GI cancer cell lines, cell culture being a relatively new experimental tool at the time. After an initial finding that sugar and amino acid transport was increased in transformed cells, he demonstrated that this resulted from an increased number of carrier proteins in the surface membrane of the cancer cells. In his pursuit of studies on gastrointestinal malignancy, he and Andrea Quaroni established the first non-transformed intestinal epithelial cell lines, which quickly became widely used in laboratories studying epithelial biology worldwide.

Scholarship

Isselbacher's research findings served as the basis for more than 400 original publications, many in leading medical and scientific journals. Although he took pride in each of those, his years as editor and contributor to *Harrison's Principles of Internal Medicine* (*PIM*) provided enormous and unique satisfaction. His involvement spanned nine editions, with service as editor-in-chief for editions nine and thirteen. The quality of the textbook mirrored some of the qualities that Kurt epitomized: attention to detail and scholarly rigor as well as near encyclopedic knowledge of the field. Few things brought anything close to the intellectual satisfaction he derived from being part of a remarkable group of editor colleagues, each a leading light of academic medicine during those years. The standard of scholarship that he held himself to can also be found in each of the chapters he authored or edited over many editions. Having had the privilege myself of co-authoring some of those chapters (and many other publications), the experience was always a tutorial in excellence. He was an exemplar of clarity in writing, and no co-author of Kurt's would ever again take a comma for granted or fail to stop and pause to think whether "the" is actually needed. Through the many editions of *PIM* in which he participated, Kurt's impact extended to physicians around the world, who came to trust *Harrison's* as a gold standard source of medical knowledge.

Mentorship

It might seem a cliché, but for Kurt it was a lived experience that the MGH GI Unit and all of those that came to work with him were a second family, and he served as a mentor and colleague in that spirit. Captured in sheer numbers, his record is striking: 115 clinical-research fellows in gastroenterology and another forty in oncology. More than thirty of them went on to become chiefs of divisions of GI units in many of the most prominent medical schools and academic medical centers. Six of his former trainees eventually succeeded him as president of the American Gastroenterological Association. Many trainees have assumed leadership positions well beyond gastroenterology, whether in academia or industry. Others provide expert care as academic or community clinicians.

Kurt took true satisfaction in the accomplishments of his trainees. As I noted on the occasion of his ninetieth birthday, his impact as a mentor was distinct in a number of ways. First, he guided by example—both in rigor as an investigator and in his empathy and expertise as a physician. Second, his impact as a mentor was integrally linked to his temperament and manner—the latter embodied in his ability to convey interest and personal bond in a mere gesture, sometimes just a shrug of his shoulders. Third, he set high expectations beginning

with himself, and one did not have to be a member of the MGH GI unit or cancer center very long to see the power of high expectations. One learned the distinction between very good and excellent. Finally, despite ostensible differences in status, Kurt treated those with whom he worked, even the most junior colleagues, with respect, a posture that was almost disorienting when I first encountered Kurt as an undergraduate summer student after he had recently been elected to the National Academy of Sciences. This, as much as anything, was a fundamental reason that Kurt engendered the bond of affection that endured for those who trained with him.

Clinician

Although the majority of Kurt's time and attention was devoted to his academic work, throughout the years patients and colleagues sought him out for his clinical expertise. While many were motivated by his prominence as an authority in the field, many others were motivated by word of mouth from prior patients and the praises that they sang for him as a caring physician. For those who had the privilege of caring for patients alongside Kurt, it was a memorable example for at least two reasons. First, Kurt consistently tried to truly understand the nature of the illness rather than focus simply on the pragmatic task of making a diagnosis. Although a minimal elevation of a liver function test result might seem like a trivial finding, Kurt would ponder how it could be related to the patient's condition or a specific disease when the diagnosis was clear. This discipline of mind was an ingrained habit. It often led to a more nuanced understanding of the disease and, importantly, informed a more rational approach to treatment. Second, even though Kurt was rigorous and analytical in making a clinical assessment, he was a truly empathic physician, and I have no doubt that was at the root of the affection that so many of his patients held for him. In accompanying him on rounds, I soon noted that he never left a patient's room without having touched the patient, a laying on of hands.

Academic Leadership

As noted already, when Kurt was appointed chief of GI at MGH in 1957, he had no formal training in gastroenterology. Kurt enjoyed recounting on many occasions that he was reassured by Bauer: "People aren't born gastroenterologists, you will learn to become one." Kurt proved him right and in relatively short order established himself as a next-generation leader in the field. His own evolving research program, described above, was a cornerstone in shaping a revitalized GI unit built on an embrace of newer sciences. It became a leading unit and an example for other institutions nationally. Most significantly, that transformation attracted generations of talented trainees who were the lifeblood that sustained the enduring preeminence of the unit. Beyond his own discoveries, he had a transformative impact on the field by bringing the techniques of cell biology, biochemistry, and molecular biology to bear on both fundamental questions of GI function and disease pathogenesis.

After thirty-one years of leading the GI unit, Kurt was asked to take on a new and important leadership assignment at the MGH: establishing a cancer center. Once again, Kurt proved his ability to spot, attract, and develop talent, and the Mass General Cancer Center has emerged as a national leader in cancer research. Locally, beyond his leadership roles within the MGH, Kurt served for many years as the chair of the executive committee of the Departments of Medicine of hospitals affiliated with the Harvard Medical School as well as in many other ways as a widely respected member of the faculty for decades.

On a national and international level, Kurt provided creative leadership for several academic societies. He served as president of the American Association for the Study of Liver Diseases in 1967 and the American Gastroenterological Association in 1974, the preeminent academic organizations in the field worldwide. In 1977, he served as president of the American Association of Physicians, arguably the most prestigious of all academic medical societies in the United States. He had formerly also served as vice president of the American Society of Clinical Investigation.

Accolades

Not surprisingly, given his accomplishments, Kurt was the recipient of many honors over the course of his career. In addition to his leadership of professional societies referenced above, in 1983 he received the Distinguished Achievement Award in Basic Science and in 1985 the Julius Friedenwald Medal from the American Gastroenterological Association, the highest honors of that society. In 2001, he received the George M. Kober Medal from the Association of American Physicians, that society's highest honor. He was an elected a fellow of the American Academy of Arts and Sciences, and in addition to the National Academy of Sciences, he was also an elected member of the National Academy of Medicine (formerly the Institute of Medicine).

Family and Friends

Nothing superseded Kurt's love and commitment to his family. His wife, Rhoda (née Solin), was truly the love of his life from the time he first met her when she was a second-year law student at the University of Pennsylvania. They married within a few short months after a whirlwind courtship; Rhoda subsequently transferred to Harvard Law School as a prelude to a successful career as an attorney, and they began life together in Boston. Kurt remained devoted to

her throughout their long marriage until her passing in 2015. Throughout those years, Rhoda was Kurt's greatest admirer, staunchest advocate, and most trusted adviser. Together they raised four children. Eldest daughter Lisa passed away at an early age in 1999 following a long battle with cancer. Son Eric became a cardiologist and associate professor of medicine at MGH and Harvard Medical School, daughter Karen (Katie) became a general internist, and daughter Jody became a lawyer. All live in Newton, Massachusetts, where they were born and raised. All told, at the time of his passing, Kurt had eight grandchildren and two great granddaughters.

Throughout his life, Kurt had a talent for friendship. Beyond his family, he left behind legions of friends who mourned his passing, with many dating back to Kurt's days as an undergraduate, but also from every stage of his life that ensued. Among those were many, like myself, who first encountered Kurt as a mentor but in the course of time became part of what was for Kurt a second family of colleagues and trainees.

Concluding Reflections

Kurt Isselbacher had both the intellect and the heart that ultimately made it possible for him to make many important contributions that benefit patients worldwide and inspire future generations. He enriched the lives of all who had the privilege of knowing him, whether it was through the example he set or the integrity and sincerity that were an unwavering hallmark. No doubt those early years in which his family fled their native Germany sparked in Kurt a determination and sense of obligation to lead a life with meaningful contributions, deserving of that good fortune. Although five years have passed, his legacy remains vibrant in his children and their families, in his many contributions and research discoveries, and in the legions of trainees, friends, and patients who were the better for having known him.

Note

Special thanks to the American Gastroenterological Association for permission to use the image of Kurt J. Isselbacher. Much of the information on Kurt in this memoir comes from the author's 2015 essay "Reflections on Mentorship on the Occasion of Dr Kurt J. Isselbacher's 90th Birthday" for *Gastroenterology* (149:268–269) and Lawrence S. Friedman's and Daniel K. Podolsky's 2019 tribute to him: "Kurt J. Isselbacher (1925–2019)" in *Gastroenterology* (157:1173–1174).

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