Maria Gordon Buse, MD: A Family Affair Through Six Decades of Diabetes Discovery

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Maria Gordon Buse, MD, is a product of wartime Europe. She completed her professional education in four languages on three continents and continues a nearly 60-year career as an investigator, educator, and practicing endocrinologist. This brief reprisal is written collaboratively by her biological offspring and intellectual progeny, an appropriate reflection of a career where family and work were joyfully intertwined in an irresolvable way.

THE EARLY YEARS

Maria Gordon Buse was born Maria Felice Gordon in Budapest, Hungary. Her mother, Elizabeth Szana, was the "great beauty" of her social circle, and her father, Geza, was an earnest accountant who tried his hand at several failed entrepreneurial activities before buying a café on the Danube near the symphony hall. In that venture, Elizabeth's charms and Geza's practical business acumen resulted in a successful enterprise that was a gathering place for students, artists, and the middle class in Budapest. Maria was raised speaking German in the home and only learned Hungarian when she went to school. She mastered French as a third language in middle school. Maria loved poetry, literature, theater, art, music, walking in the woods during trips to the nearby mountains, and ice skating. She aspired to become a poet and a journalist. She was 16 in 1943 when German troops occupied Budapest. Through the intercession of friends, Maria and her mother took refuge in a cloister, and her father, in a monastery. Her mother was fearless about going out into the city through bombings and gunfire, leveraging her many social connections to find food and supplies. Maria never takes for granted how lucky she and her family were to survive. As the Allies approached to "liberate" Hungary, she recalls laughing at the sky, seeing the showering bombs as symbolic of their impending freedom and the justice that the Axis powers would face. She welcomed her Russian liberators in that spirit, only to discover that they were as cruel as the Nazis. She was briefly interred in a labor camp. Her childhood left her with an absolute intolerance of any hint of fascism or prejudice and a drive to take advantage of any opportunity for enjoyment of the simple pleasures that she had been exposed to as a child—learning, good food, beauty in all its forms, and nature. Maria says, "I really wanted to be a writer. But my mother and everyone else explained to me that I would never make a living. And I had always been interested in science and medicine. I sort of thought it might be fun to be a doctor." Fascination and fun with science has been the hallmark of her career.

Maria Gordon Buse, MD, in front of a rack of Langendorff baths used to perfuse isolated beating rat hearts circa 1972. These studies resulted in important findings about cardiac fuel metabolism and changes induced by epinephrine, glucagon, and nutritional states with continuing relevance to diabetes treatments today (courtesy of the Waring Historical Library, MUSC, Charleston, SC).

At the war's end in 1945, her parents divorced. When her mother remarried a childhood sweetheart, Bartholomew Richter, she gained a stepbrother, Paul, who would become an oncologist in Atlanta.

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Maria started medical school at the Pázmány Péter University School of Medicine in Budapest. However, as it was essentially destroyed, she left to continue her studies at the University of Basel from 1946 to 1948. As a foreigner in Switzerland, she knew that she could not be licensed to practice medicine there and immigrated to Argentina with the assistance of an uncle. She had to learn Spanish adequately to pass the exams required to enter the University of Buenos Aires as an advanced medical student without losing the 2 years of credit she had completed in Europe. Her mother, stepfather, and Paul joined her shortly afterward. She received her MD in 1952. After housestaff training in the Hospital Rivadavia, she was able to do research in Nobel Laureate in Physiology Bernardo Houssay's institute with Drs. Houssay, Eduardo Braun-Menéndez, and Carlos Rapela. Her work on the seasonal variation in catecholamine production in the toad resulted in the faculty prize for best thesis in 1956. When asked "Why toads?" she replied, "Toads are cheap. You could catch them in the courtyards of his institute." Frugality and opportunism in research would become a recurring theme in her career.

Top: Maria Gordon Buse, MD, and John F. Buse Jr., MD, circa 1970, standing in front of the Beckman model 121 amino acid analyzer that was almost like their fourth child, only more expensive, fussy, and ill-behaved. Bottom: Maria Gordon Buse, MD, circa 2003 (both courtesy of the Waring Historical Library, MUSC, Charleston, SC).

The prize allowed her to travel to Philadelphia to continue her studies with Dr. Francis D.W. Lukens at the George S. Cox Medical Research Institute at the University of Pennsylvania. Dr. Lukens sent a shy endocrine fellow from South Carolina named John Buse to pick her up at the airport. Thus began an almost 50-year partnership in research, teaching, clinical medicine, and child-rearing. They published their first article together on the action of sulfonylureas in animal models in *Diabetes* in 1957. They were married in August 1957 and borrowed a car and honeymooned on the Blue Ridge Parkway on the drive to Charleston, SC, where they both joined the faculty of the then-named Medical College of South Carolina, now called the Medical University of South Carolina (MUSC).

"Dr. Maria" and "Dr. John," as they came to be known, were the first trained endocrinologists in the state. Maria was appointed in the Departments of Medicine and Biochemistry. The couple shared an office suite and laboratory focused on metabolism research and worked in the same clinic and hospital wards. In Maria's first few months at the new job, the hospital recognized the need to establish a unit to explore and harness the diagnostic and therapeutic power of radioisotopes in medicine. Given that Maria had completed a 1-week course on the subject at Woods Hole while a fellow, she was asked to establish the Nuclear Medicine Laboratory. She led the unit from an endocrine-oriented hospital service to a full section of Nuclear Medicine in the Department of Radiology and participated in its practice for nearly 50 years.

Their first child, John, future President, Medicine & Science of the American Diabetes Association, was born in 1958. After the Hungarian Revolution, Maria's father Geza immigrated to Charleston, became a successful print framer and art dealer, settled into a nearby apartment, and shared dinner with the family every day until he died in 1976. Maria settled into a life balancing family life, raising three children, medicine, and science. She read to the children or helped with homework every night, returning to the dining room table to her slide rule and piles of data and journal reprints to write manuscripts and grants. Having been raised in a landlocked country, she loved the ocean and spent almost every weekend and a month in the summer with her family at the Isle of Palms, where John bought her a small beach front cottage while they were still renting an apartment in town.

THE 1960s

In the early years in Charleston, Maria and John shared equally in the clinical and laboratory duties. Their initial research involved organ culture exploring the effects of denervation on glucose uptake and insulin action in muscle. Together, with John as principal investigator, they wrote a grant application to the National Institutes of Health (NIH) entitled "Factors that modify insulin action." On first review they were unsuccessful, with the critique including the stinging rebuke that they wrote "as if paid by the word instead of by the thought." On resubmission in 1960, they received the first NIH grant awarded to the state of South Carolina, which continued through 10 competitive renewals through 2014. She rather humbly suggested that having one of the longest continuous grants at the NIH was due to coming up with a grant name that could accommodate the evolving focus of the grant.

For Maria and John, the constant mixture of marriage, scientific and medical partnership, child-rearing, training, and research mentorship blurred the distinctions between family and work. Maria did not drive and always thought that taxicabs were an extravagance. So, they bought a house just two blocks from the medical school in 1962, where for over 50 years there was an endless stream of trainees and colleagues that were an accepted part of the family even among the three children (John Buse, MD, PhD; Paul Buse, MD; and Elizabeth Buse King, MBA).

In 1960, based in part on Maria's Hungarian accent as an impediment to patient care and John's lesser interest in writing manuscripts and grants, they began to differentiate. Maria took more of the lead in the laboratory aspects of their collaboration, while John continued work as one of the most respected

Maria Gordon Buse, MD, and a portion of her extended family of colleagues, trainees, and progeny in Angkor Wat, Cambodia, July 2007. Left to right: Anne Peters, Mark Harmel, Maggie Burant, Charles Burant, Maria Gordon Buse, Linda Cann, Richard Kahn, Stephanie Kahn, and John Buse (courtesy of Mark Harmel).

clinicians in the medical school. This partnership was a boon to the multiple clinician-scientists who worked with Maria. All of them can remember sitting in the laboratory when John would drop by and suggest that they put on a white coat (mostly to cover the rather informal laboratory attire) and accompany John to the wards, which were just down the hall from the laboratory. There, John would demonstrate some interesting physical finding in his inimitable manner, such as xanthomatous eruptions from "the greasy blood." This manner delighted the patients, who were quickly put at ease, and allowed the students to learn. Indeed, in an era before institutional review boards, many times Maria would instruct that blood be obtained from interesting patients to do additional studies.

Maria Gordon Buse, MD, circa 2012, engaged in conversation on the porch of her beach house (courtesy of Katherine Buse).

Maria transferred her experience from using isotopes in radioimmunoassays, clinical thyroid imaging, and treatment to their use in translational studies, becoming the first person to use radioisotopes at MUSC in research. In a landmark article published in the *Journal of Clinical Investigation* in 1962 (1), she administered ^{131}I-insulin to women (after first treating with potassium iodine) prior to birth and determined that little, if any, insulin crossed the placenta. This showed that any increase in size of the fetus in a mother with diabetes was due to increased production of insulin by the fetus and not due to transplacental insulin transfer. When talking about this study, she would point out that this was her first use of a computer in her studies. Accessed through The Military College of South Carolina (The Citadel), she used a Donner analog computer for curve fitting the observed degradation of insulin. It was likely the first "portable" computer used at MUSC.

In addition to her work with radioisotopes, Maria began studies that would occupy a significant portion of her research career, the effect of insulin and branched-chain amino acids (BCAAs) on skeletal muscle metabolism (2,3). Although it was known that exercise could have a profound effect on insulin sensitivity, the effect of immobility on insulin action had not been studied until 1959, when Maria, working with John in some of their first studies in South Carolina, began a series of experiments that showed that denervation of diaphragms or hind limbs of rats resulted in a rapid and marked decrease in insulin responsiveness to glucose uptake and to amino acid uptake and protein synthesis.

The initial report (2), published in 1959, was one of the first ever to assess insulin binding to whole-tissue mammalian tissue. Using ^{131}I-insulin, Maria showed that there was no significant difference in insulin binding between innervated and denervated hemidiaphragms when assessed both in vitro and in vivo, demonstrating the first "postreceptor" defect in insulin action, a topic that she would continue to investigate throughout her career. These were heroic experiments performed in the laboratory by injecting up to 10 μCi of ^{131}I-insulin intravenously into rats, their cages shielded by lead bricks. These rather crude studies have stood the test of time and have been confirmed by multiple researchers using more sophisticated techniques. The initial

studies investigating the effects of denervation were done in hemidiaphragms following phrenectomy. Over the years, hundreds of phrenectomies and diaphragm isolations were performed in the laboratory and nearly every procedure was done personally by Maria. She was, and continues to be, proud of her surgical skills and insisted that she was the only one skilled enough to perform phrenectomy and diaphragm isolation properly, though more than one graduate student and postdoc suspected that she simply wanted to continue to participate in the "hands-on" portion of the studies and, importantly, participate in the camaraderie that was part of the enjoyment of working in the Buse laboratory.

THE 1970s

In studying the effect of insulin in skeletal muscle, Maria's studies found that fatty acids had a unique effect to increase the oxidation of BCAA in muscle and heart with a pronounced effect on leucine oxidation as opposed to valine and isoleucine. The observation that conditions that are associated with increased levels of fatty acids, such as uncontrolled diabetes or insulin resistance, were associated with increased catabolism of BCAA and muscle wasting led to another seminal article in the *Journal of Clinical Investigation* (4) that demonstrated that leucine, but no other amino acid, stimulated the uptake and incorporation of ^{14}C-lysine into hemidiaphragm proteins. This effect was modulated minimally by insulin but could be affected by fatty acids, diabetes status, and denervation of muscle. In addition to stimulating protein translation initiation, blocking transcription or translation also showed that leucine had the ability to simultaneously reduce protein breakdown. Over the past three decades, it has become clear that much of the effect of leucine to alter metabolism is via the activation of the enzyme mammalian target of rapamycin (mTOR), an enzyme complex that is a primary sensor of nutrient status, a primary mediator in the regulation of skeletal muscle protein dynamics (5).

THE 1980s AND 1990s

During this time, studies in the laboratory centered on the continued exploration of insulin action in denervated skeletal muscle as well as defining BCAA metabolism. Some of the first studies ever to examine the activation of the insulin receptor kinase in intact animals (6) showed that the rapid decline in insulin-stimulated glucose uptake was not due to alterations in the autophosphorylation or the kinase activity of the insulin receptor, but defined the signaling disruption as a postreceptor defect, subsequently found to be due to impaired insulin receptor substrate-1–mediated increase in phosphoinositide 3-kinase activation (7). The regulation of BCAA metabolism continued to be studied with detailed examination of the rate-limiting step in BCAA metabolism, the multisubunit ketoacid dehydrogenase complex, which shares several subunits with the pyruvate dehydrogenase enzyme. Detailed studies showed regulation in the muscle, liver, and other tissues by fasting/refeeding, high-fat diets, insulinopenic diabetes, glucocorticoids, and endotoxins, among others. The data showed an intimate relationship between BCAA metabolism and the control of protein synthesis and degradation in tissues under pathological states. These studies helped clarify the beneficial effects of both BCAA and their ketoacids in disease states (8).

In the 1990s, Maria's research interests also evolved to investigations around the way in which glucose, amino acids, and other nutrients modified insulin signaling, including posttranslational modification of insulin receptors and their downstream targets and alteration in glucose transporter function glucosamines (9,10). These studies showed that modification of serine residues by glucosamine could have a significant effect on the signaling in cells and tissues.

THE 21st CENTURY

The focus of the Buse laboratory increasingly focused on the regulation of insulin receptor signaling and the potential for posttranslational changes in signaling molecules in insulin-resistant states. Maria identified a novel muscle-specific variant of the glutamine:fructose-6-phosphate amidotransferase-1 (GFAT-1), the rate-limiting enzyme of the hexosamine synthesis pathway, which alters enzymatic activity and may predispose muscle to insulin resistance in high-glucose conditions (11). She described the sites of O-linked β-N-acetylglucosamine modification in a number of proteins and showed that these modifications altered their function, likely part of the broad array of changes in the insulin-resistant, diabetic state that is part of the alteration in insulin signaling (12). Thus, she continued a line of research that stretches back to before the vast majority of her trainees were born.

Clinically, her career came full circle. After retiring from radiology, based on her vast experience as a "dot spotter" (John's characterization of her work in nuclear medicine), she returned to the endocrine division to precept fellows and students. When her funding from the NIH ran out in January 2014, her family encouraged her to use funds at her disposal to continue with her passion for research and teaching. She refused, insulted at the suggestion, relating that if her ideas were not good enough for the NIH, it was time to call it quits. Her last article (13), with first author Katherine (Katy) Robinson (who worked with Maria for over 28 years), described the activity of Go-6976, an inhibitor of "conventional" protein kinase C (PKC) isoforms PKCα and PKCβ, and the mTOR inhibitor rapamycin to alleviate insulin resistance induced in 3T3-L1 adipocytes by incubation in high-glucose media. They found that Go-6976 did induce a partial alleviation of insulin resistance, but it likely was working through alterations in mTOR signaling, not PKC-mediated pathways. It seems fitting that after 50 years of studying BCAA effects, the molecular entity that mediates the effect of BCAAs would be the focus of Maria's latest contribution to the literature. There may be still one more future article based on the continuing efforts of her last fellow, Dr. Lauren Ball, who continues the work in Charleston.

SUMMARY

In a career that spanned nearly 60 years, Maria believed that being able to do science and to share in the lives of trainees was a sacred gift. At the same time, she was selfless in her devotion to the tasks of an academic clinician and selfish in that she was doing what she loved. Her pioneering efforts in South Carolina as an investigator, clinician, and faculty member were recognized by numerous awards from the state and her institution. Her most prized recognition was receiving the American Diabetes Association's

Albert Renold Award in 2003 because it carried the name of a respected friend and colleague and because it recognized her for her accomplishment as a mentor, which she saw as the highest possible calling in academia.

The freedom that Maria allowed the trainees in the laboratory encouraged risk-taking, provided it was based on some reasonable hypothesis—the "idiot experiments." Maria says, "Only an idiot would try it, but sometimes idiots are geniuses in disguise." Maria was a fixture in the laboratory, almost never pushing for studies to be completed, but rather discussing, critiquing, and encouraging discovery. She instilled an infectious desire to find out the answer. As often happened, the first results of an experiment would be obtained and a grand theory would be based on the initial results. As often as not, the theory would be destroyed by the subsequent findings, but the thought experiments were considered valuable by the trainees as a way to think about the project, the techniques, and the holes in the theory. Few minded these sometimes rambling, but always entertaining, discussions as they always knew more at the end than when they started, mostly because Maria had an amazing mastery of the literature. She got this by reading voraciously and encouraged trainees to do the same, often arranging for a couple hours of library time (before the advent of the Internet). She instilled a sense of inquiry for not only science but also politics, cultures, and personal relationships. Likely because she had fearlessly traveled all her life to virtually every corner of the globe, Maria encouraged and supported her trainees to travel abroad for meetings for the science and perhaps more for the cultural exposure that it provided. She traveled abroad almost every year, usually on the pretext of a meeting but extending the trip for a week or more.

The Buse laboratory was always the "place to be," with the numerous medical students, graduate students, postdocs, and MD/PhD students, the latter of which seemed in particular to gravitate to Maria's laboratory. Maria was instrumental in the creation of the Medical Scientist Training Program at MUSC, and she had a hand in training about half of the first groups of students in the nascent program.

The people in her laboratory learned to work hard and to play hard. They enjoyed the famous fruit daiquiris on Friday afternoons in the conference room, and the party often migrated to Maria and John's home (two blocks away) for a cookout and "a touch of the red," the latter a wonderful wine that lubricated lively discussions of science, politics, travel, inevitable reminiscences, and even an occasional robust recital by Maria of the Hungarian national anthem. The care and nurturing both in and outside of the laboratory gave rise to the feeling that one was truly part of a family, with John and Maria at the head of the table. This tradition continued after her beloved John died in 2001. She travels very little these days, but enjoys reading, movies, and visits with family or colleagues, technicians, or trainees who come by to take her for dinner or a movie. Even after a long, successful, and enjoyable career, Maria continues to be a source of friendship, comfort, and wisdom to her biological and adopted family.

Acknowledgments. C.F.B. and K.A.R. are two of among dozens of "SOBs" (Sons or Sisters of Buse), the designation provided by Maria for the most deserving of her professional progeny. C.R.B. is one of her nine grandchildren and J.B.B. is her son. They all are heavily conflicted by their love for Maria. Special thanks to E. Brooke Fox (University Archivist, the Waring Historical Library, MUSC, Charleston, SC); Mark Harmel, MPH, CDE (University of Southern California and Harmel Health and Communications Consulting, Los Angeles, CA); Katherine Buse, MA, MPhil (University of California, Davis, Davis, CA); and Lyn Reynolds (American Diabetes Association Editorial Office) for help in editing the manuscript.

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