Daniel H. Mintz (1930–2020): An Extraordinary Physician-Scientist and a Pioneer in Islet Transplantation

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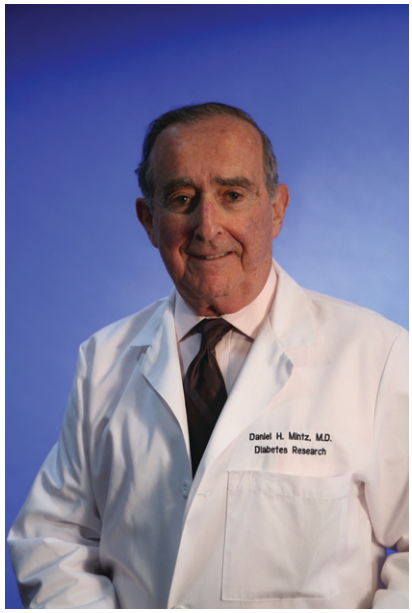
EARLY YEARS

Daniel H. Mintz was born in Far Rockaway, New York, in 1930 to European Jewish parents, Jacob and Fanny, and grew up on Long Island, New York, where his parents immigrated in the early 1900s. In his youth he excelled both in sports (basketball) and academically; he was accepted as a premed student at St. Bonaventure College, where he completed his Bachelor's degree cum laude. He entered New York Medical College, which had no quotas for Jewish students (unlike many other schools at that time), and completed his medical training in 1956. While serving his internship at Henry Ford Hospital in Detroit, Michigan, he met his future wife, Dawn, a hospital nurse. In 1961, Dan entered residency at Georgetown University School of Medicine and joined the faculty, initiating his research career under the mentorship of Dr. Larry Kyle, Chairman of Medicine, studying parathyroid and bone disorders (1).

Dan's first love was clinical medicine, so it is no surprise that he was appointed Chief of Medicine at the then District of Columbia General Hospital in 1964. He once recounted the story that kept him in academic medicine after planning to start a private practice in Leesburg, Northern Virginia. Dr. Kyle called him into his office and told him in no uncertain terms that he was making a mistake and should remain in academia. As Dan recalled years later, "In those days you did what your boss told you to do!" This career-changing decision was a testament to Dan's primary reason for entering medicine—to be a healer of the sick. His capacity for responding to people in need strongly influenced his initial decision of a career devoted to the care of sick people. Despite Dan turning to an academic future, this devotion continued to frame his professional and personal life.



Daniel Mintz in 2006.

CONTRIBUTIONS TO DIABETES RESEARCH

In 1965 Dan moved to the University of Pittsburgh School of Medicine as Associate Professor and Chief of Medicine at Magee-Womens Hospital, one of the largest academic obstetrical and gynecologic hospitals in the country. He established the first-of-its-kind comprehensive women's medical service. With Division Chief James Field, MD, he studied growth hormone and its disorders (2–7) but quickly turned his focus to diabetes. With Ronald Chez, MD, he discovered that fetal β-cells, unlike neonatal β-cells, produce insulin in response to tolbutamide but not to glucose or arginine (6), even though maternal glucose passes through the

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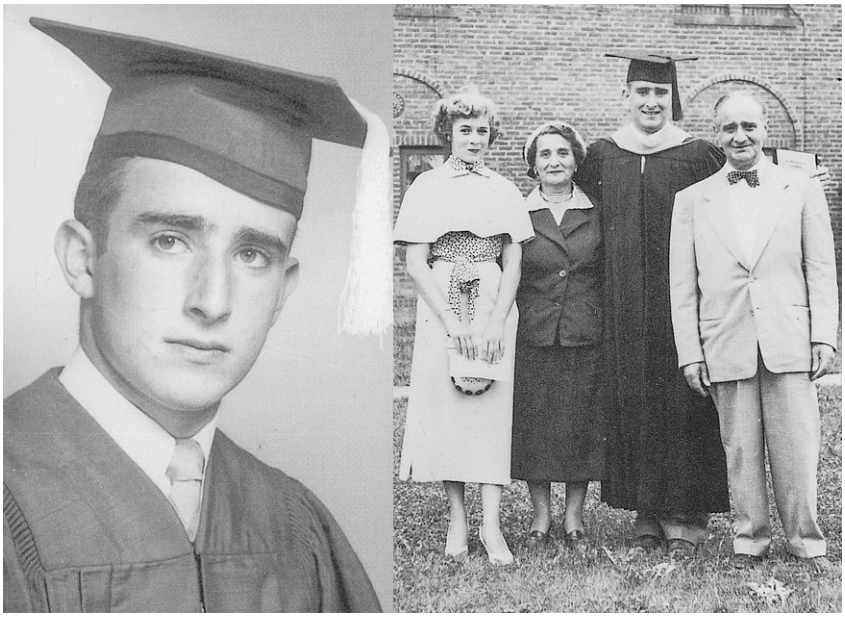
placental barrier (8). Using a streptozotocin nonhuman primate model, they demonstrated that maternal hyperglycemia contributes to the fetal hyperinsulinemia occurring later during a diabetic pregnancy. These observations were foundational to understanding the effects of maternal diabetes on the fetus and impacted diabetes management guidelines during pregnancy.

In 1969, William Harrington, Chairman of Medicine, recruited Dan for the new University of Miami School of Medicine as Professor of Medicine and the first Chief of Endocrinology and Metabolism (serving until 1980). Dan noted, "I was fortunate to come to a medical school which was not boxed in by traditions. They gave me enough rope to either hang myself or lasso a prize." He began building the division and initiated a fellowship training program, an inpatient endocrinology consult service, and outpatient endocrinology and diabetes clinics. He was Co-Director of the National Institutes of Health (NIH)-supported Clinical Research Unit at the University of Miami (1969–1977).

Establishment of the Islet Transplantation Program and the Diabetes Research Institute at the University of Miami

Dan's scientific interest in diabetes was noticed by several South Florida parents of children with type 1 diabetes. They saw in him an investigator who might be able to help their children. In 1971, they asked him to help find a cure for their children and offered their full commitment in this endeavor. It was about this time that Dan had become aware of a report describing the successful skin grafting from an unrelated donor to an immunosuppressed mouse. Dan's vision recognized the scientific opportunity this afforded for transplantation of isolated donor islets to cure insulin-deficient diabetes—and for a physician's passion to respond to people in need. Thus was born the islet cell transplantation program at the University of Miami. At its core was the hope and belief that type 1 diabetes could be cured by the transplantation of isolated donor islets. The parent group began a fundraising program and within two short years the Diabetes Research Institute (DRI) and the Diabetes Research Institute Foundation (DRIF) were established. The DRIF, based in South Florida but with an extensive national presence, continues to be the heart and soul of the research effort. Over time it has raised more than 250 million endowment dollars for the DRI and the School of Medicine. As Gary Kleiman, one of the young people with type 1 diabetes who was involved, and who subsequently became the DRI Senior Medical Development Officer, succinctly put it, "The creation of the DRI was his response to the fearful parents who met with him to plead for his help and to find out what he needed to speed his research. He provided these families with the science-based hope and trust that would inspire a growing community." Dan remembered that pivotal time this way: "we created a bond of hope between scientists and parents; both sides were working equally hard, and hope was fueling the process."

The DRI began as a multispecialty clinical/research center in 1975 with Dan as Scientific Director of a small group of researchers. In 1980 Dan was appointed to the first endowed chair at the School of Medicine, named by DRIF parents to honor their daughter with type 1 diabetes. As Dan saw it, the mission of the DRI needed to be entirely focused on the cure of type 1 diabetes if there was to be success and it was unique in this regard. Dan envisioned that all DRI faculty would have departmental appointments, to develop synergies and attract more talent and resources to the mission. Among the new DRI faculty was Jay Skyler, who with Dan translated the early experimental studies of diabetes in pregnancy using the newly introduced self-monitoring of blood glucose in pregnant women with diabetes, improving their glucose control and paving the way for improved outcomes (9,10); Skyler went on become a leader in prevention and intervention trials for type 1 diabetes. Dan also recruited Alex Rabinovitch, with whom he developed islet cell culture methods, explored the potential for β-cell replication, and studied various aspects of β-cell biology (11–15). He later recruited Ricardo Pastori, and together they employed molecular biology approaches to identify CD44 isoforms involved in the migration of lymphocytes to the islets in nonobese diabetic mice (16).



Daniel Mintz as a young student, and with his parents and sister at his medical graduation ceremony, New York Medical College, 1956.

Islet Transplantation—From Rodents to Dogs to Humans

Once in Miami, with funding from the NIH (maintained until he retired from the laboratory in 1996) and the Florida JDRF, Dan initiated studies using the new technique of monolayer culture of neonatal rat islets, described by Paul Lacy (17). Dan took a sabbatical in 1976 to work with Albert Renold and Philippe Halban, University of Geneva, both

leaders in islet cell research. He formed long-lasting bonds, professionally and personally. In letters to Dan from 1999, Halban wrote, "With Albert, you served as my mentor and role model"; the late George Cahill, MD, wrote, "Dan and I were younger brothers to Albert, at times his equal and at other times, he was our mentor and patron." On his return from Geneva, Dan established an islet transplantation program in a rat model at the University of Miami, and by 1978 the demonstration that donor islets from adult rats could be used successfully in place of neonatal tissue to reverse rodent diabetes was an important advance (18).

Following this success Dan decided to evaluate islet transplantation in a higher mammalian species as a forerunner to transplantation in humans. In 1980 he recruited Rodolfo Alejandro, who became central to establishing islet transplantation in the dog and thence to humans. However, islet yield from pancreata of large mammals was suboptimal because these organs are more fibrous than in rodents. Through manipulation of methodologies and reagents for the preparation of canine islets, a new isolation procedure with a high level of purity from a single canine donor pancreas became possible (19). Initial islet autografts in dogs demonstrated diabetes reversal with persistence of islet cells and insulin secretion on extended follow-up and highlighted graft site and time as critical factors (20). It remained to be demonstrated in larger mammals whether an islet cell mass that is initially adequate in a heterotopic site such as the liver can remain functionally competent over a prolonged period. An even greater challenge was posed by allograft transplantation because of immune rejection. Thus, the group undertook the characterization of cells expressing immunogenic antigens in the islet grafts in different species (rat, dog, human) (21–23) using monoclonal antibodies generated in Dan's laboratory; these were also used to reduce rejection by removing islet-resident antigen-presenting cells (24). They then tested cyclosporin, which was being used for solid organ transplantation, demonstrating that cyclosporin suppressed rejection of intrahepatic islet allotransplants in pancreatectomized dogs; most recipients achieved fasting euglycemia (25).

These studies in dogs critically demonstrated feasibility and highlighted the challenges to islet cell transplantation in humans. The group undertook a pilot human islet trial in 1985 in four patients with long-standing type 1 diabetes and end-stage renal disease who had kidney transplantation performed and therefore required immunosuppression with cyclosporin; he studied intraportal infusion of human islets (26) after treatment to remove antigen-presenting cells (21,23). One of the new procedures introduced was percutaneous intrahepatic portal vein cannulation. However, only one patient demonstrated function beyond 7 weeks. It was felt that both the relatively low yields of islets from a cadaveric pancreas and the heightened vulnerability of islet allografts to rejection remained to be addressed.

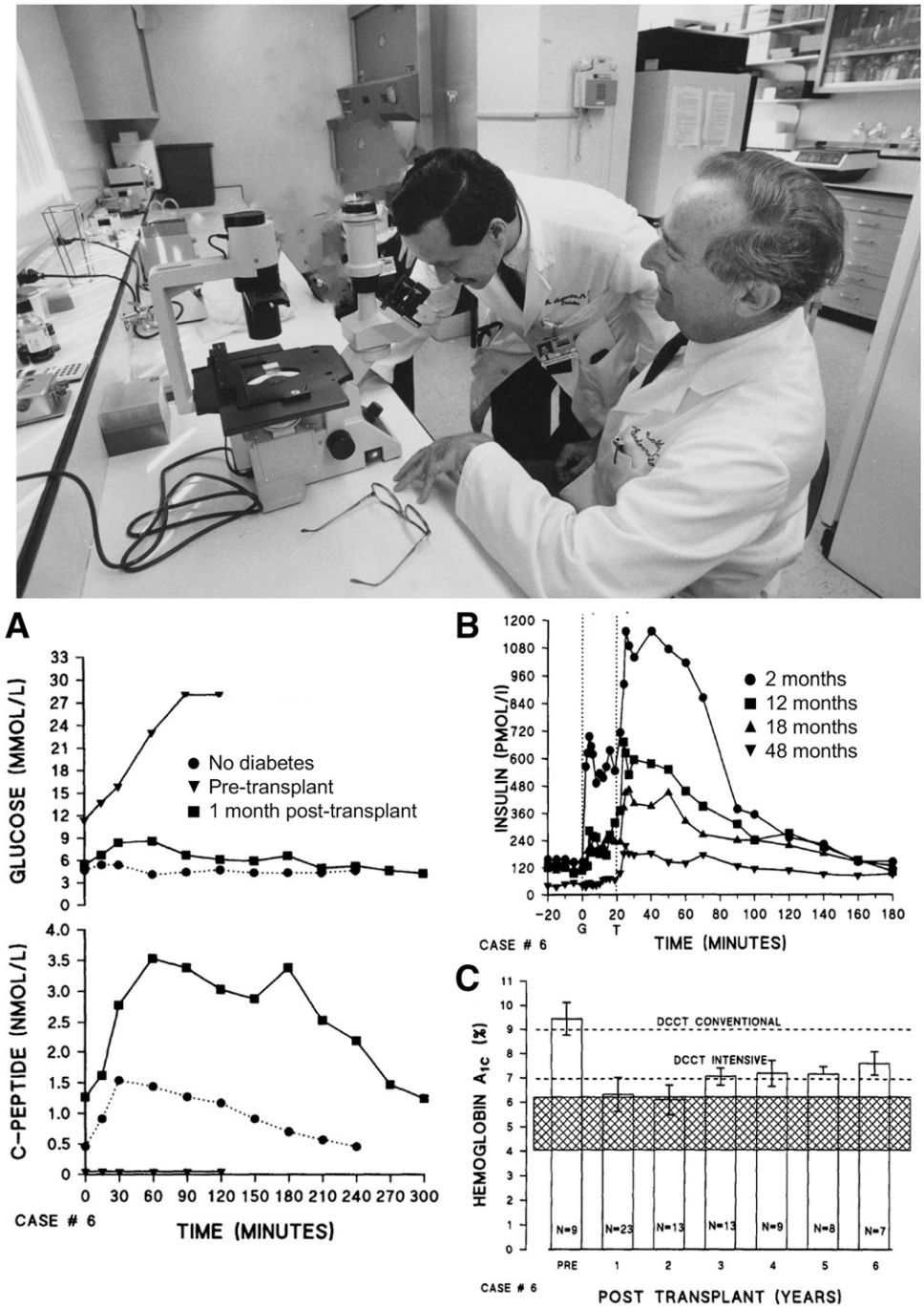
The opportunity for Dan and his group to further advance human islet transplantation came in 1989 as a result of several new developments. First, he and his colleagues began collaborating with Camillo Ricordi, MD, who had a developed a more efficient automated method for islet isolation at the Washington University School of Medicine in St. Louis (27). This was enhanced by islet purification on discontinuous density gradients using the COBE 2991 cell processor (28). All equipment for islet isolation was engineered, in a strange twist of fate, by a DRIF parent of a child with type 1 diabetes, Ramon Poo. Second, a new more effective immunosuppressive drug, FK506 (tacrolimus), had become available (29). These developments convinced Dan and Alejandro to initiate a clinical trial of islet transplantation in collaboration with Thomas Starzl, Andreas Tzakis, and Camillo Ricordi at the University of Pittsburgh. This pioneering study involved nine patients who underwent upper abdominal exenteration with resection of abdominal organs for advanced malignancies within the confines of the surgical field, and replacement of the liver by a cadaver transplant followed by a portal vein infusion of pancreatic islets from the same donor using tacrolimus immunosuppression (30). Although three individuals had a stormy postoperative course, developed diabetes, and died within 4 months, the remaining six patients were insulin free for 5–16 months. In 1990 this was the first demonstration of successful clinical islet cell transplantation.

This study was the crowning success of Dan's research that had begun with optimizing β-cell culture methods and culminated in the prevention of diabetes after pancreatectomy by islet allografts 20 years later. Human islet transplantation had come of age and this proof-of-concept study paved the way forward to islet allotransplantation in patients with type 1 diabetes. The improvements in islet isolation using gradient centrifugation (28), the use of a safer percutaneous transhepatic technique for infusion of islets into the portal vein obviating the need for a laparotomy (31), and the application of the dithizone staining procedure, which improved islet visualization (32), were all introduced to the field and/or implemented (30) by Dan and his colleagues as the DRI grew into one of the largest independent centers worldwide for islet transplantation in type 1 diabetes. To commemorate Dan becoming Emeritus in 1999, the late Paul Lacy, MD, wrote, "You were a pioneer in the development of the field of islet transplantation many years ago. Throughout all of this time, you have adhered to the ultimate goal of human islet transplants without the need for continuous immunosuppression."

Dan and Alejandro later published work on their long-term experience with islet transplantation in 8 patients with type 1 diabetes (33). Although two of the recipients experienced graft rejection, the remaining six had persistent graft function with reduced insulin requirements and near normalization of glycemia; the two subjects with the longest graft survival achieved near normalization of HbA_{1c} during 6 years in the absence of severe episodes of hypoglycemia. These results provided cautious optimism for the continued application of islet allotransplantation as a treatment modality for type 1 diabetes.

A MENTOR AND TEACHER

Over the years Dan was mentor to many young scientists and physicians. He saw this as a most important academic role, and he obtained an NIH Institutional Training Grant (T32) that supported many predoctoral and postdoctoral trainees who in turn contributed to the research program and beyond. He was an outstanding teacher and loved interacting with medical students, seeing in them young fertile minds with boundless opportunities. One



Daniel Mintz and Rodolfo Alejandro in the research laboratory, mid-1980s, leading to successful allogeneic islet transplantation with long-term function in a patient with type 1 diabetes. The study involved eight recipients with type 1 diabetes who had previously (or, for one patient, at the same time) received a kidney graft for correction of end-stage renal disease. Between 1990 and 1993, patients received multiple islet infusions in the liver from two to five donors. Data from a patient with successful long-term function are shown. *A*: Patient's glucose (top) and C-peptide (bottom) responses during the mixed-meal tolerance test (Sustacal test) performed before and 1 month after transplantation, compared with individuals without diabetes. *B*: Posttransplant frequently sampled intravenous glucose tolerance test on extended follow-up. G, glucose stimulation; T, tolbutamide stimulation. *C*: HbA_{1c} levels before and after transplantation, during the 6 years' follow-up, compared with expected levels if Diabetes Control and Complications Trial (DCCT) conventional and intensive regimens were followed, reveal superior control of glucose metabolism. The patient required 65% less insulin after transplant (0.31 units/kg/day). Of note, the patient was managed using the novel "TeleDoc" computer-based system developed by Albisser and Mintz. Using a touch-tone telephone available 24/7 the patient reported information about daily blood glucose values, diet, exercise, stress, and hypoglycemia, in turn receiving automated, algorithm-derived advice to optimize management. The study demonstrated that transplantation of an islet allograft mass comparable with that of whole organ pancreas transplants results in long-term islet function, with significant reduction of insulin dose requirements, leading to near normalization of blood glucose HbA_{1c} levels, in the absence of severe hypoglycemic episodes typically seen in intensive insulin regimens. Modified from Alejandro et al. (33).

of Dan's skills was listening. Whether with a patient, a colleague, or a friend, he had a unique ability to provide insightful comments and advice by listening and reading what was behind the spoken word. This ability was a key feature in his teaching as well. Quite often he would invite a patient to the classroom, asking the patient to describe the symptoms to the students. This technique illustrated a condition through the patient's words and taught students how to interact with a patient, recognize symptoms, and make a diagnosis. He engaged and challenged students with questions to develop their critical thinking. He was rigorous, had high expectations, and shared frank criticism. He desired people to learn, improve, have self-confidence, and be prepared for any challenge in life. There are many stories about his impact on trainees and colleagues. Author and colleague Alessia Fornoni shared her own story: "Discussions with Dan drove me to embrace experimental therapeutics and precision medicine approaches to patient care. Dan introduced me to the bedside-to-bench-and-back exercise that I believe is the basis of my success as a physician-scientist. He made me understand that the job of a physician scientist is one job, not two jobs done by the same person."

A "COMPLEAT PHYSICIAN"

After retiring from the DRI Scientific Directorship, Dan expanded his involvement in patient care, his first love. The passion, enthusiasm, creativity, perseverance, and intellectual curiosity he had applied to searching for a cure for type 1 diabetes he now channeled with unbridled empathy into caring for people with diabetes. He started slowly and methodically, dusting off the cobwebs of time, rediscovering the joy of clinical medicine and the opportunity to continue making a difference in the lives of people affected by diabetes. His colleague and friend, Luigi Meneghini, remembers, "He had a way of connecting with people, making them feel at ease and willing to open up to him. His trainees in Pittsburg nicknamed him "Sweetlips" for his ability to connect even with the most uncooperative patients! Witnessing Dan perform a history and physical and weaving his findings into a clinical assessment, taking as much time as was needed, was like

Daniel Mintz, a caring physician, consulting with his young patient, Katelyn, 2007.

attending a symphony where the master conductor, understanding all the moving parts of a complex ensemble, delivers a work of art." His patients had his mobile number and were told to call him day or night should they be in need. He would make home visits when asked, or when he thought it was needed, and he often helped his patients navigating life challenges. His patients loved and revered him.

Dr. Meneghini recalls, "Dan was interested in new technology for diabetes management. With Mike Albisser, they pioneered a telemedicine computer-based electronic case manager years before this technology became mainstream" (34). One of his most cherished honors was an invitation to address the medical student class at their commencement. That compelling speech, entitled "Touching," contained the following stirring words: "To the extent that you are able to reach out and touch the sick, to place your arm around the shoulders of the bereaved, and to give of yourself when you think there is little left to give, you will be serving the noblest instincts of man."

Patient Gwen Berlin remembered, "Dr. Daniel Mintz was a world-renowned scientist, a brilliant doctor and a counselor. To me and his other patients, he was the passionate 'family' doctor from back in the days . . . who everyone loved . . . who genuinely cared about each of his patients. . . . They just don't exist anymore. I'm afraid they never will again."

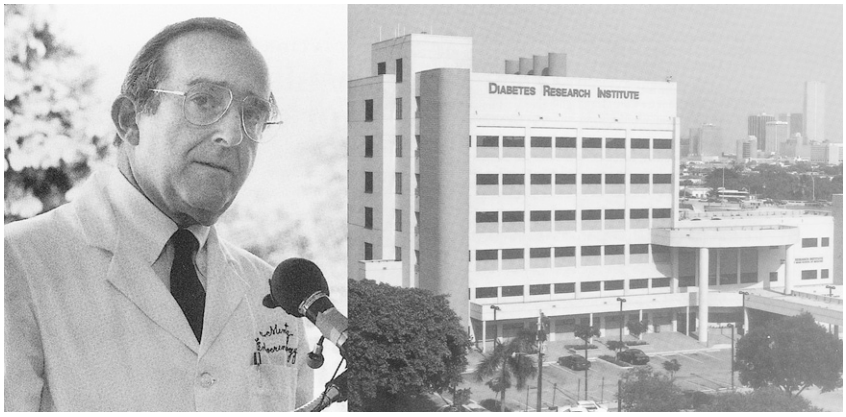
Murray Epstein, a nephrologist at the University of Miami, believed Dan exemplified the "Aequanimitas" that Sir William Osler, the father of American Medicine, presented in his 1889 farewell address at the Pennsylvania School of Medicine (35); Dan possessed "coolness and presence of mind under all circumstances, calmness amid storm, clearness of judgment in moments of grave peril," Osler's defining qualities of the "Compleat Physician." His stature as a physician-scientist was recognized by his election to the prestigious American Society for Clinical Investigation and American Association of Physicians.

A FAMILY MAN

Dan was a deeply committed family man. Dawn, whom he married in 1963, was his strongest supporter, and together their high ethical standards, their belief in serving others, and their love and respect for each other were models for their children, David, Denise, and Debbie. As his son David, speaking on behalf of his sisters, put it, "He was a father in many of the same ways that he was a physician . . . caregiving, dutiful, self-sacrificing, and ethically committed to doing good. His first impulse was always to see to the needs of others. He was compelled to problem solve, and to try to heal." Sadly, Dawn took ill, and Dan left work to care for her in her final days. He asked Ron Goldberg, MD, a long-standing colleague and friend, to supervise her medical treatment. "Watching Dan's exquisite care for Dawn in those moments of agony," he recalls, "was a selfless enactment of all he stood for as a husband, physician, and human being".

A few years later he was once again confronted with the illness of someone close to him. Marty Kleiman, his wife Marge, and their sons Gary and Glenn were one of the original founder families of the DRIF, and all were very close friends of Dan and Dawn. Marty Kleiman had become seriously ill. Dan, in an extraordinary act of devotion, moved

Family picture. Dan Mintz with wife Dawn, son David, and daughters Denise and Debbie.



Daniel Mintz speaking at the dedication ceremony of the DRI building, 1994.

into the Kleimans' home in his final days to help ease his passing. In the years that followed, Dan Mintz and Marge Kleiman, each having lost a life partner, drew closer and married in 1996. In a final extraordinary twist of fate, it was as if two people, who had each in their own way devoted themselves to seeking a cure for diabetes, were enabled, with the memories of their departed partners and friends, to celebrate their work together. Marge recalls an apt wedding message from a family member referring to their lives together "as being like two stage plays that were really one." "He was my best friend," she said.

Dan developed Parkinsonism and after a long illness died in 2020. At his memorial service his granddaughter, Mika Mintz, a third-year medical student, remembered him "as an extraordinary man, whose purpose was rooted in integrity, whose heart was fueled by altruism, and whose life was devoted to the betterment of others."

THE LEGACY OF DANIEL MINTZ

Dan founded the Division of Endocrinology and Diabetes at the University of Miami School of Medicine, establishing an academic center of excellence for diabetes teaching, care, and research. He developed an islet transplantation program in a unique partnership with a lay foundation of people as dedicated as he was to curing type 1 diabetes. He created a research institute that has attracted scientists and clinicians from around the world, enriching the scientific enterprise and establishing a leading center for islet transplantation and cure-focused research. As the program expanded and more clinical and laboratory research space was needed, Dan orchestrated a partnership between the DRI/DRIF and the Building and Construction Trades Department of the American Federation of Labor and Congress of Industrial Organizations; the resulting Dollars Against Diabetes campaign, known as D.A.D.s Day, raised funds for an 87,000 square foot facility on the medical school campus consisting of a state-of-the-art clinic and a six-floor research tower. Dan saw the new building, inaugurated in 1994, as one of the great accomplishments of the program. "It represents hope to the millions of men, women and children who suffer from diabetes," he wrote, and a plaque in the lobby displays his simple but compelling message: "Research provides the only hope that the future will be different from the past." Camillo Ricordi, recruited as Co-Director in 1993, later succeeded Dan as the DRI Scientific Director. The institute Dan fathered embodies the inspiration and hope he engendered and the devotion he had to the alleviation and suffering of people with type 1 diabetes and beyond.

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