Saul Genuth, MD: Clinical Researcher and Leader in Developing Modern Diabetes Treatment

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Saul Genuth was born to David L. and Anna Einhorn Genuth on 13 March 1931 in Norwalk, Connecticut. His father was an orthodox rabbi and his mother was a housewife. David Genuth was born and raised in Hungary but immigrated to the U.S. to escape induction into the Romanian army (the area of Hungary where he lived ceded to Romania after World War I). Anna's parents came from Poland, seeking a better life for their future family. David became an orthodox rabbi, while Anna remained a homemaker and a rabbi's wife (which Saul states was a profession in and of itself).

Saul was 4 years old when his family moved to Cleveland, Ohio, and he has made Cleveland his home through most of his medical training and his entire professional career. Saul noted that he and his two younger sisters grew up "somewhat poor in a lower middle class neighborhood but were never hungry or deprived." He remains close to his one surviving sister, a retired attorney in Portland, Maine. When asked about his childhood, he admits he was not the athletic type growing up but could shoot a mean game of marbles. Today his main source of recreation is reading. Saul's subtle sense of humor comes through as he explains, "I hope printed books never disappear. I don't read e-books, they have never 'kindled' my interest." He is also devoted to classical music and regularly attends Cleveland Orchestra concerts and local recitals.

Saul Genuth, MD

Saul met Molly Goodman, the love of his life, in 7th grade. He told the story of them sitting near each other in homeroom because their last names both began with "G." They became fast friends, and as a 13-year-old, Molly told her mother that one day she was going to marry Saul Genuth. Saul counted that as his very good fortune. By age 17, the couple had fallen deeply in love and remained so for the whole of their life together. The two were married in 1953, 10 days after they graduated from college (Saul from Harvard and Molly from Flora Stone Mather College of Western Reserve University, as it was known then).

Their children, a son and a daughter, both became public schoolteachers. Their granddaughters are graduate students, one at University of California in San Francisco and the other at Stanford, and one grandson just graduated from the University of Vermont and the other is in his third year at the Air Force Academy. Saul is justly proud of their achievements.

Molly steadfastly supported Saul's professional work and his time commitment to it. Through the years, the couple traveled the globe reaching every continent including Antarctica. They had been married 56 years when Molly passed in 2009 at the age of 78. Saul is emphatic when he says that Molly was the best thing that ever happened to him.

The second best was being awarded a full scholarship (tuition, room, and board) to Harvard College. He readily admits that seeing his maternal grandmother suffer from type 1 diabetes, as well as other illnesses, influenced his decision toward a career in medicine. Saul became interested in science during his undergraduate years at Harvard when he took a course in biochemistry. He found those years "intellectually exciting." During his senior year, he performed his thesis research in the laboratory of Fritz Lipmann, winner of the 1953 Nobel Prize for the discovery of CoA. Saul found the

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Dr. G and wife Molly vacationing in the Canadian Rockies

experience so exciting that he skipped physical chemistry classes to spend extra time in the laboratory, thereby registering his only "C" at Harvard. The discovery of a career direction as if by chance has been a recurring theme throughout Saul's work life. His interests and objectives often did not come from an a priori plan but through opportune exposures that molded his decisions.

After graduating from Harvard, Saul returned home to Cleveland for medical school at Case Western Reserve University. Taking the opportunity to do research as a medical student, he was the first person to synthesize the compound leucyl-AMP, which the laboratory then demonstrated was the high-energy activated form of amino acids required for them to be incorporated into the biosynthetic pathway of protein synthesis (1). Saul remained in Cleveland to do his medical residency at Mount Sinai Hospital. Not clear about his professional direction, he took the suggestion of his chief of medicine and applied to the National Institutes of Health for a clinical associate position at the National Cancer Institute (NCI). Saul also interviewed for a position in the National Institute of Arthritis and Metabolic Diseases, the forerunner of National Institute of Diabetes and Digestive and Kidney Diseases and his preferred choice, but the NCI called first. During his time at the NCI, Saul participated in the first successful trials of methotrexate for choriocarcinoma. Despite the excitement of this groundbreaking research, he was not set on a career in oncology and cancer research. Still needing to complete his internal medicine training after his time at NCI, Saul decided to return to his first interest in endocrinology and completed his training at Duke University.

RESEARCH ON TYPE 2 DIABETES AND OBESITY

During his fellowship at Duke, Saul initiated his research and his first focus on obesity and type 2, then called "maturity-onset," diabetes. His earliest research sought to develop a better understanding of metabolism using animal models. Upon returning to Case Western and Mount Sinai as a junior faculty member, he incorporated human research paradigms to help dissect the pathogenesis of type 2 diabetes, thus becoming a translational researcher before the term existed.

As a first step, Saul capitalized on the pivotal development of the radioimmunoassay for insulin by Berson and Yalow and developed his own version of the assay in collaboration with Frohman and Lebovitz, using ^{125}I instead of ^{131}I (2). The ^{125}I assay had the advantage of a longer half-life and thus shelf life and less exposure to radiation for the technicians. This new method was especially useful for smaller laboratories where the number of subjects being studied did not require high-throughput capabilities. Armed with this powerful research tool that was revolutionizing endocrinology, Saul performed a series of animal and human studies that examined the impact of varying metabolic conditions on the regulation and effects of insulin.

These first studies identified the mechanism by which corticotropin has a hypoglycemic action. He showed that corticotropin has a direct stimulatory effect on the release of insulin. The hypoglycemic action conflicted with other effects of corticotropin, leading to a peculiar combination of ketosis, hyperinsulinemia, and hypoglycemia (3). Saul then used the *ob/ob* mouse model to examine whether insulin resistance, as opposed to a primary abnormality in islet cell function, was the reason for hyperinsulinemia in the diabetic state (4). His findings suggested that insulin resistance was unlikely to be the "basic genetic abnormality" in *ob/ob* mice. He next studied these mice from the period before weaning to better identify the mechanism leading to diabetes and concluded that the underlying obesity and hyperphagia could be related to a genetically determined hypothalamic disturbance (5). Saul followed this work with an examination of exposure to high-fat and high-carbohydrate diets on the development of obesity in this mouse model and showed that the combined exposure to carbohydrate and fat in the diet led to the greatest amount of obesity (6).

In parallel with these animal studies, Saul performed a series of prescient studies that examined the effects of different physiological and pathological states on insulin secretion in humans. He showed that the alterations of plasma insulin in type 2 diabetes were likely due to a defect in insulin secretion

rather than in the metabolism of insulin (7). As very low–calorie diets were then being tested to treat severe obesity, he took advantage of this approach to compare the effects of starvation states on insulin secretion in obese individuals with and without diabetes (8).

One of the most memorable and insightful studies that Saul published on the pathogenesis of type 2 diabetes was a case study that followed the course of an obese patient with diabetes as she lost and then regained weight (9). Saul's careful measurement of her glucose tolerance and insulin secretion during her clinical course clearly and succinctly demonstrated the primacy of deficient insulin secretion in the pathogenesis of type 2 diabetes. From these animal and human studies Saul advanced our understanding of the mechanisms underlying the development of type 2 diabetes.

Saul's research interests broadened as his practice grew and he became increasingly involved in teaching medical students and house officers. These led to systematic research, clinical observations, and case reports that spanned a wide range of endocrine problems, such as aldosterone secretion in anephric patients (10), osteomalacia accompanying long-term anticonvulsant treatment (11), and hypoparathyroidism and Paget disease (12).

He also turned his attention to an entirely different and pragmatic challenge that anticipated the late 20th century epidemic of type 2 diabetes: the problem of identifying people in the community with unrecognized disease. In one of the best evaluations of the utility of mass, or untargeted, screening for diabetes, he and his collaborators carried out a longitudinal follow-up study to examine the value of using 2-h post-Glucola capillary blood glucose determinations to predict development of diabetes (13). When retested 5 years after initial screening, they showed that people who had an initial positive screen (2-h value greater than 140 mg/dL) had a 22-fold increase in relative risk for diabetes in comparison with those who screened negative at baseline. However, about one-half of the positively screened individuals retested negative at the 5-year follow-up. They concluded that mass screenings were of limited value and "future programs should be directed at targeted populations to improve individual and public benefits" (13).

A TURN TO TYPE 1 DIABETES: THE DIABETES CONTROL AND COMPLICATIONS TRIAL

By the mid-to-late 1970s, Saul's interests had turned to insulin secretion and the chronobiology of normal β-cell function. The clinical question was whether more physiological insulin delivery in insulin-deficient patients would result in better metabolic outcomes. By applying new insulin delivery techniques "to mimic the time course of natural insulin in response to meal ingestion in normal subjects" (14), he examined whether this approach could induce at least a temporary remission (15). His exploration of new methods for insulin delivery was timely as interest in preventing the long-term complications of diabetes through improved blood glucose control, the "glucose hypothesis," was growing. Moreover, new methods of assessment and treatment made a large clinical trial feasible. These included the advent of self-monitoring of blood glucose methods, the newly developed glycated hemoglobin assay to reliably and objectively measure glycemia over time, the use of fundus photography to assess retinopathy, and new methods to control glycemia more physiologically. The question became "Would long-term improvement in glycemic control alter the course of complications?" Saul's original focus was not on type 1 diabetes as a clinical or research problem, so when the National Institutes of Health announced a new clinical trial to test the glucose hypothesis, he concluded that he did not have a relevant population for the trial and would not apply. But chance intervened when Bill Dahms, his younger pediatric endocrine colleague in Cleveland, thought they should team up and engaged Saul in writing the grant application together. They were successful and Case Western became one of the initial groups involved in planning and implementing what came to be called the Diabetes Control and Complications Trial (DCCT).

Saul's intellect, experience in clinical research, and quietly thoughtful mien made him a persuasive consensus builder and he became one of the key leaders of the study. Oscar Crofford, the study chair, sought his counsel and nominated him as vice-chair of the study group. Saul also served as the chair of the treatment committee, charged with designing the "experimental" and "standard" control arms of the study.

Unexpectedly, the greatest challenge for Saul and his committee was not the development of the experimental, later to be called "intensive," intervention, but of the control intervention. It was clear from the outset that neither the study investigators nor participants could be masked to treatment assignment for practical reasons. The challenge in the design of the standard treatment was to provide a therapy that was ethically acceptable and safe, provided a facsimile of conventional care in the community, and would maintain a higher level of glycemia over time than in the experimental group.

Saul and the treatment committee were concerned about the potential for downward drift in glycemia in the standard treatment group. Self-monitoring of glucose and even insulin pump use were becoming increasingly popular. Would it be possible to withhold information regarding glucose testing results from the standard treatment participants? If the DCCT standard group participants or the DCCT clinicians had the A1C results, would they act on them and reduce the differences in glycemia between the two treatment groups?

Community practice at the time was to treat patients with diabetes to minimize clinical symptoms. Saul reasoned that as long as clinical symptoms of hypoglycemia and hyperglycemia were minimal, standard group participants and clinicians could be masked to both A1C and blood glucose levels. Thus, the treatment committee, under Saul's leadership, opted to mask the standard group to their glycemic levels, unless symptoms of poor control were present or a safety threshold was reached. The safety threshold would be two standard deviations above the 9% mean, which was established in a pilot group of patients with type 1 diabetes treated with standard therapy. The two standard deviation safety threshold used throughout DCCT was 13%, a value that was acceptable at the time as the importance of tight control had not been established outside of pregnancy.

The decisions by Saul and the treatment committee regarding the components of standard therapy were important elements in the success of

the DCCT. A difference in A1C was maintained over the full course of the study, with the experimental group achieving a mean of ~7% and the standard group 9%. Saul always credits the volunteer participants for the success of the study and notes that their dedication was essential. However, without the expert and motivated clinic teams, including physicians, nurses, dietitians, and behavioral specialists, providing support to and bonding with the participants, the study would not have succeeded.

When the DCCT ended in 1993, the core results were published and the study has become the most widely cited diabetes trial in history (16). "Intensive" therapy has been adopted worldwide as the standard of treatment for people with type 1 diabetes.

THE EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS STUDY

At DCCT end, consideration was given to continuing follow-up of the participants as potentially important questions remained. However, the challenges of an extension study were formidable. Moreover, there were few models available for trials turned into observational studies on which to base the DCCT follow-up. A careful rationale and plan was required. Saul led the effort in devising that rationale, which was focused most directly on whether the salutary effects of intensive versus conventional therapy on relatively early-stage complications during the DCCT would translate into a beneficial effect on more advanced complications and cardiovascular disease. Acceptance of this logic and the recognition of the success of the DCCT led to the Epidemiology of Diabetes Interventions and Complications (EDIC) study.

With Oscar Crofford's retirement, Saul assumed the role of co-chair (with David Nathan) of the EDIC study. Saul's leadership encouraged scientific excellence, a collaborative environment both within the study group and with external investigators, and, above all, respect for the participants. After more than 250 publications, including the recent summary articles published in *Diabetes* and the special DCCT/EDIC 30th anniversary *Diabetes Care* issue, the imprint of DCCT/EDIC on the modern-day treatment of type 1 diabetes is indelible (17–22). Saul has promoted and helped guide the development of a large number of ancillary studies, including epigenetic evaluations to understand the mechanisms of metabolic memory, detailed examination of lipid profiles to evaluate factors related to cardiovascular outcomes (23), cognitive follow-up to determine if hypoglycemia posed a long-term risk to brain function (24), and the assessment of urologic complications of type 1 diabetes (25), among others.

TEACHER, CLINICIAN, AND RESEARCHER

Saul is the classic academic—devoted to the three components of that role: teacher/mentor, clinician, and researcher. At the medical school, he led the teaching of endocrinology and metabolism. He also chaired the faculty Committee on Medical Education, which has overall responsibility for the entire 4-year curriculum. As a teacher, he has been devoted to his students and fellows. He has always worked closely with them with an open door and one-on-one meetings that were never rushed. He has taken particular interest in guiding annual fellow grand rounds presentations by carefully going over the selected topic, the questions that needed to be addressed, and detailed reviews of the slides and approach to the presentation. While he carefully scrutinized the fellows' work, it was never done with a judgmental or heavy hand, rather with a shared interest in learning from each encounter. He has been a great listener in these interactions, using the time to lead students carefully through the problem at hand so that the sessions often feel more like peer-to-peer learning rather than from a boss. His queries reflect his considerable knowledge base and are thought-provoking. His focused interest in his students makes them want to do better and use the constructive and detailed feedback as part of a learning journey.

As a clinician, he has practiced patient-centered personalized medicine long before it became a buzz word. Like his students, his patients respect him for the same unrushed approach. His inquisitive nature and approach to learning infuse his approach to patient care.

SERVICE

Saul continually gives back to his students, colleagues, and the field of diabetes through his knowledge, service, and leadership. He has served as an ad hoc member on the American Diabetes Association's Scientific Program, Research Grant Review, and Diabetes Physician Recognition Program committees. Government health agency activities include chair of the Data Monitoring Board for the Diabetes Prevention Program and the National Diabetes Advisory Board to Congress, as well as ad hoc member of the Metabolism Study Section of the National Institutes of Health. He also co-chairs the EDIC study. Saul has served on the editorial board of *Metabolism* and has been a reviewer for numerous medical and scientific journals, among them *Archives of Internal Medicine*, *Diabetes*, *Diabetes Care*, *Diabetologia*, *Journal of the American Medical Association*, *Journal of Clinical Endocrinology & Metabolism*, *Journal of Clinical Investigation*, and *The New England Journal of Medicine*. Saul's work earned him the 1992 American Diabetes Association's Outstanding Physician-Clinician Award.

SUMMARY

Saul Genuth, MD, represents the best of the tradition of academic physician by combining the skills of a researcher, clinician, and teacher. In addition to his personal research program, he has taken on major leadership responsibilities in guiding the DCCT and EDIC studies over the past 30-plus years. He has provided leadership, quietly and thoughtfully, making wise decisions that have stood the test of time.

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