PROFILES IN PROGRESS

Guenther Boden, MD (1935–2015): A Pioneer in Human Studies of Nutrition and Obesity—And the Mystery of Insulin Resistance for Handling Glucose

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Diabetes Care 2020;43:2910–2915 | https://doi.org/10.2337/dci20-0041

Professor Guenther Boden, MD, was drawn to the field of diabetes research through an unconventional route, but in that journey he brought a perpetually fresh set of eyes to help unravel the relationships between nutrition, obesity, and defects in insulin action.

Early Life

Guenther Boden was born on 8 January 1935 to Dr. Alwin Boden, an internist who practiced from a home office, and Irma Boden (*née* Godelmann), a homemaker who had trained as a medical technologist. During his early years, the family lived in Ludwigshafen am Rhein, an industrial city in southwestern Germany. The place and time would leave Guenther with vivid memories of a childhood spent during, and immediately after, World War II.

Guenther once wrote that when Allied bombing of key industrial sites in Ludwigshafen began, the bombs were, from an 8-year-old child's perspective, "more a matter of excitement than threat for me[,] and together with my friends, we would rush out of the cellar after the air raids to look for bomb shards, which we boys considered a valuable collection item. This lost much of its attraction as the air raids became more frequent. . . ." When his father was drafted as a medical officer in the *Luftwaffe* (Air Force), Guenther's mother took him and his two sisters to the relative safety of her parents' home in Heidelberg.

Early life promoted an independent spirit, a healthy skepticism of authority, and remarkable resourcefulness. Rough lessons came at a personal level, from the "sadist" who taught his 3rd and 4th grade classes—using frequent corporal punishment—and from Guenther's childhood experiences of hunger—today called food insecurity. Hard lessons also came from learning of the genocidal war criminals in the Nazi government who had ruled his birth country.

Guenther often told the story of an episode during World War II when his paternal grandfather, Dr. Alois Boden, also a physician, took his young grandson on a house call to see a patient on a nearby farm. At that time, food was rationed, and if you got caught with extra food, you were in serious trouble. The farmers often paid the doctor with food rather than money. That particular time, his grandfather was paid with half of an old sheep or mutton. On the way home, it was already dark. *Opa* (Grandpa) Alois, was trying to keep a low profile with his illegal treasure in the trunk. He drove his old car with the lights turned off along the winding country road toward home. But there was a mechanical problem with the car horn. Every time they made a right turn, the horn honked. Both were sweating

A delighted Guenther Boden in ski gear, Elk Mountain, PA, 1980

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Young Guenther Boden with mother Irma and two sisters, Marianne and Ilse, in Dürkheim, Germany, 1950

blood and tears during that journey. They eventually made it home safely without being caught, and, for over a year, this mutton was served for meals. This is why Guenther never ate lamb afterward, even though lamb never tasted like mutton. Perhaps he just did not want to be reminded of those sad and horrible times.

Looking back, Guenther felt fortunate under the circumstances that Heidelberg was occupied by the Americans, not by the Soviets, and so Guenther began to take English lessons. Years later, he wrote, "My first words were: 'Give me chocolate, please!' I practiced my English with GIs [American soldiers] . . . . I occasionally stole cigarettes and oranges from them. Cigarettes in particular were the only currency. . . . I was 10 years [old] at that time."

In Kaiserslautern, near Ludwigshafen, Guenther attended high school—*Gymnasium* in German—which brought formal instruction and an emphasis on science, meaning biology, chemistry, and physics. Guenther was also on the track and field team and remained athletic his entire life, skiing into his late 70s. In the German system, medical school begins with preclinical studies right after high school. Guenther attended the Heidelberg University School of Medicine for his master's degree and then the Munich University School of Medicine for his MD. Years later, Guenther remembered, "Because Germany had eliminated the death penalty, there was a shortage of cadavers and we had to autopsy a deer to learn anatomy," (K.J.W., personal communication).

Early Career in Medicine and Research

After final exams in medical school, Guenther trained in a series of different specialties: 4 months as a surgical assistant (passing out once from an ether leak during anesthesia of a patient), 6 months in internal medicine, 4 months of obstetrics and gynecology, and then, in 1961, 6 months of inpatient psychiatry in Berlin. Guenther wrote that he had "witnessed the building of the [Berlin] Wall, right in front of my room . . . . As a west German, I could pass through the Wall and did visit . . . . After dinner one night [in the eastern sector], I crashed my 2CV ['*deux chevaux,*' a popular small, inexpensive Citroën automobile] into the Wall from the east. The police let me go. [It was noted] in the west newspaper as another unsuccessful effort to flee."

At that time, Guenther's wish was a career in psychiatry/neurology, and he landed a position in Munich. Unexpectedly, "this became so boring that I quit after 2 months. To finish my 24 months of mandatory [medical internship time], I found a job at the *Hautklinik* (Dermatology and Venereology) in Stuttgart."

In 1963, an opportunity opened up by chance at the Biochemistry Institute of Tübingen, Germany, owing to the departure of one of their young researchers. Guenther obtained his first position to study metabolism, specifically, the effects of insulin. He would remain with the topic for the rest of his life.

Before Yalow and Berson's radioimmunoassay (1,2), the only way to assay insulin concentrations was by bioassay, using the responses of rat diaphragms and epididymal fat ex vivo. A prominent professor at the Biochemistry Institute had developed a tripeptide that seemed to be equally as effective as insulin. This tripeptide looked like a possible answer to concerns that clinical demands for injectable insulin would outstrip the supply from pigs and cattle. Diligent from the start, Guenther Boden could not reproduce the results—and later discovered that a technician had added bicarbonate to the buffer to help dissolve the tripeptide. "The entire insulin-like effect of [the tripeptide] was due to the bicarbonate. (H. Krebs had described this bicarbonate effect in the 1920s)," Guenther later wrote.

Early Career in the U.S.

In 1965, Guenther was recruited from Tübingen to the Joslin Research Laboratory in Boston, Massachusetts. His wife Irene (*née* Dingeldein) recalls Guenther telling her later that he had applied to several research institutions in the U.S. Guenther sent a letter directly to Dr. George Cahill, a pioneer in diabetes research and then the research director of Joslin, even offering to work for free. His letter to Cahill and the favorable response he received are still in the possession of the Boden family.

Among Guenther's early work there, he and his coauthors published the first report of the glucose suppression test for the diagnosis of acromegaly, using what was then state-of-the-art technology of a new radioimmunoassay for human growth hormone (3).

Guenther then had to move to Rochester, New York, to complete his clinical training, from 1967 to 1970, as a medical resident at Rochester General Hospital. While in Rochester, Guenther met his wife, Irene. Irene recalls, "I, at that time, lived with relatives in Rochester and worked in the biochemistry lab at the hospital. When Gertrud [his long-time lab technician] left, she [Gertrud] suggested

Guenther Boden in 1965, the year he came to the U.S.

The Temple University Section of Endocrinology, Diabetes and Metabolism, 2013. Left to right, front row: Dr. Elias S. Siraj, Dr. Kevin Jon Williams (succeeded Dr. Boden as Section Chief), Dr. Victor Adlin, and Dr. Guenther Boden; second row: Dr. Ajay Rao, Dr. Cherie Vaz, Dr. Vijay Balakrishnan (clinical fellow), Dr. Dan Rubin; third row: Dr. David Ni, Dr. Tatiana Gandrabura (clinical fellow), Dr. Pankaj Sharda (clinical fellow), nurse practitioner Victoria (Tori) Maffey (not pictured: Dr. Carol Homko)

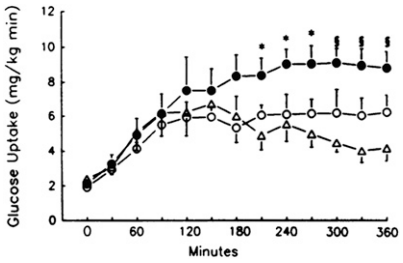
to Guenther to ask that 'German girl' in the biochemistry lab, if she wanted to work for him. So he did, I worked for him and eventually after three years we married."

In 1970, after completing his clinical training in the U.S., he accepted a position at Temple University in Philadelphia, Pennsylvania, where he remained for the rest of his career. At Temple, Boden combined his three professional passions—namely, the clinical care of patients with diabetes, research into the causes of diabetes, and teaching generations of physicians and scientists. The major focus of his research was why overeating and obesity cause insulin to lose its ability to control the level of glucose in the bloodstream. It is a huge medical problem, and Guenther made major contributions to our understanding of this problem.

He became Director of the Diabetes Outpatient Clinic at Temple (1975), then Chief of the Section of Diabetes (1978–1987), Chief of the newly merged Section of Endocrinology, Diabetes and Metabolism (1987–2009), and Program Director of the General Clinical Research Center (1989–2003). He also became a proud American citizen.

During his long tenure at Temple, Guenther worked with a team of endocrinologists and diabetologists consisting of Drs. Charles Schumann, Bertram Chanick, Alan Marks, and Victor Adlin, a partnership that lasted for more than 35 years, which was an unusually successful and durable collaboration for such a large group. It was also during this era, in 1973, when Guenther met one of authors of this article (E.S.H.) at a diabetes conference in Snowmass, Colorado. They shared common interest not only in diabetes research but also skiing. This started a long-standing friendship, both professionally and between their families.

Guenther had come to Temple University in large part out of respect for two greats: Dr. Oliver Owen, a distinguished diabetes researcher who at that time was the Director of the General Clinical Research Center at Temple, and Dr. Sol Sherry, the great thrombosis researcher who at that time was Chairman of the Department of Medicine at Temple and whose work led to the development of thrombolytics. Guenther collaborated with Dr. Owen in his research, including their description of the effect of glucagon in healthy human volunteers to alter amino acid metabolism through "increasing their inward transport, their degradation, and their conversion into glucose" (4). From a collaboration with



*Effects of three steady-state levels of plasma NEFAs (~50, 550, and 750 μmol/L) on rates of glucose uptake in healthy volunteers during euglycemic-hyperinsulinemic clamping. Plasma NEFA levels were increased by intravenous infusion of a 20% triglyceride emulsion, without or with heparin to release lipoprotein lipase into the circulation to rapidly hydrolyze the triglycerides. Indicated are low (filled circles, n = 6), medium (open circles, n = 4), and high NEFA concentrations (open triangles, n = 4). Shown are mean ± SE. Comparison of individual time points: *P < 0.05, §P < 0.01, comparing filled circles vs. open triangles. Reproduced from the top panel of Fig. 3 in Boden et al. (8), with permission.*

Dr. Alan J. Garber, who was training at Temple University at that time, came another seminal article from that era, in which they directly measured the increase in hepatic ketogenesis and gluconeogenesis in humans undergoing a 3-day fast (5).

Key Studies in Human Volunteers: Coagulation in T2DM, Fatty Acids, and Satiating Power Per Calorie

Guenther also successfully collaborated across disciplines at Temple. Of particular note are his more than 10 years of National Institutes of Health–supported work with Dr. A. Koneti Rao, a prominent researcher in thrombosis. Together, their laboratories focused on the effects of hyperglycemia and hyperinsulinemia, in healthy subjects and in subjects with diabetes, on prothrombotic and immunostimulatory mechanisms, particularly the tissue factor pathway of coagulation. One of their important findings is their description of activation of blood coagulation mechanisms and platelets by combined hyperglycemia-hyperinsulinemia even in healthy human subjects without diabetes (6). The work provides a mechanistic basis for the well-known hypercoagulable state in type 2 diabetes.

During this time, Guenther's laboratory made several additional seminal observations. Perhaps the most influential finding from the Boden laboratory was when they became the first to demonstrate that elevated plasma levels of nonesterified fatty acids (NEFAs, also known as free fatty acids) produce peripheral resistance to the glucose-lowering actions of insulin (7–9). Moreover, the Boden laboratory found that lowering of chronically elevated plasma NEFAs in obese patients with either impaired glucose tolerance or frank diabetes was able to substantially, though only partially, improve sensitivity to the glucose-lowering actions of insulin (10). These results have since been widely confirmed and suggested that elevated circulating NEFAs may account for up to 50% of insulin resistance for handling glucose in obese patients with impaired glucose tolerance or type 2 diabetes. An additional contributor to impaired insulin action that they found in humans is the ability of hyperinsulinemia to induce endoplasmic reticulum stress, also known as the unfolded protein response (11).

Drawing on his early training in obstetrics, Guenther performed seminal studies of carbohydrate metabolism during and after pregnancy and the relationship between NEFAs and insulin resistance for handling glucose in obese women during pregnancy (12,13). These studies in the 1990s began a long-term partnership with Dr. Carol Homko, a nurse-PhD who was an expert in patient-oriented research and became a prominent leader in the American Association of Diabetes Educators (now known as the Association of Diabetes Care & Education Specialists). In 2000, Guenther formally recruited Carol to become the Nurse Manager of Temple's General Clinical Research Center, and the two of them coauthored over 30 articles together, all on research in humans. Their partnership lasted two decades, throughout the rest of Guenther's life.

Another research area of Guenther's was the relationship between nutrition, insulin action, and body weight. In a major publication in 2005, his team

The Boden family in America. (Left panel) Proud parents, their four children, spouses, and the first five grandchildren, on the beach, August 2012; top row: Guenther, Irene, Liz, Eric, Dirk, Amie, David, and Kevin; bottom row: Stephanie, Elisabeth, William, Andrew, Abbie, and Karin. (Right panel) The happy couple dancing: Mrs. Irene and Dr. Guenther Boden at the wedding of son Eric and daughter-in-law Liz at the Hotel Du Pont, Wilmington, DE, September 2009

addressed a mystery that was poorly understood at the time: how does a low-carbohydrate diet, such as the popular Atkins diet, cause people to lose weight? There were at least four different mechanistic explanations, including the leading idea of "different utilization of calories [meaning] that people on low-carbohydrate diets can eat more calories than people on high-carbohydrate diets and still lose more weight" (14). But the leading idea was wrong. By placing human volunteers with obesity and type 2 diabetes on different diets that were available ad libitum in his inpatient metabolic unit, Guenther and his research group demonstrated that people on the low-carbohydrate diet freely "chose" to eat about 1,000 kcal less per day, and this effect on intake "completely accounted for" the weight loss (14). The low-carbohydrate diet had no effect on energy expenditure. Despite the large drop in daily caloric intake, the low-carbohydrate diet also had no significant effects on "feelings of hunger, satisfaction provided by the diets, feelings of comfort or discomfort, [or] energy levels" (14).

During just 2 weeks on the low-carbohydrate diet—and reduced caloric intake—the volunteers' 24-h glucose profiles, insulin resistance for handling glucose, plasma triglyceride concentrations, and even hemoglobin A_{1c} levels all improved. That work proved Guenther's favorite phrase, "calories in, calories out," indicating that what mattered in weight management was the caloric amounts consumed and burned, not necessarily the source of the calories. Most importantly, the Boden group had shown that some calories are more satiating than others (14), a crucial finding that has withstood the test of time (15) and continues to have broad implications for individual and population health.

A few weeks before his death, Guenther published new research indicating how normal, healthy volunteers who overeat for just a few days already show signs of impaired insulin action (16).

A major strength of Guenther's work was that he conducted most of his investigations in human volunteers, meaning that his findings were directly relevant to patient care. He specifically disliked the use of imperfect—and therefore often misleading—animal models. "Are we mouse doctors?" he asked.

Colleagues, Friends, Trainees, and Family

Since 1982, Guenther was an elected member of the prestigious Interurban Clinical Club, founded by Sir William Osler in 1905 to encourage dialogue and exchange among academic physician-scientists in Baltimore, New York, Boston, New Haven, and Philadelphia. The Club meets twice a year, and its mission is to support collegial interactions that promote shared goals including state-of-the-art, high-impact biomedical research and the training of physician-scientists.

In 2006, Guenther recruited one of the authors of this article (E.S.S.) to come to Temple and serve as a clinical diabetes researcher and Endocrine Fellowship director. Having trained in Germany, Elias had an immediate connection with Guenther, and Guenther greatly influenced Elias's subsequent approach to diabetes research and teaching of fellows.

In 2009, another author of this article (K.J.W.)—also formerly a student in Germany—was recruited to Temple to succeed Guenther as a Chief of the Section of Endocrinology. As he took over the Section, some higher-ups pulled Kevin Jon aside to warn him about Guenther's "strong personality"! But the two men hit it off immediately and became great scientific partners and coauthors. Their professional and personal associations continued throughout the rest of Guenther's life, including riding ski chairlifts together, often with Ed Horton, while discussing insulin.

Another highlight of Guenther's career is his impact on students and trainees at Temple, many of whose names can be found on his scientific publications. With his enthusiasm for teaching and his knack at describing complex concepts in a straightforward way, his impact was profound. He always promoted scientific discourse at all levels. Guenther did not care much about long administrative meetings, but the moment a scientific concept was raised he immediately became animated. Science, in and outside of medicine, continued to be source of fascination for Guenther until his death.

We will sorely miss Guenther—his deep insights, sharp wit, decency, and generosity. Guenther did indeed have a strong personality—and no tolerance for nonsense. And "nonsense" was the mildest word we ever heard him use for foolish things that he did not like.

He was a risk-taker in his professional life, but personally and politically conservative. "A capitalist without capital," he described himself. Guenther had the old-fashioned passion for medicine as a calling—a profession, not just a trade—and he inspired the rest of us.

Our thoughts are with his wife, Irene, their four children and 10 grandchildren, and the rest of the Boden family.

Acknowledgments. The authors would like to acknowledge and thank Mrs. Irene Boden, the wife of the late Dr. Guenther Boden, for giving them a more complete picture of his early life and for sharing his photographs and other original documents. The quotations from Dr. Boden come from notes he wrote during the last 3 months of his life that were provided to K.J.W. courtesy of the Boden family. The authors are also indebted to Dr. A. Koneti Rao, a friend and collaborator of Guenther's at Temple University, for insights he gave regarding Guenther's long professional career at Temple. They also thank Dr. Victor Adlin of Temple University for sharing information regarding the early days of Guenther at Temple University.

Duality of Interest. K.J.W. reports an ownership interest in Hygieia, Inc., and in Gemphire Therapeutics, Inc., and has served on the Medical and Scientific Advisory Board of Gemphire Therapeutics, Inc. Over the last 12 months, E.S.S. has served as a consultant and speaker for Novo Nordisk, Boehringer Ingelheim, and Eli Lilly, all in the area of diabetes management. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. K.J.W. and E.S.S. wrote the original draft of the manuscript. E.S.H. reviewed and edited the manuscript.

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