John E. Gerich: Father of Modern Physiology of Glucose Homeostasis, Counterregulation to Hypoglycemia, and Mechanistic Treatment of Diabetes

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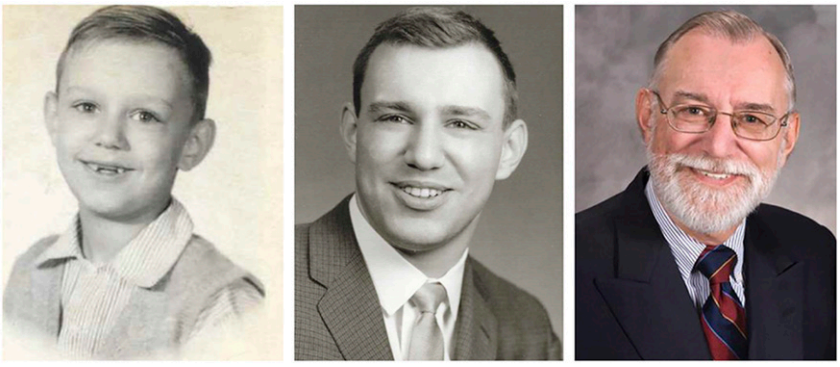
PROFILES IN PROGRESS

When the letter from *Diabetes Care* arrived inviting me to write a Profile in Progress on John Edward Gerich (Jack, to his friends), I assumed it was because of my long-term research association and friendship with him. I felt, in a way, like a dwarf asked to report on a giant standing in front of me. After initial hesitation, I decided to accept this challenging task to acquaint younger professionals who do not know Jack Gerich with what kind of scientist—and also what kind of man—he is. To ensure that my narrative did not miss any aspect of his extraordinarily large and multifaceted research, I consulted with several of his former fellows who had been associated with him and contributed so much to the golden era of clinical research in metabolism over the last few decades.

My interest in Jack's work started in 1979 when I came across his legendary paper in the *Journal of Clinical Investigation* on the relative roles of glucagon, catecholamines, and growth hormone responses in glucose counterregulation to acute, insulin-induced hypoglycemia (1). At that time, in my small laboratory in Perugia, Italy, I was able to measure plasma glucagon, catecholamines, and other counterregulatory hormones during hypoglycemia experiments in humans, but I had no idea how to plan, organize, and critically interpret solid mechanistic studies. The concept of glucose turnover, the rates of appearance and disappearance of glucose, as described in Jack's paper (1), were for me at the same time interesting, totally new, and quite mysterious. So, when I received the positive response letter from Jack accepting me as a fellow in his lab in Rochester, Minnesota, my attraction toward Jack became a love, and it has remained so ever since. It was a cold and snowy March in 1982 when I first joined Jack under the Fulbright Program. The world-famous Minnesota winter was not a barrier for me. I enjoyed Jack's lab, full of international fellows, all friendly and proudly busy at their basic and clinical research. Jack discussed several clinical projects with me, and soon I, too, became quite busy conducting clinical studies and collecting results. At lab



John "Jack" E. Gerich as a young child (left panel); at graduation from medical school, age 26 (middle panel); and at present (right panel).

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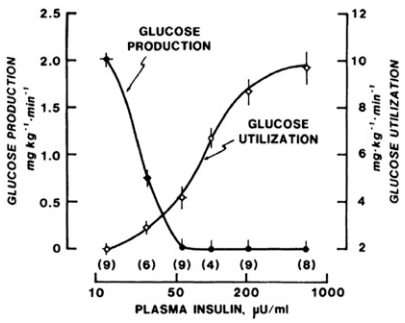
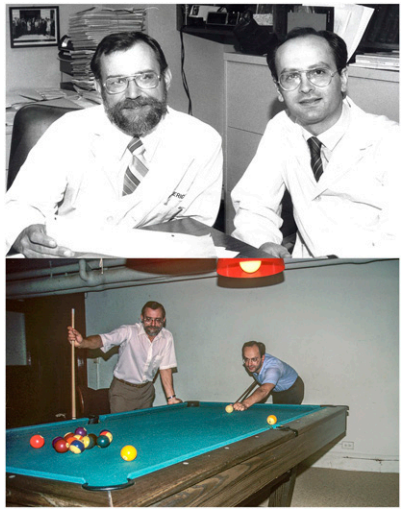
meetings I benefited from critical comments about my preliminary results from Jack's colleagues Robert Rizza, Morey Haymond, John Service, and John Miles, all of whom were at that time at the Mayo Clinic Endocrine Research Unit. Research enthusiasm was high. The data obtained from one study called for additional studies, and the answer to one question immediately led to another. Jack emphasized writing up completed studies in a timely manner while the data were still fresh, telling fellows "G.I.O." (Get It Out), i.e., write the paper and submit it to a journal within a few days after the final results from the lab were available. To speed up the process of writing papers, Jack would have me, and subsequently other fellows, visit his home in the evening after finishing work at the lab. After a short respite and a few relaxing games of pool in his basement, we would spend several hours before and after dinner working on papers. In addition to actually writing a paper, Jack did the statistical calculations and drew the figures. In the era before computers, he would work hours with a pencil on graph paper to compose, erase, and redraw again and again classic teaching figures. In another room, his wife Donna and later his son Mark patiently created the final figures as ink drawings copied exactly from the pencil proofs and enriched by the addition of transfer-type symbols and characters. The graph shown is one example, among many others, of his scientific communication through a clear, elegant figure that is easy to interpret. Around midnight, after having smoked several cigarettes (sometimes many!) and enjoyed an additional game of pool, our day would finally be over. All this intense



Original graph, hand drawn by John and completed by his wife, is a classic teaching example of the insulin dose-response curve. Printed with permission of the American Journal of Physiology *(6).*



Top: Jack writing papers with one of his fellows (author Geremia Bolli) at the Mayo Clinic. Bottom: Jack and the author playing a game of pool in Jack's basement.

interaction between Jack and his fellows underlay the dozens of papers that appeared in a short time period in the '80s and '90s. This was not only my experience as a fellow but also that of many others in the lab. When I left Jack's lab 2 years later, a large volume of data from our clinical studies was still waiting to be written up and published. I went back each summer for several years to visit Jack (in Rochester, MN, Pittsburgh, PA, and La Jolla, CA, where he had moved) and to finish our papers.

This is my personal experience as a fellow working with Jack, but Jack has had nearly 50 fellows over the years (see Table 1), and his interaction with them was as active, as productive, and ultimately as successful in their different areas of research as his interaction with me. Jack often told me that his scientific legacy would be his fellows rather than his research. As a testimony to this concept and his devotion to them, his former fellows have achieved remarkable academic successes. Many are professors of medicine: Robert Rizza (who became President, Medicine and Science, of the American Diabetes Association [ADA] and received the 2010 ADA Banting Medal for Scientific Achievement), John Miles, Asimina Mitrakou, Marian Mokan, Walkyria Pimenta, Timon van Haeften, Trond Jenssen, Christian Meyer, and Michael Stumvoll, among others.

Today, Jack Gerich has more than 500 publications, 286 of which are indexed in PubMed. His record year was 1984, when 24 PubMed papers were published. Much of what we know today of the physiology of glucose homeostasis, lipid metabolism, glucose counterregulation to hypoglycemia and its abnormalities in diabetes, and the relative role of liver, adipose tissue, muscle, and kidney in glucose metabolism is the result of Jack's work over several decades. He is currently Professor Emeritus of the University of Rochester (New York).

John E. Gerich was born on 22 September 1943 in Nutley, New Jersey, the son of an accountant and a bookkeeper. He attended a local Catholic grammar school (St. Mary's) and subsequently a Jesuit high school (Saint Peter's Prep) in Jersey City. There he specialized in languages and took no science courses. Scholarships that he received allowed him to become the first in his family to go to college. His family encouraged him to become a doctor. Accordingly, when he went to Cornell University in Ithaca, New York, he took the science courses required by medical schools but majored in classics (Latin and Greek) and signed up for as many humanities courses as he could, reasoning that, as a doctor, he would be exclusively reading scientific literature. (He advised his twin sons, Mark and Brian, to do the same, believing that a liberal education background would enrich their lives.) Jack almost went to law school instead of medical school. He had applied to both, but before taking the test for law school he played poker all night and won much more than he needed to take the law test the next day. Even today, Jack believes this must have been a divine sign to go to medical school. Jack received his MD and did residency training in internal medicine at Georgetown University.

His initial goal in medicine was to be a family doctor in private practice, like the one who lived across the street from his family. But just before starting medical school, Jack's father died and this placed financial constraints on his options. Consequently, to augment his loans and scholarships, he worked during medical school on faculty research laboratory projects. His fascination with lectures on diabetes and ketoacidosis led to his conducting research as an intern on the pathogenesis and treatment of hyperosmolar nonketotic coma. He collected and treated cases, working during his elective at the local Veterans Affairs

Table 1—List of research fellows supervised by John Gerich

Mara Lorenzi, MD	1972–1975
John Davis, MD	1975–1977
Robert Rizza, MD	1977–1980
John Miles, MD	1980–1982
Carlos Verdonk, MD	1980–1982
Lawrence Mandarino, PhD	1980–1983
Karl Mackes, MD	1980–1981
Gerard Reach, MD	1980–1981
Mitsuyasu Itoh, MD	1980–1982
George Dimitriadis, MD	1981–1984
Barbara Baker, MD	1982–1983
Greg Pehling, MD	1982–1983
Frank Fisher, MD, PhD	1982–1983
Irving Gottesman, MD	1982–1984
Geremia Bolli, MD	1982–1984
Christine Pellisard Martin, MD	1983–1984
Peter Campbell, MD	1983–1985
Frank Kennedy, MD	1984–1985
Emmanuel Opara, PhD	1984–1985
Mustafa Kutlu, MD	1984–1986
Timon van Haeften, MD	1984–1985
Asmina Mitrakou, MD	1985–1988
Agostino Consoli, MD	1985–1988
David Kelley, MD	1985–1986
Linda MacGorman, MD	1985–1986
Louise Lecavalier, MD	1985–1986
Nurjahan Nurjhan, PhD	1985–1990
Trond Jenssen, MD	1987–1988
Margrit Shoemaker, MD	1987–1989
Wayne A. Evron, MD	1988–1989
Marian Mokan, MD	1989–1991
Thiemo Veneman, MD	1991–1993
Walkyria de Paula Pimenta, MD	1991–1993
Arthur Bucci, MD	1991–1992
Paul S. Strumph, MD	1991–1992
Gabrielle Perriello, MD	1992–1993
Per-Andres Jenssen, MD	1992–1993
Michael Stumvoll, MD	1993–1995
Veena Nadkarni, MD	1994–1997
Christian Meyer, MD	1995–1998, 2000–2002
Jean Dostou, MD	1996–1998
Nazmul Islam, MD	1998–2000
Juergen Woerle, MD	1999–2001
Emilia Popa, MD	1999–2001
Niyaz Gosmanov, MD	2001–2004
Ervin Szoke, MD	2002–2004
Regina Dodis, DO	2004–2006
Antoni Gofron, MD	2004–2006
Muhammad Shrayyef, MD	2006–2008
Ajikumar Aryangat, MD	2007–2008
Mazen Alsahli, MD	2008–2010

hospital on in vitro studies of rat adipose tissue, liver, and pancreas. These studies led to the publication of two papers in *Diabetes*. As a result, Jack received a fellowship with Peter Forsham, Gerald Grodsky, and John Karam at the University of California, San Francisco (UCSF). More importantly, because of this lab experience, he strove to mimic the rigor of laboratory experiments in his approach to clinical research, specifically designing clinical studies to minimize extraneous variables by doing paired studies where each subject served as his or her own control, and meticulously matching experimental and control groups. Another point that Jack learned, and endeavored to teach his fellows, was to design studies to yield a "yes" or "no" answer to an explicit hypothesis. He often asked his fellows who proposed a study, "What's the question?" He believed that once the question was defined, the optimal experimental design would become readily evident.

Among his several awards and honors, Jack has delivered the Lilly Lecture (1988) and received the Rolf Luft Award (1990) and the Novartis Prize for Long-standing Achievement in Diabetes (2007). Prior to retiring and becoming Professor Emeritus, Jack served as Program Director of the National Institutes of Health–funded Clinical Research Center at the University of Rochester (New York) and was an active faculty member of the university's Clinical and Translational Science Institute.

The major contributions of Jack Gerich in scientific research can be summarized in four areas.

The Counterregulatory Hormones

Jack took advantage of the newly discovered hormone somatostatin for his research. At that time somatostatin became available in Dr. Peter Forsham's unit at UCSF as a gracious gift from Roger Guillemin. Using it to inhibit glucagon secretion, Jack made several original observations about the role of glucagon in causing hyperglycemia in humans with diabetes, in causing the metabolic abnormalities of ketoacidosis, and in defending against hypoglycemia. In 1973 his landmark original discovery of deficient glucagon response to hypoglycemia in people with type 1 diabetes was published in *Science* (2). He showed that the defect was selective for glucose, since the response to amino acids was preserved.

This early observation has been pivotal to the subsequent understanding of the risk of hypoglycemia in people with diabetes on intensive treatment, as shown years later by the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study in type 2 diabetes, as well as the syndrome of hypoglycemia unawareness.

In 1975, Jack described in the *New England Journal of Medicine* the key role of glucagon in the pathogenesis of diabetic ketoacidosis (3). Taken together, these two observations have established that type 1 diabetes is a disease characterized by a bihormonal defect of the pancreatic islets, with a deficiency of insulin and an excess of glucagon and yet a paradoxical deficiency of glucagon in response to hypoglycemia. In 1975 the Juvenile Diabetes Foundation awarded its most prestigious prize, the David Rumbough Award, to Gerich and Forsham for these outstanding contributions.

After moving to the Mayo Clinic in Rochester, Minnesota, as Director of the Endocrine Research Unit, Jack began a long-term cooperation with Philip Cryer, at that time already a pioneer in the measurement of plasma catecholamines. Along with one of his most eminent fellows, Robert A. Rizza, Jack performed an additional milestone study on the physiology of glucose counterregulation, establishing the primacy of glucagon in defense against acute, insulin-induced hypoglycemia along with the role of adrenaline, the second line of defense, which becomes important primarily when the response of glucagon is missing (1). Although subsequently in the more relevant clinical model of prolonged hypoglycemia, glucagon and adrenaline were shown to be similarly important (4), Jack's pioneering study was pivotal in establishing the modern comprehensive picture of the physiology of glucose counterregulation, including the hormones important in the early phase (glucagon and adrenaline) and those important later after the onset of hypoglycemia (growth hormone and cortisol) in defense against hypoglycemia. Jack also continued research on counterregulatory hormones after moving from the Mayo Clinic to Pittsburgh, La Jolla, and Rochester, New York. He was the first to describe the hierarchy of responses to hypoglycemia, with hormonal responses occurring earlier during decline of glucose, followed by the appearance of symptoms accompanying a continuing fall of plasma glucose from normal values, and deterioration of cognitive function occurring only after plasma glucose has fallen below 55–50 mg/dL (5). This observation led to subsequent studies reporting the effect of antecedent hypoglycemia on glucose thresholds of response to hypoglycemia, a key modern concept in the interpretation of hypoglycemia unawareness syndrome as secondary to frequent, recurrent hypoglycemia.

Physiology of Insulin Action

One of the most classic observations of more than 45 years ago, subsequently confirmed and today universally accepted, is the insulin dose-response relationship in the physiology of glucose and lipid metabolism, as studied with the euglycemic glucose clamp technique combined with measurement of turnover rates of glucose and glycerol. These observations are the basis for understanding glucose homeostasis in the fasting state, where small changes in insulin concentration continuously modulate the rates of hepatic glucose production and lipolysis in adipose tissue, and in the postprandial condition, where a 10- to 20-fold increase of plasma insulin response to meal ingestion, in comparison with fasting levels, stimulates muscle glucose uptake (6).

Pancreatic β-Cell Function and Liver and Muscle Insulin Resistance in Type 2 Diabetes

Jack Gerich has contributed to the present understanding of pathogenesis of type 2 diabetes with a series of studies on β-cell function and measurement of insulin action in humans. He was a pioneer in establishing impaired insulin secretion as the main mechanism of inappropriately elevated hepatic glucose production, primarily gluconeogenesis, causing hyperglycemia in type 2 diabetes and impaired glucose tolerance. The modern concept that hyperglycemia in type 2 diabetes derives primarily from excessive hepatic glucose production both in the fasting state and after a meal stems from Jack's work (7). Muscle, despite being insulin resistant, does not play an appreciable role in inducing hyperglycemia because glucose uptake is in fact normal or even supranormal due to compensation by hyperglycemia. Even today, very few people understand that in type 2 diabetes, hyperglycemia compensates for insulin resistance and therefore maintains normal glucose utilization in muscle. Muscle never develops complications in diabetes, and perhaps one reason is that the flux of glucose remains normal despite insulin resistance. These concepts have important implications as they show that inhibition of glucose production by the liver, both in the fasting state and during a meal, not stimulation of muscle glucose uptake, is the principal target of diabetes treatment. In fact, today we understand that in type 2 diabetes, basal insulin is needed to keep glucose production by the liver under control, not to increase muscle glucose uptake, and that when prandial insulin is added, it further suppresses excessive hepatic glucose production after a meal rather than, as is often thought, stimulating muscle glucose disposal. Jack contributed greatly to our understanding of the importance of controlling glucose production by the liver.

Physiology of the Kidney in Glucose Homeostasis

As a result of his finding that glutamine was a major gluconeogenetic precursor, whereas the liver takes up little of this amino acid, Jack began to look at kidney metabolism because the kidney was the only other human organ capable of gluconeogenesis. He demonstrated that the kidney is an important source of glucose production—approximately 20% of endogenous glucose production derives from renal gluconeogenesis—and that adrenaline but not glucagon increases kidney glucose production. In other studies, he showed that kidney glucose production was increased as much as liver glucose production in type 2 diabetes and that the kidney is equally as important as the liver in glucose counterregulation. He also proposed the concept of liver-kidney reciprocity, i.e., the kidney can increase glucose production to maintain glucose homeostasis if hepatic glucose production is not sufficient and vice versa.

Jack has loved his time in the lab with the fellows as much as he has reading classical books, playing cards, and fishing. During his time at Mayo, every year in October the famous fishing trip to the Minnesota lakes, primarily Leech Lake,

Jack, fishing on Beaver Lake (Pennsylvania).

took place. Participants included not only fellows and colleagues at Mayo but also researchers in metabolism from other states. As a fellow, it was very special for me to meet people like Denis Bier, Richard Bergman, Alan Cherrington, and David Shade while sharing a fishing boat; later that evening at the cabin my mentor Jack would cook dinner for all of us, and then we would play cards together! He still enjoys fishing for relaxation.

Jack keeps his scientific interests alive by still writing papers, lecturing, and consulting for government and private companies. He is usually present at international congresses, where his wise comments and interpretations are well appreciated and respected. He likes to travel to Europe as frequently as possible and is familiar with European culture, perhaps in part because of his family's Hungarian roots. Today, Jack is a seasoned and happy man with various cultural interests, in addition to those in science, where he has been one of the primary actors for decades.

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