PROFILES IN PROGRESS

Gerald M. Reaven, MD: Demonstration of the Central Role of Insulin Resistance in Type 2 Diabetes and Cardiovascular Disease

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Gerald M. Reaven, MD, could easily be epitomized as the "Father of Insulin Resistance." (For those who do not know Dr. Reaven, he would humbly raise objection to being called Dr. Reaven rather than Jerry.) That said, Jerry is credited with developing the insulin suppression test, the first quantitative method to measure insulin-mediated glucose uptake in humans (1). Using this technique, he established the importance of insulin resistance in human disease, and importantly, in type 2 diabetes (2,3). In nondiabetic individuals, he demonstrated the role of insulin resistance/compensatory hyperinsulinemia in the development of *1*) hypertriglyceridemia (4) and low HDL concentrations (5), *2*) decreased urinary uric acid clearance and hyperuricemia (6), *3*) decreased LDL particle diameter (7), *4*) enhanced postprandial lipemia and remnant lipoprotein accumulation (8), *5*) increased levels of plasminogen activator inhibitor-1 (9), *6*) salt sensitivity (10), *7*) essential hypertension (11), and *8*) increased sympathetic nervous system activity (12).

In addition to emphasizing the role of insulin resistance/compensatory hyperinsulinemia in increasing the likelihood of an individual developing one or more of the consequences listed above, he first pointed out the clustering of these abnormalities. It is clear now that this group of clinical abnormalities, initially designated Syndrome X, is an important factor leading to cardiovascular disease. Syndrome X was introduced to the medical community in his now famous Banting Lecture in 1988 (13) and only later became known as metabolic syndrome.

Jerry was born in Gary, IN, on 28 July 1928, but spent most of his precollege years living in Cleveland, OH, thus accounting for his lifelong allegiance to the Cleveland Indians baseball team and a great deal of frustration on his part during their many less-than-stellar seasons. Jerry matriculated at the University of Chicago and graduated in 1949, also the year of his marriage to his wife Eve. He remained at the University of Chicago, receiving his medical degree in 1953, and continued on at the University of Chicago as an intern in medicine.

After his internship, Jerry came to Stanford University School of Medicine (which was then located in San Francisco) for 1 year as a research fellow with Dr. John Leutscher, the head of endocrinology who was involved in studying the actions of a relatively newly discovered hormone, aldosterone. Jerry's training was interrupted by having to spend 2 years in the U.S. Army Medical Corps; however, this proved to be an exciting time personally as he and Eve were stationed in several locations in Europe, providing time for exploration, children, and an almost endless number of stories for future occasions.

Gerald M. Reaven, MD

Following military service, Jerry completed his training in internal medicine at the University of Michigan in Ann Arbor and then returned to Stanford University School of Medicine to complete his fellowship training in 1959, the year that the medical school moved from San Francisco to the university campus in Palo Alto. Jerry joined the faculty at the medical school the following year and has remained at Stanford ever since, becoming Emeritus (Active) in 1995. As of October 2013, Jerry has published 760 peer-reviewed articles with over 500 coauthors, displaying an amazingly high and consistent level of productivity for the past 40 years (Fig. 1). As recognition of

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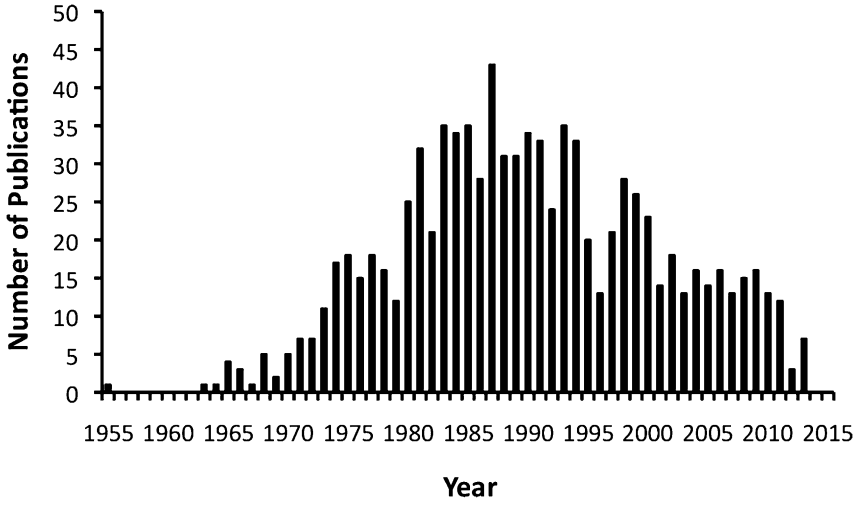

Figure 1—Number of publications by year produced by Dr. Reaven.

the value of his work, his articles have been cited in other publications over 53,000 times. Jerry has won numerous awards through the years, including the William S. Middleton Award for outstanding achievement in medical research from the Veterans Administration, the Banting Medal for Scientific Achievement Award from the American Diabetes Association, the Banting Memorial Lecture from the British Diabetes Association, the Fred Conrad Koch Award from The Endocrine Society, the Distinction in Clinical Endocrinology Award from the American Association of Clinical Endocrinologists, and the National Lipid Association Honorary Lifetime Member Award, to name a few.

A consistent theme among mentees and colleagues is Jerry's devotion to rigorous scholarship and his intellect, creative curiosity, enthusiasm for science and medicine, and lifelong devotion to scientific inquiry. Jerry has always been a truly independent thinker and one who never accepted dogma or consensus views. He has a unique ability to gather a varied research team, consider input from everyone, produce high-quality studies exploring the physiology and pathophysiology of carbohydrate and lipid metabolism in humans, and see the bigger picture among the details. Jerry has always ardently and vociferously defended his work, often to the consternation of many, but always based on his belief in the value of appropriately designed experiments and the data generated. He has always credited those on whose scientific observations he has built his own work. In particular, he has taken the opportunity on many occasions to credit the work of Sir Harold Himsworth in the 1930s (14) for generating experimental data suggesting the notion that not all patients with diabetes were alike and that some responded effectively to insulin, whereas others did not (the concept of insulin resistance in type 2 diabetes that Jerry has pursued throughout his career).

One of Jerry's earliest colleagues and scientific sounding board at Stanford was Dr. John (Jack) W. Farquhar, now Emeritus Professor of Medicine at Stanford. Dr. Farquhar recalls: "I can fit well into one corner of Jerry's long, fruitful, and continuing research career. He and I worked together closely and *very* amicably for about 7 years from the time I arrived at Stanford until I chose a different path in 1969. . . . From 1958 to 1962, I had done nutrition research using liquid formula diets at The Rockefeller University in the Lipid Metabolism Laboratory of Dr. E.H. Ahrens. Although trained in cardiology, as a new assistant professor of medicine at Stanford, I found a safe haven in joining Jerry's then advanced work in the field of diabetes in the Division of Endocrinology and Metabolism. As a neophyte in endocrinology, I found Jerry's inquiring mind infectious and soon we were planning experiments that dipped into some of my past work on dietary determinates of plasma triglyceride concentration, and his work that had clarified how plasma insulin and oral glucose tolerance were related. He and I published many articles over the next 7 years, often alternating as first author, given our complete sharing in the scientific query under study. The single strongest attribute that powered this remarkable productivity is Jerry's strong belief in science. He has always remained hopeful that carefully assembled, logical, and reproducible animal/human research can win over preconceived and prejudicial notions. The scientific world has and will continue to benefit by the convictions that underlie his creative and insightful research career."

The second postdoctoral fellow in Jerry's laboratory at Stanford was Dr. Lester Salans, who later became director of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases of the National Institutes of Health (NIH) and then dean at the Mt. Sinai Medical School. Dr. Salans wrote: "My first encounter with Dr. Jerry Reaven was in 1961 at the bedside of a comatose woman in renal failure with a host of complicated metabolic abnormalities of unknown cause. I was a newly arrived medical intern at Stanford University Hospital, daunted by the challenge my patient presented. Fortunately for me, and the patient, my attending physician was an enthusiastic, smart, young Jerry Reaven. For the next 72 hours of the patient's gradual recovery, I learned more medicine under Jerry's tutelage than in all 4 years of medical school. Among the most critical lessons was the importance of the scientific basis of clinical medicine and evidence-based decisions. Jerry's scientific and clinical curiosity and acumen was infectious then, and has had a profound influence on my professional career, including house staff training, clinical practice, my research career, and my years at the NIH. Indeed, I am still learning from him. My experience is shared by the many others he has mentored."

Salans continued: "As a postdoctoral research fellow in Dr. Reaven's laboratory at Stanford, I set up the rat epididymal fat pad assay to measure plasma insulin-like activity in order to test Jerry's 'maverick' hypothesis that impaired insulin action on peripheral tissues of people with type 2 diabetes (T2DM) might play a role in the pathogenesis of their dysglycemia. Dr. Reaven challenged the then prevailing theory that defective insulin secretion adequately explained the hyperglycemia of T2DM, postulating that insulin resistance might be as, or more, important. Few others were as prescient. The initial insulin-like activity studies from Reaven's

laboratory supported this hypothesis (15), and although the results were met with resistance from most of his peers, Jerry persisted, amassing and publishing a large body of data supporting not only the existence of insulin resistance in T2DM, but its presence as a hallmark of, and key contributor to, the disease. At about the same time, publications from Yalow and Berson (16–18) demonstrated hyperinsulinemia in the plasma of T2DM patients. Those observations, together with the evidence from the Reaven laboratory, established the existence and central importance of insulin resistance in the pathogenesis of T2DM, revolutionizing both the understanding of its pathophysiology and its treatment. Today, insulin resistance is recognized as pathognomonic of T2DM. In large part, this is due to Reaven's pioneering work. It led to an explosion of basic and clinical investigation on insulin action and diabetes, an enormous body of research that continues to this day."

Dr. Jerrold Olefsky, professor of medicine at the University of California, San Diego, and a Banting awardee, was a postdoctoral fellow of Jerry's from 1970 to 1972. Dr. Olefsky noted: "I arrived at Stanford to do a fellowship with Jerry Reaven in 1970, fresh out of a medical residency at the University of Illinois. At that time, I had absolutely no research experience, and I'm not sure I knew what the inside of a laboratory looked like. When I began my fellowship, Jerry was collaborating closely with his fellow faculty member Jack Farquhar, and I started off working with both of them in their programs. However, Jack was mostly interested in lipids and heart disease, whereas Jerry was on the diabetes and insulin resistance side, and I quickly gravitated to that orb. Since I had no experience doing research, all of my foundational ideas about science and how to conduct research were gained during my time with Jerry. He was a terrific mentor and his guidance shaped the rest of my future career. Coincidentally, he also had a profound impact on my personal life. Since my fellowship involved clinical research, on day one I was introduced to the head research nutritionist, Phyllis Crapo. A few years later, we were married, have had children and grandchildren, and, in this way, Jerry helped shape my nonprofessional life as well. Our relationship grew well beyond mentor/student, since Jerry, his wife Eve, a top scientist in her own right, and Phyllis and I became very close personal friends.

"His mentorship style encouraged creativity, independent thinking, and self-reliance, which turned out to be a perfect fit for me. A key lesson he taught me was the concept of scholarship. Jerry would preach this quite a bit, trying to imbed in me his ideas of what scholarship really was. It wasn't simply a matter of reading papers and working hard; it was more than that. For example, a critical skill I learned directly from him was how to write scientific papers. His method was meticulous and painstaking. He thought over every word and every sentence in every paper and was a writing perfectionist. I remember countless hours sitting with him going over manuscripts line by line. Sometimes it would take us 20 minutes to craft one sentence until we got it just the way he liked. In this way, you're forced to think through every detail of every figure, all the possible implications, and how every relevant prior literature reference fits into the picture. I remember times when I would give him a draft of a paper and he would give it back completely marked up, crossed out, re-pasted (I mean literally pasted, because these were the days before computers and red tracking), and rewritten in longhand with notes all over the margins and in between the lines. There were very few words left from the original, but he would hand it back and say, "Good job, now let's go over the changes." This would then lead to a marathon sit-down session, going through the manuscript line by line, rewriting, editing, etc. Although these sessions were arduous, they were great learning experiences and very enjoyable and ultimately taught me what he meant by the word scholarship."

Dr. Henry Ginsberg, Irving Professor of Medicine and director of the Irving Institute for Clinical and Translational Research at Columbia University College of Physicians and Surgeons, was a fellow in endocrinology with Jerry from 1972 to 1974. "I can truly state that everything about those two years at Stanford was transformational for my medical career. When my wife and I began driving down University Avenue toward the Stanford campus to interview for a position, we thought we had arrived in paradise; nothing in Brooklyn looked like Palo Alto. Our first response to seeing the medical school was that it could not be an academic hospital but rather a hotel near the hospital. I was scheduled to interview with John Leutscher, the head of endocrinology, but because he was undergoing back surgery, I was 'shunted' to Jack Farquhar and Gerald Reaven. I spent about 90 minutes with Jack, learning about his community-based studies in prevention of heart disease, and about 15 minutes with Jerry, who was on the way to the airport (surprise, surprise). But that was all it took to become infected by his enthusiasm and energy.

On the first day of my fellowship, Jerry Olefsky handed over his ongoing clinical research project to me. I, like Dr. Olefsky, had never done research and actually did not plan to continue to do research after my fellowship. But the energy and excitement of the group, primarily driven by Jerry, made me a quick convert. I was soon up to my neck in insulin suppression tests, glucose tolerance tests, and triglyceride turnover studies. In addition, Jerry taught me how to write and how to present. I can't remember how many rehearsals we had before my first presentation later that year at the wonderful Carmel meeting of the Western ASCI. By the time I spoke, with my quadruple-spaced, large-print presentation in front of me, I not only had memorized every detail of my work but also nearly every relevant reference, particularly those of some of our competitors who would be there to ask questions. What I am most proud of, and what is most revealing about the kind of mentor Jerry was, was the study I designed to show that we could use the insulin suppression test to assess insulin resistance in hyperglycemic patients with type 2 diabetes. Prior to my study, the suppression test, for technical reasons, had only been used in normal and insulin-resistant, but not diabetic, individuals. Jerry was very skeptical that the test could provide interpretable results in subjects who were hyperglycemic at the start of the protocol, but he allowed me to develop and carry out the study in stages, with each result determining the next phase. The result was a *JCI* paper in 1975 extending the concept of insulin resistance to people with type 2 diabetes mellitus (2).

What was most transformative for me, however, was Jerry's competitiveness, which was not softened by the fact that most of the 'competitors' did not believe in insulin resistance. The competition to prove the insulin resistance hypothesis added to the energy of being in a great laboratory with terrific scientists and being involved in a very important and rapidly evolving area of medical research. Jerry taught me that if you believe you are doing something important and work hard to achieve your goals, you will be successful. Those simple insights had deep and lasting effects on me and helped me through the ups and downs that all of us deal with in our careers. I, like many others, was very fortunate to have been taught and inspired by Jerry Reaven."

Dr. Fredric B. Kraemer, professor of medicine and chief of the Division of Endocrinology, Gerontology and Metabolism at Stanford University, was a postdoctoral fellow with Jerry from 1978 to 1982 and has been his colleague on the faculty since 1983. "Having interacted with Jerry first as a trainee and then as a colleague within the same institution for over 35 years, I can categorically say that he has been instrumental in shaping my professional career. Early on he provided me an outstanding environment for training in both clinical and basic investigation in metabolism and later provided me the path, encouragement, and support for developing my own independent career. Throughout this time, I have been indebted to him for his sage advice and acumen in how to navigate an academic medical career. Jerry O. (as he was called to differentiate him from Jerry R.) and Henry have very accurately captured what it was like to be a trainee in Jerry's lab, and, particularly, the processes involved in writing manuscripts and preparing presentations—though this did change in later years with the widespread use of computers and Powerpoint presentations (much to his chagrin). What never did change, however, is Jerry's devotion to his work and his focus on trying to uncover all aspects of insulin resistance and its interrelationships with physiologic and pathophysiologic responses. Throughout all the time that I have known Jerry, I have never seen his energy or enthusiasm for science wane, no matter what other crisis, minor or major, may have been ongoing. I have always been in awe of his ability to critically evaluate scientific work and to hone in on the important details and bigger picture. Jerry remains a great mentor and friend."

In addition to his achievements as a clinical investigator and mentor, Jerry has many interests outside his professional life. He is devoted to his family (wife, children, and grandchildren) and friends. Jerry has always been an ardent baseball fan, particularly of the Cleveland Indians, and a pretty good baseball/softball player in his younger days. Moreover, he is extremely well-read, focusing on classic and modern literature alike. He has always loved to travel and has explored countries across the globe, interacting with friends and colleagues over good food and drink. Jerry has achieved many academic accolades, but what many colleagues admire most is his passion for his work. He once said, "I plan to continue doing what I have been doing as long as granting agencies will provide support and journals will publish the results." Amazingly, and appropriately since his scientific insights and productivity remain unabated, both granting agencies and journals are continuing to do just that.

Acknowledgments. When first presented with the opportunity to author this Profile about Jerry Reaven, we readily agreed. Then came the quandary of how to concisely convey Jerry's substantial impact on the scientific community in general, and on the many individuals with whom he has worked and interacted throughout his long career.

To provide readers with a description of Jerry, both as a researcher and as a person, we solicited input from several of his colleagues over the years. We would like to thank John Farquhar, Lester Salans, Jerrold Olefsky, Carl Mondon, Yii-der Chen (Harbor-University of California, Los Angeles), Ann Coulston, Tracey McLaughlin (Stanford University), and Sun Kim (Stanford University) for their help in this endeavor. Regrettably, because of space limitations, we were only able to include comments from a select group of his many mentees and colleagues. We hope that with this undertaking the readers have gained insight to his influence in the field of diabetes not only from his direct scientific contributions but also from his substantial influence on those who followed him into the field of diabetes.

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