The Reaven syndrome: a tribute to a giant


Credit: Peter D. Reaven, M.D.

Professor Gerald (Jerry) M. Reaven from the Stanford University School of Medicine passed away on 12 February 2018, at the age of 89. Many scientists all over the world interested in chronic societal diseases such as type 2 diabetes mellitus (T2DM) have been sitting on the shoulders of this academic giant, whose science and spirit will remain.

1988 Banting lecture

Among the numerous outstanding and seminal scientific contributions that Jerry (his preferred name) made to the field of endocrinology and metabolism, one of his most impactful legacies was a notion that he introduced at the Banting Lecture of the American Diabetes Association annual meeting in 1988 (REF.[1]). During this well-deserved award lecture, he proposed that the most prevalent cause of cardiovascular disease (CVD) was not an increased concentration of cholesterol but rather a constellation of risk factors (including hyperinsulinaemia, high levels of triglycerides and low levels of HDL cholesterol, dysglycaemia and hypertension) resulting from a state of insulin resistance. Under his groundbreaking model, insulin resistance (a central feature of this syndrome) would not only be key in the development of glucose intolerance and T2DM, but it would also be a highly prevalent cause of CVD. Professor Reaven first used the term 'syndrome X' to describe this condition[2,3]. Jerry and the exceptional team of fellows that he has trained were also pioneers in showing that insulin resistance was key in the aetiology of T2DM at a time when it was felt that this disease was the result of a deficiency in insulin secretion[1,2]. His model initially stirred up debates and discussions but is certainly no longer controversial 30 years later as countless studies have shown that insulin resistance is a central component of a constellation of abnormalities that increase the risk of T2DM and CVD[2].

Influencing others

Many outstanding fellows have and will provide testimonies of how Professor Reaven has played a pivotal role in getting them hooked to research and passionate about a career in academic medicine[4]. As far as my own scientific journey goes, Jerry's influential papers have contributed to shaping my thinking since the start of my career as an independent investigator in 1986. One situation in which I was very proud to learn that Jerry had paid attention to our work was in 1996 when we reported in the *New England Journal of Medicine*[5] that fasting hyperinsulinaemia — proposed by Jerry as a crude but convenient marker of insulin resistance in individuals without diabetes mellitus — was an independent predictor of incident coronary heart disease in our prospective cohort of middle-aged men of the Québec Cardiovascular Study. Our results provided further support to Jerry's concept that a hyperinsulinaemic or insulin-resistant state was a prevalent cause of coronary heart disease, even among individuals who did not yet have diabetes mellitus. Since then, it has always been a pleasure for me to see and hear Jerry at meetings and discuss science and life. He was always candid in his opinion but he had such passion and a big charismatic smile that even lively scientific discussions with him would always have enjoyable human dimensions. He was a true gentleman and his passion was contagious.

Among the discussions that we have had over the years, Jerry initially did not really believe in the link between obesity and insulin resistance nor was he convinced that waist circumference was bringing any additional information in the discrimination of the health risks related to insulin resistance. He would appropriately argue, firstly, that he could find non-obese individuals who were insulin resistant and patients with obesity who were insulin sensitive and, secondly, that physical activity and/or fitness was a key confounder in the relationship between obesity and insulin resistance. My point to him was that indices of total body fat such as BMI (or even waist circumference, which is moderately superior to BMI when used in isolation) were misleading because computed tomography and MRI studies had revealed that the 'invisible enemy' within was rather the excess of inner fat (visceral adipose tissue and ectopic fat depots, including liver fat)[6]. Sadly, I will not be able to further sort this out with Jerry.

The metabolic syndrome

Jerry's definition of syndrome X required the measurement of insulin resistance (even with a simple marker such as fasting insulin). However, a syndrome X had already been defined in the field of cardiology (angina pectoris with normal coronary arteries[7]). It was therefore felt by some clinical investigators that another terminology was required to describe this cluster of metabolic risk factors. In addition, efforts were devoted to identify simple clinical tools and/or criteria to diagnose individuals likely to be characterized by the constellation of abnormalities linked to insulin resistance: the metabolic syndrome was born[8].

It would not be useful to get into the debate of the respective values of both terms in this article. In a 2005 review that Jerry wrote on the topic, he was satisfied with the term 'insulin resistance syndrome' (REF.[3]). To me, Jerry's syndrome X is the ground breaking concept, whereas the metabolic syndrome was an attempt to diagnose the most prevalent form of insulin resistance in clinical practice. We now have robust evidence from several international cardiometabolic imaging studies that the most prevalent form of the constellation of metabolic abnormalities associated with insulin resistance is found among individuals who have excess levels of visceral adipose tissue and ectopic fat (including excess liver fat)[6]. As previously pointed out by Professor Reaven, insulin resistance also has a genetic basis and can be substantially modulated by environmental and behavioural factors such as physical activity or exercise[2].

Jerry's contribution has been monumental and his legacy will continue to inspire countless investigators for decades. He should not and will not be forgotten. I will therefore reiterate a suggestion that I have made previously[6]: the insulin resistance syndrome (or Jerry's syndrome X) should be named the Reaven syndrome. Lastly, in order to fully appreciate the huge implications of insulin resistance as a clinical and public health issue, it would be

more than appropriate to let Jerry have the last words "As the world becomes more obese, and less active, the problems associated with the insulin resistance syndrome are the plague of the 21st century"(REF.[3]).

Personal note

Many years ago, Jerry gave me a nice tie with mitochondria as motifs designed by his wife Eve (who was also in academia herself as an electron microscopist). It is a gift that I was obviously honoured to receive and that I will now cherish for the rest of my life. I will wear it with pride at plenary lectures. Thank you Professor Reaven. You were an outstanding clinical investigator, a rigorous and competent mentor, a gentleman and, above all, you were a proud family man; a true role model in academic medicine and for all of us who knew you. I am looking forward to finding you among the brightest stars one day to chat about science, family and life.

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https://doi.org/10.1038/s41574-018-0013-5

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Competing interests

The author declares no competing interests.