Role of insulin resistance in human disease

Peter Grant

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Peter Grant is Professor of Medicine and Honorary Consultant Physician at the University of Leeds and Leeds Acute Trust.

The desire to clump rather than divide in science clearly has both weaknesses and strengths. On the one hand, this approach can provide unifying theories of disease; whilst failure to identify the detail shown by 'dividers' can lead to extravagant theories that are not based on fact. As a rough guess, one might expect clinical academics to be clumpers by nature, mainly since we have to try to fit the detail of science into our everyday experience with patients and the uncertainties of medical practice.

As a budding diabetologist in the 1980s, several papers influenced the way that I thought about diabetes, my management of this condition and the research path that I subsequently followed. The first of these were the results of the Multiple Risk Factor Intervention Trial (MRFIT) that, amongst many other observations, reported the exponential increase in cardiovascular risk in people with diabetes with clustered cardiovascular risk factors.

Second was the paper that I have chosen in which Gerald Reaven proposed that clustering of atheromatous risk factors (hyperglycaemia, hypertension, raised triglyceride and decreased HDL-c) occurred in association with insulin resistance more commonly than by chance alone. From this, he went on to hypothesise that insulin resistance could be involved in the causation of three conditions: type 2 diabetes, hypertension and coronary artery disease. Although previous investigators had described clustering of risk, this ground-breaking piece of work provided a unifying hypothesis and a mechanism for the strong association between diabetes and coronary artery disease and, at a stroke, started to shift the stubbornly fixated diabetes community away from a glucocentric view of diabetes management towards one in which we manage cardiovascular risk; including, but no longer exclusively, glucose control. Reaven's paper has had a huge effect on basic and clinical science, as well as drug development and diabetes management.

A few years later, Michael Stern published the third of my 'clumper' papers in which he proposed the 'common soil' hypothesis, stating that diabetes and cardiovascular disease are the same condition underpinned by common genetic and environmental antecedents. These three papers bring together understanding of the nature of the relationship between diabetes and cardiovascular disease to start the development of a unifying hypothesis.

From a personal viewpoint, all of this was going on at a time when I was trying to establish my own academic career, working clinically in diabetes, but having no real academic interest in glucose metabolism. Having spent a year in Switzerland learning the molecular biology of fibrinolysis, I returned to Leeds in late 1989 hoping to bring together insulin resistance, gene environment interactions, thrombosis and cardiovascular risk. The late Michael Davies had demonstrated the importance of the platelet-rich fibrin plug in the pathogenesis of myocardial infarction; and others, notably Irene Juhan Vague in Marseille, had already started to investigate some of the molecular changes in fibrinolysis that might account for these associations.

The world and his dog had similar plans to mine of course, and many thousands of papers on the subject later, the insulin resistance syndrome has become an inflammatory atherothrombotic risk cluster, whilst arguments continue to rage over whether or not its twin brother, the metabolic syndrome, either exists or has clinical utility. Now, two thirds of the way through a reasonably successful clinical academic career, I am increasingly aware that all most of us ever achieve is to place a little cement between the bricks in the wall of knowledge that the scientific community is building. The 1988 Reaven paper and accompanying Banting Lecture at the American Diabetes Association was different, it influenced thinking and developments in the field on a grand scale. At a smaller, personal level, this work helped me to develop and synthesise my own research ideas, clumping thrombotic risk with the more established features of the insulin resistance syndrome and placing my small personal contribution to the cement between our bricks of knowledge.

Reaven GM (1988) Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* **37**: 1595–607