DIABETICMedicine

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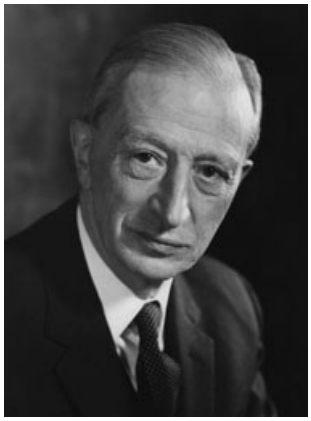
Editor's Selection: This Month's Featured Article

Sir Harold Himsworth and Insulin insensitivity 75 years on

The biological defect known as insulin resistance is regarded as a major component in the pathogenesis of type 2 diabetes. At its most generic, insulin resistance (the inverse of insulin sensitivity) may be defined as an impaired biological effect of insulin at physiological concentrations. However, constraining this consideration to glucose does a disservice to insulin, a hormone with myriad metabolic, vascular, and genomic actions.

In this issue of *Diabetic Medicine*, we commemorate the contributions to clinical science of Sir Harold Himsworth on the 75th birthday of his Lancet paper, a publication that has justly been described as seminal [1]. Decades before the development of a radioimmunoassay for insulin Himsworth showed that diabetes could be divided into what he termed 'insulin-sensitive' and 'insulin-insensitive' subtypes. In doing so, Himsworth effectively anticipated the modern classification of diabetes and its treatment. This remarkable individual achievement is recounted in a personal perspective by his son, Richard Himsworth (page 1438). These pioneering studies provided a solid foundation for a vibrant field of research that has become a cornerstone of clinical practice.

As a pre-eminent clinical researcher of the modern era it is fitting that Professor Gerald Reaven of Stanford University leads the tributes (page 1436) as our invited guest editor. In his 1988 Banting Lecture, Reaven synthesized strands of experimental and epidemiological data to catapult insulin resistance to the forefront of diabetes research. Reaven proposed a new syndrome – 'Syndrome X' – wherein major cardiovascular risk factors were intimately, perhaps fundamentally, associated with impaired insulin action in glucose metabolism. This construct carried important clinical implications for disease prevention and new therapeutic approaches. However, more than seven decades on from Himsworth's paper our knowledge of insulin action at whole-body, tissue, cellular, and intracellular levels remain far from complete. Some of the latest advances are presented in a series of invited articles. The pathological role of insulin resistance in polycystic ovary syndrome (Pauli and colleagues page 1445), sleep disturbances (Van Couter page 1455) and pathological brain ageing (Cholerton *et al.* page 1463) is explored. These highly prevalent disorders are pressing clinical and public health challenges of our time. To complement these papers Parker and colleagues (page 1476) review insights into the mechanistic aspects of severe insulin resistance that have been gleaned through elucidation of the molecular genetics of rare mutations.



Cover image: Sir Harold (Percival) Himsworth by Godfrey Argent Bromide print on card mount, 16 January 1970. Credit line: © National Portrait Gallery, London (NPG × 165745)

Refinements in investigative techniques, notably those that interrupt the feedback loop between islet β-cells and key organs such as liver, muscle, and fat have facilitated human research in the field of insulin action. The paper by Kim (page 1487) provides a timely update on the range of sophisticated techniques that researchers may now call upon. Yet Himsworth's clinical experiments retain the power to impress through their simple elegance. The construction of simultaneous capillary and venous glucose curves to estimate limb glucose extraction illustrates a careful scientific method. Subsequent studies have confirmed that skeletal muscle is the predominant site of insulin-stimulated glucose uptake during hyperinsulinaemia. Readers will find much else besides in Himsworth's work that presages current concepts of insulin physiology. For example, the hypothesis of a deficient 'insulin sensitising factor' has found support in the discovery of adiponectin. Circulating levels of this fat-derived protein, which improves insulin sensitivity, are often reduced in type 2 diabetes.

Himsworth's body of work bears the hallmark of classic research: it has stood the test of time.

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Reference

1 Himsworth HP. Diabetes mellitus: its differentiation into insulin sensitive and insulin insensitive types. *Lancet* 1936; **1**: 127–130.