

Obituary

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Sir Philip Randle
MA, PhD, MD, FRCP,
FmedSci, FRS
(1926–2006)

Sir Philip Randle, who died aged 80 on 26 September 2006 after a brief illness, was one of the world's foremost researchers into mammalian metabolism. In a career spanning some five decades, he provided a series of brilliant insights into the fundamental mechanisms that determine the selection of metabolic fuels by muscle and other tissues. Many of his findings were concerned with insulin's role in metabolism and with the control the hormone's secretion from the β -cells in the pancreatic islets of Langerhans. The ideas generated by his investigations laid the foundations for countless subsequent studies and have a direct bearing on the understanding of diabetes.

Philip Randle was born in Nuneaton, Warwickshire, and went to school at King Edward VI Grammar School in Nuneaton. He went to the University of Cambridge in 1944, where he read Natural Sciences, gaining a First in Part II Biochemistry. It was here that his lifelong interest

in metabolic regulation and insulin was first aroused by Professor T.R. Manning and Dr G.D. Greville. He went on to read Medicine at University College Hospital, London, and then returned to Cambridge where he carried out his first research studies on insulin under the supervision of Professor Frank Young. He was awarded a PhD in 1955 for a thesis entitled 'Studies on the metabolic action of insulin' and was immediately appointed as a Lecturer in Biochemistry at Cambridge. In 1964, Philip was appointed founding Professor and Chairman at the Department of Biochemistry at the University of Bristol. Under his leadership the this new department soon became one of the strongest in the country and remains so to this day. A whole generation of biochemists gained their early research education under Philip and the strong team of researchers he gathered around him in Bristol. In 1975, he was appointed as the first Professor of Clinical Biochemistry at the University of Oxford and spent the rest of his career as head of the Nuffield Department of Clinical Biochemistry (NDCB) at Oxford. Philip retired officially in 1993 and the scientific meeting held that year in Oxford to honour his achievements was an eloquent testimony to the affection and esteem in which he was held throughout the world of diabetes research. After retiring, he maintained an active interest in the topics that had occupied him throughout his career and continued to act as an editor for scientific journals, as well

as being a prominent and respected figure at scientific conferences throughout the world.

Philip Randle's strength as a researcher was an ability to go to the heart of a problem and see what was really important. It is no coincidence that many of the PhD students who studied under him found that the research topic they had been set by Philip was one that would occupy them for the rest of their scientific careers. This was certainly true for the two authors of this piece.

Philip's best-known contribution to diabetes research is probably the glucose–fatty-acid cycle. This innovative hypothesis, first put forward in a paper in *The Lancet* in 1963 with Eric Newsholme, Nick Hales and Peter Garland, was based on the demonstration that muscle tissue, when given a choice between glucose and fatty acids as a fuel, preferred to use the fatty acids. In other words, fatty acids decrease the oxidation of sugar by muscle. Philip and his colleagues speculated that increased fat oxidation was responsible for the insulin resistance (i.e. failure of insulin to adequately increase glucose utilization by muscle) associated with obesity and Type 2 diabetes. A biochemical mechanism was proposed to account for this effect and, in a succession of papers, evidence was presented to support the idea. Thus, it was suggested that instead of being solely a disorder of carbohydrate metabolism, the primary event in the development of insulin resistance could be excessive release of fatty acids from fat tissue.

The fundamental importance of the glucose–fatty-acid cycle in normal physiology is now fully accepted, but it is likely that it is not the whole answer to insulin resistance.

Philip also proposed a second major hypothesis in the 1960s: this related to the key question of how increases in blood sugar levels resulted in increases in the secretion of insulin. Two experimental advances from the Randle laboratory paved the way for tackling this problem. First, together with Nick Hales, Philip developed a radioimmunoassay for insulin that allowed detection of the hormone in biological fluids. Secondly, together with Hal Coore, Philip showed that pieces of rabbit pancreas could be used to study the release of insulin and the rate of release in response to various agents could be quantified using the radioimmunoassay. These studies focused on the specificity of the insulin response to sugars and the effects of an inhibitor of glucose metabolism. It was generally assumed at the time that glucose would stimulate insulin secretion by binding directly to a 'glucoreceptor' akin to a hormone receptor. However, based on their observations, Philip and Hal proposed that it was the metabolism of glucose within the β -cell that was in some way coupled to triggering insulin release. This proved to be the most fruitful hypothesis for the control of insulin secretion ever put forward. Initially, it was not possible to test the hypothesis directly since the insulin-producing β -cells could not be separated from the rest of the pancreas of which they formed only around

1% of the total tissue. However, shortly after one of us (Steve Ashcroft) joined Philip's group as a research student, methods became available to study the metabolism of islets of Langerhans. In a long series of investigations, slowly but surely the metabolic model for glucose-stimulated insulin release, which was named the 'substrate-site hypothesis', became established. Eventually the details of the biochemical mechanisms involved were elucidated, the molecular components were identified and the power of modern techniques of molecular biology and genetics were brought to bear on the analysis of the possible contribution of mutations in these components to the development of diabetes.

When Philip moved to Oxford, in contrast to Bristol where Philip built up a large department with many research projects in various fields, he was content for the NDCB to remain as a small unit. With him he took Steve Ashcroft, with whom he continued his interest in the investigation of the control of insulin secretion, and Alan Kerbey, with whom he studied the regulation of the key metabolic enzyme pyruvate dehydrogenase, which had become a major interest for Philip because of its central importance in the inhibition of glucose utilization by fatty acids. Dick Denton, another early research student of Philip's, who had been closely involved with Philip in work on adipose tissue and pyruvate dehydrogenase, remained behind in Bristol where he pursued and expanded the study of the metabolic

effects of insulin, and eventually became Professor and Head of the Biochemistry Department at Bristol. The NDCB, despite its small size, was highly productive and gained an outstanding reputation in diabetes research under Philip's leadership.

Philip Randle was an impressive figure, both physically and mentally. He possessed an extraordinary memory for facts, data and events. At scientific meetings, he could be formidable in his ability to quote chapter and verse to support his arguments. But he was also capable of great kindness and support for those he took under his wing. A remarkable network of diabetes researchers was built up in the UK and further a field, all of whom had in some way been influenced by Philip. His death is truly the end of an era in diabetes research.

Philip received many honours for his research work. He was the first recipient of the Minkowski Prize of the European Diabetes Association in 1966, was elected to the Royal Society in 1983 and was knighted in 1985. He was President of the Biochemical Society from 1995 to 2000.

He was supported in all his activities by his wife Elizabeth, whom he married in 1952 and who sadly died 2 years ago. He also suffered the loss of a son, Peter, who died in 1971, while still in his teens, and a daughter, Susan, who died in 2005. He is survived by two daughters, Sally and Rosalind, and four grandchildren. The scientific community shares their sorrow and mourns the loss of a unique man who enriched the world in which he lived.