A tribute to the life and work of Philip Randle

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Professor Sir Philip Randle FRCP, FMedSci, FRS was a towering figure, both intellectually and physically, in diabetes research. During his distinguished career he made substantial contributions to our knowledge of both insulin action and insulin secretion.

Professor Sir Philip Randle died in Oxford at the age of 80 years on 26 September 2006. He was one of the foremost researchers into aspects of mammalian metabolism, and many of his findings have had a direct bearing on the understanding and treatment of diabetes.

Philip Randle was born in 1926 in Nuneaton (Warwickshire, UK). His father was a baker and his mother a music teacher. He went to the local King Edward VI Grammar School before studying natural sciences at Cambridge University. In his final year (1947), he obtained a first class degree in Biochemistry—a subject still in its infancy at that time. It was at this time that he first developed his lifelong interest in insulin and changes in metabolism that occur in diabetes. He moved to University College Hospital Medical School (London, UK) and completed his medical studies before returning to Cambridge as a research student of Professor Sir Frank Young. He was awarded a PhD in 1955 for studies on the metabolic actions of insulin. Immediately, he was appointed to a Lectureship in the Biochemistry Department at Cambridge University and continued his studies into various aspects of insulin action and the control of metabolism, particularly in muscle.

These studies culminated in a series of very influential papers published in 1963 and 1964 with a group of outstanding research students and fellows: Eric Newsholme, Nick Hales, Peter Garland and Hal Coore. Taken together, these papers have been cited more than 10,000 times and are still being cited frequently to this day. They set out the basic evidence both for the ‘glucose–fatty acid cycle’ of fuel selection by tissues (often referred to as the ‘Randle cycle’)

[1] and for the ‘substrate-site hypothesis,’ the means whereby increases in blood glucose cause insulin release from the beta cells in the pancreas [2]. Much of the research of Philip Randle over the next three decades was concerned with uncovering in detail the basic biochemical mechanisms involved in these two fundamental processes.

Crucially, the glucose–fatty acid cycle recognises that, given a choice between glucose and fatty acids, muscle uses the fatty acids as the main energy source. Philip Randle and his colleagues went on to reason that increased fatty acid use might be responsible for the insulin resistance associated with obesity and type 2 diabetes. The fundamental importance of the glucose–fatty acid cycle in the normal physiology of muscle and other tissues is now widely accepted [3]. However, it is now clear that many extracellular factors also influence the relationship, including insulin and other long-recognised hormones, plus many newly recognised potent cell regulators, such as leptin, adiponectin and resistin, which are released by fat, muscle and other cells and are not part of the traditional endocrine system. In much the same way, it is now evident that the insulin resistance associated with obesity/type 2 diabetes involves a remarkable complex array of changes, of which increased fatty acid utilisation is one of a number of candidates that may initiate insulin resistance. Philip Randle was fully aware of these developments, and this is well illustrated in a detailed review written by him on the topic in 1998 when he was 72 years old, 35 years after the birth of the Randle cycle [4].

The substrate-site hypothesis of insulin secretion was devised following truly ground-breaking studies on pancreatic pieces conducted by Philip Randle and Hal Coore [2], in which insulin secretion was measured by a new radioimmunoassay, which was also developed within the Randle group, by Nick Hales [5]. It was generally thought at the time that glucose stimulated insulin secretion by binding to a receptor similar to a hormone receptor. In contrast, on the basis of their observations on the specificity of the insulin secretory response to sugars *in vitro*, Coore and Randle hypothesised that it was the actual metabolism of glucose by the beta cells in the pancreas that was coupled to the release of insulin. At the time this model was suggested it was not possible to test it directly. However, when methods became available for the study of the metabolism of isolated islets of Langerhans, evidence to support the hypothesis was soon forthcoming from the Randle laboratory [6, 7]. Subsequent studies, including a long series of investigations by Steve Ashcroft with Philip Randle, fully confirmed the substrate-site hypothesis and have uncovered the underlying biochemical mechanisms.

Philip Randle moved to Bristol in 1964 and founded a new Department of Biochemistry. This was a period of expansion in UK universities, but the rapid development of

the Department of Biochemistry under his leadership was quite remarkable. Bristol University had had Medical, Veterinary and Dental Schools for many years and was also strong in many areas of medical and other sciences. However, there was no biochemistry department. Within 7 years, the new department was one of the strongest in the UK, both in research and teaching—a position it holds to this day. How did Philip Randle do this? In hindsight, it is easy to see that his most important action was a whole series of inspired academic appointments across the full range of the discipline of biochemistry. However, it was also necessary for Philip Randle to ensure that the new department had its fair share of space and investment within the university. His expansionist plans did not always get the instant support of old-established departments, who naturally saw the new department as a serious threat to their own plans! Philip Randle’s physical presence (more than 2 m tall), intellect, booming voice and strong pipe smoke undoubtedly helped in diminishing the more conservative forces that he had to overcome at that critical period in the department’s development.

During the 12 years that Philip Randle stayed in Bristol, his personal research became focused on two areas—the control of insulin secretion (largely with Steve Ashcroft) and the regulation of an enzyme, pyruvate dehydrogenase, that plays a central role in the selection of fuels in muscle and other cells (often with Dick Denton). Despite his many responsibilities, substantial progress was made in both areas. This included the first strong evidence that glucose metabolism was essential for the initiation of increased insulin secretion and that insulin activated pyruvate dehydrogenase activity in adipose tissue (important in the increased conversion of carbohydrate into fat brought about by the hormone).

In 1975, Philip Randle moved to Oxford to found another new department, this time the Department of Clinical Biochemistry. This department was very different from the large department he had developed in Bristol. Instead of more than 20 established academic staff members and their research groups, covering the full range of modern biochemistry, it had only four academic staff members, two of whom were Philip Randle himself and Steve Ashcroft, who moved from Bristol with him. This new department focused very successfully on diabetes-related research, and Philip Randle’s own major interest continued to be the regulation of pyruvate dehydrogenase, mainly in muscle. Philip Randle retired from this position in 1993. The major scientific meeting held in Oxford that year in his honour, entitled ‘Metabolic fuel selection in health and disease’, was an eloquent testimony of the esteem in which he was held throughout the world.

Over the years, Philip Randle took on many other responsibilities in addition to those in his universities.

These included appointments as Chairman of a large number of research committees and boards for Diabetes UK, the Medical Research Council and the British Heart Foundation, Vice-President of the Royal Society and President of the Biochemical Society. He played an important role in the establishment of the European Association for the Study of Diabetes (EASD) and was a member of its Council from 1968–1972, and its President from 1977–1980. In the early 1980s, Philip Randle devoted great energy to advising the government on aspects of food policy. In particular, he chaired the influential Food Policy Panel on Diet and Cardiovascular Disease. This panel developed recommendations on lowering intakes of saturated fat, simple sugars and salt [8]. This advice is still accepted today, but sadly is not always heeded.

Among the many honours that Philip Randle received were the Banting Lecture of Diabetes UK (1965), first recipient of the Minkowski Prize of the EASD (1966), the Humphrey Davy Rolleston Lecture of the Royal College of Physicians (1983), election to Fellow of the Royal Society (1983), Knight Bachelor (1985) and a Founder Fellow of the Academy of Medical Sciences (1998). In connection with the Minkowski Prize, he wrote an important article for *Diabetologia* [9].

He had a massive and enduring influence on the PhD students and young research fellows passing through his laboratory. To date, three of his research students have become Fellows of the Royal Society and the number now holding university chairs or comparable positions in the pharmaceutical industry is well into double figures. Although the death of Philip Randle is truly an end of an era, he has left a substantial legacy of both the department

he started in Bristol as well a worldwide network of researchers whose careers were influenced in a very substantial way by the time spent under his supervision.

Philip Randle 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 his son, Peter, who died still a teenager in 1971 and a daughter, Susan, who died in 2005. He is survived by two daughters, Sally and Rosalind, and four grandchildren.

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