PHILIP JOHN RANDLE
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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 the role of insulin, including the control of its secretion from the β-cells in the pancreatic islets of Langerhans, and with the regulation of glucose oxidation through changes in the activity of pyruvate dehydrogenase. The ideas generated by his investigations laid the foundations for countless subsequent studies and have had a direct bearing on the understanding of diabetes. His lifelong enthusiasm for good research has had a great influence on all who worked with him.

EARLY LIFE AND EDUCATION

Philip Randle was born in 1926 in Nuneaton, Warwickshire. His father, Alfred John, was a master baker who inherited the family bakery and store, and his mother, Nora Anne, was a music teacher who also painted. The family lived on the premises. The shop also sold bacon and cheese and the normal range of groceries, and attached to the shop was a Post Office where Philip’s Aunt Lilly was the postmistress. When Philip was a schoolboy, they had two horse-drawn carts and one pushcart for delivering the bread and other goods; motor transport did not replace the horses until after the Second World War. The horses were kept in stables

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nearby. In the summer they grazed in fields owned by his father, which is where the family built their house in 1936. Philip often helped in the shop and with deliveries to customers.

Philip’s mother was a Jireh Baptist, and both sides of the family were staunch chapel-goers. The chapel was Jireh Particular Baptist Church, Attleborough, Nuneaton, which still exists, and in his time the congregation was apparently mostly composed of close and distant relatives. Apparently, Philip would go to Sunday school twice and to church once on Sundays until he left home. The fundamentalist beliefs of this chapel include that God created the Earth in six (24 hour) days, but it is not clear when Philip began to reject these beliefs. As an adult, he seemed to take very little interest in religion. He signed the Pledge at some stage, but he quickly acquired his love of wine when an undergraduate at the University of Cambridge.

Two of his uncles were farmers and he would go to harvest camps—Philip said that he drove a tractor at times when too young to drive a car. He had an elder sister, Joan, who taught him to swim (figure 1). She must have been a good teacher because the love of swimming persisted throughout his life. He also played extensively with his cousin John Webber, the son of his mother’s sister, and the two families had many holidays together. Philip was a keen and accomplished musician when a schoolboy, playing both the piano and organ and even heading up his own six-piece dance band.

Philip attended King Edward VI Grammar School in Nuneaton (1936–1944), and it is generally accepted that he was far from a star pupil in his early years there. Not only was he completely uninterested in his studies but, by his own admission, he spent most Saturday mornings in detention. In fact he missed his first opportunity to watch a car race at nearby Donnington as he was in detention on that morning. Apparently, he was bored stiff at school and more interested in playing football or cricket and larking about. Things got so bad that evidently the headmaster suggested to his father that there was little point in him continuing at the school.

Then along came an inspirational chemistry master, ‘Crumb’ Brown, who convinced Philip that he must go to university and it seemed that medicine at the University of Cambridge became his first choice. He had, of course, to make up for all the wasted years and get on with some serious study. The school buildings were badly bomb damaged, resulting in half the boys being taught in the headmaster’s house and the other half in the girls’ High School, so teaching was severely disrupted; on top of this, the science labs had been wrecked and so there were no facilities for practical work. To get into Cambridge he would need to pass an exam in Latin. There was no Latin teacher at the school at that time and so this meant having private tuition in this subject. What a task he had set himself! No more football, no more cricket, no more larking about but presumably no more detentions on Saturday mornings. This change showed a new side to Philip: complete dedication and focus on the task in hand, which was to be a key ingredient in his future success.

His efforts bore fruit and in 1944 he gained a major scholarship to read medicine at Sidney Sussex College, Cambridge. For the first three years this degree followed selected subjects within the Natural Sciences Tripos, and he gained a First in Part II Biochemistry in 1947; it was at this time 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 complete the clinical part of his medicine degree at University College Hospital, London. Then, in 1952, he returned to Cambridge, where he carried out his first studies on insulin as a research student funded by a Medical Research Council (MRC) Research Fellowship under the supervision of Professor Frank Young FRS. To measure the concentration of insulin activity in human plasma he used
Figure 1. Young Philip receiving a swimming lesson from his sister Joan. (Photograph courtesy of Sally Randle.)
a bioassay in which the glucose uptakes of rat hemidiaphragms suspended in a physiological buffer \textit{in vitro} were compared with the glucose uptakes of rat hemidiaphragms suspended in a buffer to which the plasma had been added. The values were calibrated by reference to the glucose uptake of rat hemidiaphragms in response to known concentrations of purified insulin added under the same conditions.

Using this method, he was able to provide some of the first estimates of the concentration of insulin in blood under normal conditions and in response to changes in pituitary hormones, published in a series of single-author papers (1–3)*.

\textbf{The Cambridge years}

Philip was awarded his PhD in 1955 for a thesis entitled ‘Studies on the metabolic action of insulin’, and was immediately appointed to a lectureship in the Cambridge Department of Biochemistry, where he continued his studies into various aspects of insulin action and the control of metabolism, particularly in muscle. In 1957 he was also appointed a Fellow at Trinity Hall and director of medical studies. He established his research group in a basement laboratory of the Dunn School of Biochemistry. The open drainage system for the laboratory sinks in the building ran through his laboratory, so that when, as often happened in those days, flammable organic solvents were poured down a sink somewhere in the building, he and his group had to beat a hasty retreat—not least because Philip would almost certainly be smoking his pipe.

The next six years were an extraordinarily productive period that culminated in a series of very influential papers published in 1963 and 1964 with a group of outstanding research students—Eric Newsholme, Nick Hales (FRS 1992), Peter Garland and Hal Coore (all except Eric Newsholme were medically qualified). These papers taken together have been cited over 11,000 times. Three advances stand out: the introduction of a novel radio-immunoassay for insulin (4); establishment of a method for the study of insulin secretion \textit{in vitro} (7); and a major insight into the way mammalian energy metabolism is coordinated, formulated in the concept of a glucose fatty-acid cycle (5). These advances will be described in more detail in turn.

\textit{Insulin radio-immunoassay}

During his thesis studies, Philip had used a bioassay for some of the first measurements of insulin concentration in biological fluids. He was well aware of the limitations of such a bioassay. Therefore, it was a major advance when Yalow & Berson first described an immunoassay for insulin based upon the fact that unlabelled insulin in blood serum samples can diminish the binding of \textsuperscript{[131]I}-insulin to insulin antibodies (Yalow & Berson 1960). However, their assay required large amounts of \textsuperscript{131}I, and the necessary separation of the insulin–antibody complex from unbound insulin used paper chromatography-electrophoresis, which was cumbersome and time consuming. Philip and Nick Hales devised a major modification of the standard method. Their method was based again on isotope dilution, but with the separation of the antibody-bound and unbound insulin rapidly achieved by the use of a second antibody that bound and precipitated the insulin–antibody complex, which was then rapidly collected by microfiltration and assayed for radioactivity. This assay was simple, quick and used

* Numbers in this form refer to the bibliography at the end of the text.
[\textsuperscript{131}I]-insulin of relatively low specific activity that was easier to handle and less subject to radiation damage. It was possible to measure insulin concentrations in 100 serum samples in duplicate each day with the assay as first described by Hales & Randle in their 1963 \textit{Lancet} paper (4). This paper has been cited more than 3700 times. In due course, this assay, in a more automated form, was the basis of the first commercial radio-immunoassay for insulin. Hales went on to devise further ingenious variants of the method that he was able to apply not only to the assay of insulin but also to that of proinsulin and C-peptide (Yue \textit{et al.} 1979).

\textit{Insulin secretion}

Earlier attempts to measure pancreatic insulin secretion \textit{in vitro} had proved largely unsuccessful. Together with Hal Coore, Philip devised a method to study insulin secretion \textit{in vitro} from small pieces of rabbit pancreas (7). The tissue is suitable for this purpose as it is thin and has a relatively high concentration of \(\beta\)-cells. Using the Hales insulin immunoassay, they found that insulin secretion was stimulated by glucose and mannose but not by galactose or 2-deoxyglucose. Glucose-stimulated secretion was blocked by mannoheptulose, an inhibitor of glucose phosphorylation, the first step in the intracellular metabolism of glucose. Glucose also failed to stimulate insulin secretion when the pancreas was incubated under conditions designed to inhibit metabolism (anaerobically or in the presence of an uncoupler of oxidative phosphorylation). From the specificity of the response to sugars and from the effects of metabolic inhibitors, Coore and Philip postulated that the stimulatory effect of glucose on insulin secretion was dependent on the intracellular metabolism of the sugar rather than through binding to some hypothetical gluco-receptor, which was the expected mechanism at the time. This concept, the substrate-site hypothesis, formed the basis for decades of subsequent work and has been fully validated, as we will describe in more detail later in this memoir.

\textit{The glucose fatty-acid cycle}

Regulation of the concentration of glucose in the blood is of fundamental importance for health. Too high a concentration leads over time to the life-threatening symptoms of diabetes. Too little glucose immediately impairs brain function since, although muscle is able to utilize both glucose and fatty acids for its metabolism, the blood–brain barrier prevents the brain from switching to fatty acids for its fuel requirements. Thus to preserve glucose for the brain in times of dietary carbohydrate shortage it is important for muscle to derive more of its energy from fatty acids. In order to elucidate the mechanisms involved, Philip, together with Peter Garland, Eric Newsholme and Nick Hales, studied extensively the effects of fatty acids, starvation and diabetes on glucose metabolism in heart and diaphragm muscle. Their findings led on to the formulation of the idea of the glucose fatty-acid cycle, often referred to as the Randle cycle.

The essential features are: (i) when glucose availability is restricted (as in starvation), the release for oxidation of more fatty acids derived from muscle and adipose-tissue glycerides decreases glucose metabolism in muscle; and (ii) when glucose concentration in blood is elevated (for example, after a carbohydrate-rich meal), the release of fatty acids from these tissues is reduced because of increased glyceride synthesis.

As depicted in figure 2, in ‘the tissue phase’ fatty acids and glycerol are released from glycerides in both muscle and adipose tissue (lipolysis). The fatty acids may be reincorporated into glycerides by esterification with glycerophosphate formed from glucose (but not from...
glycerol, which is released into the extracellular fluid; alternatively, fatty acids can be oxidized (mainly in muscle), or transferred to plasma albumin (adipose tissue). In ‘the blood phase’ (see figure 3), increased uptake of glucose by adipose tissue inhibits the flow of fatty acids from adipose tissue to muscle.

Philip and his colleagues summarized the possible clinical relevance of the cycle as follows:

Evidence is presented that a higher rate of release of fatty acids and ketone bodies for oxidation is responsible for abnormalities of carbohydrate metabolism in muscle in diabetes, starvation, and carbohydrate deprivation, and in animals treated with, or exhibiting hypersecretion of, growth hormone or corticosteroids. We suggest that there is a distinct biochemical syndrome, common to
these disorders, and due to breakdown of glycerides in adipose tissue and muscle, the symptoms of which are a high concentration of plasma non-esterified fatty acids, impaired sensitivity to insulin, impaired pyruvate tolerance, emphasis in muscle on metabolism of glucose to glycogen rather than to pyruvate, and, frequently, impaired glucose tolerance. We propose that the interactions between glucose and fatty-acid metabolism in muscle and adipose tissue take the form of a cycle, the glucose fatty-acid cycle, which is fundamental to the control of blood-glucose and fatty-acid concentrations and insulin sensitivity.

They then went on to demonstrate that impairment of glucose metabolism by fatty acid (or ketone body) oxidation was mediated by the short-term inhibition of several steps in the pathway whereby glucose is oxidized to CO₂. These were glucose transport across the cell membrane; then, in the cytoplasm, hexokinase (HK) and phosphofructokinase (PFK); and finally, within mitochondria, pyruvate dehydrogenase (PDH) (see figure 4). They recognized that the extent of inhibition is graded and increases along the pathway of glucose metabolism, being most severe at the level of PDH and less severe at the level of glucose uptake, HK and PFK. Their research at the time indicated that this sequence occurs because the initial event, triggered by fatty acid oxidation, is an increase in the mitochondrial ratios of [acetyl-CoA]/[CoA] and [NADH]/[NAD⁺], both of which they showed inhibited PDH activity. It was proposed that these higher ratios also lead to an accumulation of cytosolic citrate, which in turn inhibits PFK, followed by an increase in glucose 6-phosphate, which inhibits hexokinase (6, 8).

Later work by Philip and his colleagues (see below) and many others has added much complexity to this scheme (Sugden 2007; Hue & Taegtmeyer 2009). An excellent example of the growth of knowledge in this field is the regulation of PDH, which, as we will see, became a major interest of Philip for the rest of his academic life. It should be noted that in the late 1970s an important extra dimension to the understanding of how glucose and fatty acid metabolism interact was uncovered by McGarry and co-workers (McGarry et al. 1977). They showed that an increase in glucose metabolism can lead to decreased fatty acid oxidation in liver and other tissues. This was shown to be brought about by inhibition of an early step in the pathway of fatty acid oxidation, carnitine palmitoyl transferase, by malonyl-CoA, which is increased in concentration when glucose metabolism is enhanced in many circumstances.

Despite all the developments in the field since its publication in 1963, the enduring relevance of the basic concepts set out in the glucose fatty-acid cycle Lancet paper is underlined by the fact that it has been cited over 4200 times and is still being cited about 100 times per year. Philip himself summarized the relevance of the cycle to the understanding of fuel metabolism in starvation and diabetes in two major reviews (23, 24). The 1998 review (24) was Philip’s last academic publication. It has been cited close to 600 times and is Philip’s fifth most cited publication.

**BRISTOL: FOUNDING A NEW DEPARTMENT**

Shortly after this extraordinarily productive period in Cambridge, in 1964, at the age of 38, Philip moved to Bristol to become professor of biochemistry and founding chairman of a new biochemistry department. This was a period of general expansion in UK universities, but the rapid development of the Bristol Department of Biochemistry under his leadership was quite remarkable. The University of Bristol had had medical, veterinary and dental schools
Intracellular regulatory mechanisms proposed by Philip Randle and colleagues (6, 8) to be involved in the inhibition of glucose metabolism by increased fatty acid oxidation in muscle. Increases in the ratios of acetyl-CoA/CoA and NADH/NAD$^+$ lead to both the inhibition of PDH (pyruvate dehydrogenase) and an increase in cytosolic citrate; this increase results in the inhibition of PFK (phosphofructokinase) and in turn to the inhibition of hexokinase brought about by an increase in G6P (glucose 6-phosphate).

for many years and, although a small university, it was strong in many areas of medical and other basic sciences; however, there was no biochemistry department. There were a few biochemists scattered between the departments of Physiology, Biology and Chemistry, but overall the subject at Bristol was weak by national standards. Within seven or so years, the new department under Philip’s leadership was one of the strongest in the UK in both research and teaching, a status it maintains 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. Particular research successes in the early years of the department included ground-breaking studies on mitochondrial transporters (Professor Brian Chappell), molecular enzymology (Professor Freddie Gutfreund (FRS 1981)) and protein structure (Herman Watson and Hilary Muirhead), as well as on the control of mammalian metabolism by the group headed up by Philip himself, which also included Peter Garland. A large MRC Group Grant negotiated by Philip, which funded much of the research in the groups of Chappell, Garland
and Randle during the early years of the department, was vital in funding the rapid growth of their research. The support of Sir Hans Krebs FRS, who headed the world-famous MRC Unit for Research in Cell Metabolism in Oxford, was also important.

Many of the early academic appointments were of individuals from the University of Cambridge, who also brought with them more junior colleagues and research students. The authors of this memoir were part of this substantial migration from Cambridge to Bristol; we both read biochemistry in Part 2 of the Natural Sciences Tripos, gaining our degrees in 1963. One of us (R.M.D.) moved as a PhD student to Bristol with Philip in 1964 and the other (S.J.H.A.), after a short period in Switzerland, joined Philip’s group in 1965.

It was also necessary for Philip 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 the other long-established medical science departments, who naturally saw the new department as a serious threat to their own plans within the fine new Medical School Building being constructed at the time! Philip’s physical presence (over two metres high), 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. Nevertheless, he was unable to negotiate sufficient space to house all the rapidly growing number of researchers within the new building and nearly half had to be housed in a separate building (known as the Inner Court Building) about half a mile away.

The new department had very substantial undergraduate teaching responsibilities. These included courses for the medical, veterinary and dental students as well as for a range of science degree students. Many of the courses needed to be set up essentially from scratch, of which the most pressing was the complete three years of the biochemistry BSc course. Philip set an excellent example by taking on quite a lot of undergraduate teaching himself, and this ensured that everyone in the department participated in the formidable teaching challenges with real enthusiasm and indeed great success.

In addition to having to address all these issues linked to setting up the new department, Philip closely supervised his own research group, which in the early years at Bristol was made up entirely of young and inexperienced research assistants and research students. He continued to spend a significant fraction of his time at the laboratory bench (figure 5). This was somewhat to the alarm of his young colleagues as, understandably, he was often preoccupied or interrupted with pressing departmental matters. He was still far from careful with his pipe, which, as in his Cambridge days, continued to be the cause of minor fires!

At first, research students in Philip’s group studied a range of topics linked to the research that had been so successful in Cambridge. These included studies into the role of glyceride stores in muscle (R.M.D.), growth hormone secretion (George Schofield), the regulation of HK and PFK (Paul England and Chris Pogson) and the control of the citrate cycle (Krebs Cycle) in the perfused beating rat heart (Paul England and R.M.D.). However, Philip’s research became increasingly focused on two topics: the control of insulin secretion (largely with S.J.H.A.) and the regulation of pyruvate dehydrogenase (PDH), an enzyme that plays a central role in the selection of fuels in muscle and other cells (often with R.M.D.). Despite his many responsibilities, substantial progress was made in both these fields.

**Insulin secretion**

The insulin-producing β-cells in the islets of Langerhans represent only around 1% of the total pancreas and are dispersed throughout the organ; hence, at the time of Hal Coore’s secretion
experiments, biochemical measurements on the islets were not feasible. However, shortly after S.J.H.A. joined the Randle group a major advance occurred in the study of insulin secretion when methods were introduced to separate the endocrine cells from the surrounding acinar pancreas, first by microdissection (Hellerström 1964) and later by the use of collagenase to disperse the pancreas (Lacy & Kostianovsky 1967). This permitted studies, for the first time, to test the substrate-site hypothesis by measuring rates of glucose uptake and oxidation from the isolated islet cells in vitro. These studies provided overwhelming evidence for the substrate-site hypothesis. The key findings were:

1. Glucose oxidation by isolated islets of Langerhans containing around 90% β-cells showed the same sigmoidal dependence on glucose concentration as did insulin secretion (11).
2. Only sugars capable of being metabolized by islets of Langerhans could stimulate insulin secretion (14).
3. Inhibition of glucose metabolism by islets caused a parallel inhibition of insulin secretion (16).
4. Hal Coore and Philip had shown that glucose-stimulated insulin secretion was inhibited by mannoheptulose, an inhibitor of glucose phosphorylation, but not by phloridzin, an inhibitor of glucose transport (7). They surmised that this meant that the rate-limiting step for glucose uptake into β-cells is phosphorylation of the sugar, as in liver, rather than membrane transport, as in muscle. They further suggested that since the $K_m$ for glucose stimulation of insulin release is around 6 mM, the enzyme catalysing glucose phosphorylation should have a similarly high $K_m$ for glucose, i.e. that the β-cells may contain glucokinase as in liver rather than the low $K_m$ hexokinase found in other tissues. These predictions were amply borne out by experiments on the metabolism of isolated islets (11, 14, 16) and glucokinase was identified in extracts of islets (10). Clinical relevance was later provided by studies from Andrew Hattersley
(FRS 2010) (Stoffel et al. 1992), who found that a mutation in β-cell glucokinase was one cause of maturity-onset diabetes of the young (MODY).

**Pyruvate dehydrogenase (PDH)**

The studies of R.M.D. while he was a research student of Philip were largely on the metabolism of adipose tissue, and Philip encouraged him to continue in this area after completion of his PhD. His subsequent studies showed that insulin acting on fat cells increased fatty acid synthesis from glucose not only by enhancing glucose transport into fat cells (which had been shown previously by others) but also by activating PDH (13). PDH is a remarkable complex of proteins that, with the help of tightly associated co-enzymes (thiamine pyrophosphate (TPP), lipoate and flavin adenine dinucleotide (FAD), catalyses the series of steps involved in the conversion of pyruvate to acetyl-CoA (Patel et al. 2014)—see figure 6 for more details. The basic enzymology and structure of the complex was largely determined by Lester Reed and his colleagues in Austin, Texas, in the 1960s (reviewed in Reed 1981). In 1969, Reed’s group then demonstrated that the complex was regulated by reversible phosphorylation (Linn et al. 1969). As summarized in figure 7, phosphorylation by a tightly-bound PDH protein kinase in the subunit (E1α) that catalyses the first step results in complete loss of activity. Dephosphorylation by a weakly-bound Mg2+ -dependent protein phosphatase (PDH phosphatase) restores activity of the complex. R.M.D.’ with Rick Martin, Hal Coore (returning briefly to the Randle group) and Philip, quickly showed the activation of PDH in fat cells incubated with insulin was the result of the dephosphorylation of PDH (12). These studies had the effect of greatly rekindling Philip’s interest in PDH. In the studies done in Cambridge, he had concluded that PDH was the most important site of inhibition of glucose metabolism by increases in fatty acid oxidation in heart and other tissues and that the inhibition of PDH was achieved through direct end-product inhibition by increased ratios acetyl-CoA/CoA and NADH/NAD++. The following five years of collaboration of Philip with R.M.D. and other colleagues into the regulation of PDH in mammalian tissues included the following highlights:

1. PDH phosphatase was shown to be activated by Ca2+ (15). This observation led eventually to R.M.D. and colleagues demonstrating that activation by Ca2+ of PDH and two other dehydrogenases in mitochondria was central to matching adenosine triphosphate (ATP) supply to the increased need in activated muscle and other tissues (Denton 2009).

2. Detailed studies of the regulation of PDH kinase confirmed its inhibition by pyruvate and adenosine diphosphate (ADP) (as found earlier in Reed’s laboratory), but in addition demonstrated that the kinase was activated by increasing ratios of NADH/NAD++ and acetyl-CoA/CoA. Thus increases in these ratios inhibited the activity of PDH not only by direct inhibition of catalytic activity but also by the increased phosphorylation of the E1α subunits (18).

3. Increased oxidation of fatty acids in the heart in a wide range of conditions (including after short-term starvation or experimental diabetes) was shown to result in increased phosphorylation (and hence inhibition of PDH activity), and this was probably brought about by PDH kinase activation following increases in acetyl-CoA/CoA ratios within mitochondria (19).
Figure 6. (a) Overall reaction catalysed by pyruvate dehydrogenase (PDH). (b) Sequence of reactions catalysed by PDH subunits E1, E2 and E3. The lipoate groups attached to E2 units allow a cycle of reactions, catalysed in turn by E1 (with TPP), E2 and E3 (with FAD). PDH in animal tissues is a large complex of more than 150 separate proteins (about 9 MDa). It is based on a hollow regular dodecahedral core made of 48 E2 and 12 E3 binding proteins (E3BP): bound to this core are 20 to 30 E1 molecules and 6 to 12 E3 molecules together with PDH kinase and PDH phosphatase. Each E1 molecule is a tetramer made up of two $\alpha$ and two $\beta$ subunits. (See Patel et al. 2014 for a recent review.)

4. The activation of PDH kinase by pyruvate could be mimicked by dichloracetate—this raised the important possibility of manipulating PDH activity in man by specific drugs (17).

While at Bristol, Philip gave the Banting Lecture of the British Diabetes Association (BDA, now Diabetes UK) in 1965 and was the first recipient of the Minkowski Prize of the newly formed European Association for the Study of Diabetes (EASD) in 1966. His Minkowski Prize lecture, published in 1966, was an important review of fuel metabolism in diabetes (9). He began to take an increasingly important role in the international diabetes research community, becoming chairman of the BDA Research Committee in 1971 and a member of the EASD Council in 1969.

The Bristol Department of Biochemistry under Philip was an exciting and enjoyable place to work in. His influence on the research students he supervised there, including both authors of this memoir, was immense. His intellectual rigour, his ability to identify and focus upon the essential aspects of important biochemical problems and his quite remarkable memory left an indelible impression on all those who worked with him. The young department had a happy atmosphere and a flourishing social life. On Sunday mornings Philip and many of the department were often to be found at the, then, brand-new university swimming pool. This could occasionally prove hazardous if one happened to become engaged in conversation with him while in the pool, since the conversation would usually take place in a part of the pool where he could comfortably stand but those of shorter stature were required to swim round
Figure 7. Regulation of PDH by reversible phosphorylation. Phosphorylation of sites in the α-subunits of E1 by ATP-linked PDH-kinases (PDK 1–4) result in near complete inhibition of overall PDH activity. Dephosphorylation of these sites by PDH-phosphatases (PDP1–2) results in the full recovery of activity. The PDKs are all activated by increases in acetyl-CoA/CoA and NADH/NAD\(^+\) and inhibited by increases in the concentration of ADP and pyruvate. PDP-1, but not PDP-2, is activated by Ca\(^{2+}\). (See Patel et al. 2014 for a recent review.)

and round to avoid drowning. Other social activities included picnics, cricket matches, discos and some memorable Christmas parties and a pantomime. Photographs of this period have proved difficult to find, but we have come across one (figure 8) of Philip playing cricket (he was still a formidable batsman) and another (figure 9) that shows Philip presiding (as ‘Baron Randle’) over a medieval banquet accompanied by departmental members and partners as his courtiers. This banquet, in Caldicot Castle, was organized in his honour just before he moved to the University of Oxford in 1975. His enormous contribution to Bristol biochemistry is still appreciated within the now School of Biochemistry. There is an undergraduate student prize in his name and a fine large-framed photograph of him in the entrance to the School.

**OXFORD: ANOTHER NEW DEPARTMENT**

In 1975 Philip moved to Oxford to found another new department, the Nuffield Department of Clinical Biochemistry (NDCB). This department was very different from the Bristol Department of Biochemistry. In marked contrast to the large Bristol department, the NDCB remained small (no more than three permanent academic staff) and highly focused on diabetes-related research, for which it soon gained an international reputation. The department had few undergraduate teaching responsibilities and the routine hospital laboratories were largely self-running. The great attraction of the post was probably the opportunity to spend increased time on his research interests and to be in a world-renowned clinical setting. Interestingly, the equivalent post became available in Cambridge at much the same time. This post was filled by Nick Hales—a co-author of the 1963 *Lancet* glucose fatty-acid cycle paper (5)!

Of his two long-standing Bristol colleagues, R.M.D. remained in Bristol to continue work on insulin action, mainly in adipose tissue and on the role of Ca\(^{2+}\) in mitochondria (both projects had grown out of his collaborations with Philip and both involved PDH), while S.J.H.A. moved with Philip to Oxford to pursue further studies on insulin secretion. These were extended now to include studies of the control of insulin biosynthesis; it was shown
Figure 8. Philip at the wicket in Bristol in 1974. (Photograph courtesy of Sally Randle.)

Figure 9. ‘Baron’ Philip presiding over his court. Caldicot Castle, 1975. (Photograph courtesy of Andrew Halestrap.)
that the specificity and concentration dependence of glucose-stimulated insulin synthesis corresponded with islet cell metabolic flux, suggesting that the substrate-site hypothesis was also applicable to synthesis of the hormone (Ashcroft et al. 1978; Ashcroft 1980).

As described above, S.J.H.A. had established while in Bristol that glucose metabolism within the β-cells was the key link between extracellular glucose concentration and the rate of insulin secretion. It had also been shown by Hales (Milner & Hales 1970) that a rise in intracellular Ca\(^{2+}\) concentration was a trigger for the secretion process. However, the link between metabolism and intracellular Ca\(^{2+}\) was unknown. The major breakthrough was the discovery of the key role of an ATP-dependent K-channel (K-ATP channel) in the insulin secretory response to glucose (Ashcroft et al. 1978). An increase in the rate of glucose metabolism within the β-cell leads to an increase in the intracellular ratio of ATP/ADP, which closes the K-ATP channels, leading to depolarization of the cell membrane and a consequent influx of Ca\(^{2+}\) ions through voltage-dependent K-channels. The increase in cytosolic Ca\(^{2+}\) concentration may lead in turn to activation of the mitochondrial pyruvate, iso-citrate and 2-oxoglutarate dehydrogenases with further increase in [ATP]/[ADP] and further Ca\(^{2+}\) entry. The K-ATP channel was also shown by Hales to be the site of action of the sulphonylureas long used to treat type 2 diabetes (Sturgess et al. 1985); by binding directly to a subunit of the K-ATP channel, sulphonylureas cause channel closure and subsequent insulin release. Philip took a keen interest in these developments and was always ready with encouragement and advice. He became especially interested in the effects of fatty acids on insulin secretion and wrote at length on this in his last published scientific paper (24).

Philip concentrated his own laboratory research on the regulation of PDH, initially with Alan Kerbey, who also moved from Bristol with Philip. This was to remain his main focus for the next 18 years until his retirement, aided by some very able research students and post-doctoral colleagues. Overall, although clearly productive (nearly 100 peer reviewed publications), this research did not quite match the impact of that carried out during his time in Cambridge and Bristol. Philip realized from studies in Bristol and then Oxford that the activation of PDH kinase in heart and other tissues during starvation and experimental diabetes was not fully explained by increases in acetyl-CoA/CoA resulting from elevated rates of fatty acid oxidation. PDH kinase activity was also increased in part by a longer-term mechanism (taking a day or two) and hence probably involving changes in gene expression and in turn protein synthesis. With Alan Kerbey, Philip found evidence for increases in an ‘activator’ protein that enhanced the rate of phosphorylation of PDH (22). In parallel studies with Peter Sugden and other colleagues, Philip also studied the role of the three different sites of phosphorylation on the E1α subunits of PDH (20). These studies concluded that one site (site 1) was phosphorylated first and was most important in inhibiting overall PDH activity, whereas phosphorylation of the other two sites (sites 2 and 3) might inhibit reactivation by PDH phosphatase. Subsequent studies in the laboratories of Robert Harris, Mary Sugden and others showed that four different isoforms of PDH kinase existed and that these isoforms are expressed in varying amounts in different tissues and under various conditions (Wu et al. 1998; Sugden & Holness 2003). Some of the observations of the Oxford group could now be explained. The ‘activator’ protein is probably one particular PDH kinase (PDK4), which is increased in amount in starvation and diabetes. Interestingly, all the isoforms phosphorylate site 1, but phosphorylation of sites 2 and 3 is probably restricted to PDK4 and PDK1 respectively. This means that the extent of multisite phosphorylation and its potential effect...
on PDH phosphatase is dependent on the expression of these isoforms and is, for example, greater in the heart than in the liver.

Philip also became very interested in the regulation of branched-chain oxo-acid dehydrogenase (BCOADH). This is an intramitochondrial enzyme complex that is catalytically and structurally closely related to PDH. It plays a central role in the metabolism of the essential amino acids leucine, isoleucine and valine. Philip and his colleagues were among the first to show that the enzyme, again like PDH, was regulated in the short term both by end-product inhibition and by reversible phosphorylation. They went on to investigate the kinase and phosphatase enzymes involved and their regulation in liver and other tissues, (21). Their observations explained how activity of BCOADH might be adjusted in the liver so that metabolism of the three essential amino acids matched their dietary input.

While at Oxford, his huge contribution to the understanding of the regulation of mammalian metabolism was recognized with a number of major academic honours. He gave the Humphrey Davy Rolleston Lecture of the Royal College of Physicians in 1983; he was elected to Fellow of the Royal Society in 1983; he was awarded the Portland Press Excellence in Science Award in 1984; he received a knighthood in 1985; and he became a Founder Fellow of the Academy of Medical Sciences in 1998.

During his time in Oxford, Philip took on many national and international responsibilities. These included appointments as chairman of a large number of research committees and boards for Diabetes UK, the MRC and the British Heart Foundation. He was also president of the EASD (1977–1980); vice-president of the Royal Society (1988–1989); and president of the Biochemical Society (1995–2000).

In the early 1980s, Philip devoted much of his great energy to advising the government on aspects of diet and food policy. In particular, he chaired the influential Food Policy Panel on Diet and Cardiovascular Disease that reported with great publicity in 1984. The advice within the report (sometimes called the Randle Report), reflecting the consensus view from research available at the time, concentrated on the need to reduce saturated fat in the British diet. The report had comparatively little to say on the problems of excess intake of sugars (except that it is associated with tooth decay!) and even less on the effects of ‘junk’ or ‘ultra-processed’ foods, which now are seen as at least as important as high dietary intakes of saturated fatty acids. It is also interesting that much of the advice on how the saturated fat content in the British diet may be reduced was addressed to individuals and the extent to which they should reduce the amount of meat, dairy products and other foods high in saturated fat in their diet; the report placed much less emphasis on the extent to which manufacturers should change the composition of their products.

In 2020, 57 years after publication of the Lancet paper on the glucose fatty-acid cycle (5) and 36 years after the ‘Randle Report’ on diet and cardiovascular disease, a session of the Annual Conference of the American Diabetes Association was devoted to ‘The Randle Debate: the effects of dietary carbohydrate, fat and caloric intake on metabolic disease’. This is an excellent example of the extent to which the research and scholarship of Philip Randle has fuelled debate, over nearly six decades, on the links between diet, balances between carbohydrate and lipid metabolism, obesity and a group of important metabolic diseases including cardiovascular disease and type-2 diabetes. There is now abundant evidence that the interactions of glucose and fatty acid metabolism as set out in the Lancet paper (see figures 2–4) are basically correct. Moreover, these interactions are a fundamental part of the changes in metabolism during the ‘feeding/fasting’ and ‘exercise/rest’ cycles that occur every
What has proved much more contentious is the hypothesis Philip and colleagues put forward in the *Lancet* paper that increased circulating fatty acids (and other lipids) may be linked to reduced effects of insulin on glucose metabolism in muscle, liver and other tissues, resulting in high circulating blood glucose concentrations.
and hence type-2 diabetes. One potential way of reversing this could be to activate pyruvate dehydrogenase by inhibiting PDH kinase activity, and Philip’s early studies in Bristol using dichloroacetate to inhibit PDH kinase were promising (17). However, neither dichloroacetate nor later more specific and potent PDH kinase inhibitors have proved useful in the treatment of type-2 diabetes, although these inhibitors may prove useful in other contexts, including cancer (Stanley et al. 1997; Zhang et al. 2015). In fact, it has become clear in the last 10 years or so that the crucial problem in type-2 diabetes is inadequate insulin release from the β-cells of the islets of Langerhans rather than muscle and other tissues becoming insulin-insensitive. The underlying cause of this failure of the β-cells and how this is linked to obesogenic diets and genetic factors have not been established (Kahn et al. 2014). It is even possible that long-term increases in blood lipids, including fatty acids, may play an important role in β-cell failure, which would not be so far from the basic hypothesis put forward by Philip and his colleagues in 1963!

**Personal and Family Life**

Philip’s cousin, John, recounts that, while Philip was single-mindedly focusing on his PhD studies,

his [Philip’s] social life was non-existent. So much so that when it came to my 21st birthday party he had to appeal to me to find him a partner. I had not had the same difficulty with my social life.
Philip married Elizabeth in 1952 (figure 10) and she was his constant companion until her death in 2004. They had a son, Peter (b. 1954), and three daughters, Rosalind (b. 1953), Sally (b. 1956) and Susan (b. 1959). It is noteworthy that in 1963, the year of publication of the glucose fatty-acid cycle paper in *The Lancet* (5), Philip’s children were 10, 9, 7 and 4 years old! A family portrait from this time is shown in figure 11.

Despite a lifelong devotion to science, Philip was very much a family man. Sally remembers him buying ice creams every day for his four children on holiday and later doing the same for his grandchildren, Milly, Lydia, Dexter and Stella; building elaborate cars out of sand on the beach for his children and grandchildren; lining his four children up along the wall on the beach and going back and forth with a bucket to collect water to wash the sand off their feet so they could put their shoes on.

Philip also loved good food and wine and good company. Elizabeth and he frequently entertained, and he had the great fortune to be married to a superb cook, although he was a pretty good cook too and used to make many meals on holiday. He also loved to eat out at restaurants. The family frequently went out for meals together when the children were young,
which in those days was unusual. Sadly, Peter died in 1971 while still a teenager. The death of his son at the age of 16, from an aggressive cancer, was a terrible blow to Philip and his family. Philip found some solace by immersing himself in the study of the regulation of PDH. He suffered also the loss of his wife in 2004 and his daughter Susan in 2005.

**Retirement**

Philip retired from his Oxford post in 1993. The major international scientific meeting held in his honour that year in Oxford was an eloquent testimony to the affection and esteem in which he was regarded throughout the world (figure 12). The meeting also celebrated the thirtieth anniversary of the publication of the glucose fatty-acid cycle paper in *The Lancet* (5), and it brought together all four distinguished authors (figure 13). For many years Philip remained academically active by writing review articles and refereeing papers for numerous journals. He died at the age of 80 on the 26 September 2006 at his home in Iffley, Oxford, from a sudden massive intracerebral haemorrhage. He left behind, however, an enormous legacy in his published work, the Bristol Department of Biochemistry and a worldwide network of past students and post-doctoral fellows who benefitted so much from his wise supervision.
and subsequent generous support. A permanent collection of Philip’s published work and other memorabilia has been established at the Oxford Centre for Diabetes, Endocrinology and Metabolism. His legacy is also remembered by the Sir Philip Randle Lecture of the Biochemical Society. This prestigious lecture is awarded every two years to a scientist from any part of the world on the basis of their contribution to the understanding of mammalian metabolism.

**HONOURS, DEGREES AND AWARDS**

*Civic honour*

1985 Knight Bachelor

*Degrees*

1947 BA First Class Honours, Cambridge  
1951 MA, Cambridge  
1950 MB, BChir, Cambridge  
1955 PhD, Cambridge  
1964 MD, Cambridge, by published work  
1964 MRCP, London, by published work  
1975 MA, DM, DPhil, Oxford (by incorporation)

*Fellowships*

1972 Royal College of Physicians of London (by election)  
1983 Royal Society  
1998 Founder Fellow of the Academy of Medical Sciences

*Other distinctions*

1965 Banting Lecturer, British Diabetic Association  
1966 Minkowski Prize, European Association for the Study of Diabetes  
1967 Bronze Medallist, Université Libre de Bruxelles  
1972 Copp Lecturer, La Jolla, CA  
1981 Wellcome Travelling Professor, Basic Medical Sciences  
1983 Humphrey Davy Rolleston Lecturer, Royal College of Physicians of London  
1984 Portland Press Excellence in Science Award  
1985 Ciba Medal, Biochemical Society  
1988 Honorary Fellow, Trinity Hall, Cambridge  
1989 Leithead Memorial Lecture, University of Addis Ababa  
1990 Albert Renold Memorial Medal, EASD  
1991 Honorary Fellow, University College London

*Appointments*

1951 House Physician to Professor M. L. Rosenheim (University College Hospital, London)  
1951 House Surgeon to Mr Julian Taylor and Mr W. R. Merrington
1952 House Physician to Dr J. B. Harrnan, St Helier Hospital, Carshalton
1952–1955 MRC Research Fellow
1954–1957 Sidney Sussex College, Cambridge, Research Fellow
1955–1964 University of Cambridge, Lecturer in Biochemistry
1957–1964 Trinity Hall, Cambridge, Fellow and Director of Medical Studies
1956–1964 Honorary Consultant in Chemical Pathology, United Cambridge Hospitals
1961 Visiting Professor of Physiology, Vanderbilt University
1963 Visiting Professor of Physiology, University of Buenos Aires
1964–1975 Founding Professor and Chairman, Department of Biochemistry, University of Bristol
1964–1975 Honorary Consultant in Biochemistry, United Bristol Hospitals
1975–1993 Founding Professor and Chairman, Department of Clinical Biochemistry, University of Oxford
1975–1993 Professorial Fellow of Hertford College, Oxford
1975–1993 Honorary Consultant in Chemical Pathology, Oxford Area Health Authority
1963 Visiting Professor of Physiology, University of Buenos Aires
1981 Wellcome Visiting Professor in the Basic Medical Sciences, Pennsylvania State University, Hershey, PA
1984 Visiting Professor of Medicine, Washington University, St Louis, MO

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The frontispiece portrait was taken in 1983 and is © Godfrey Argent Studio.

AUTHOR PROFILES

S. J. H. Ashcroft

Steve Ashcroft is Emeritus Fellow of Magdalen College, Oxford. He joined Philip Randle’s group in the newly formed Bristol Department of Biochemistry in 1975. Here he took his PhD and became a lecturer in biochemistry. In 1975 he moved to Oxford with Philip Randle, where he was appointed lecturer in clinical biochemistry and tutor in biochemistry for Magdalen College. He was made reader in clinical biochemistry in 1990 and retired in 2002. In 1979, he was awarded the Minkowski prize of the EASD for his research into the mechanisms regulating insulin production by the β-cells of the islets of Langerhans. The main focus of these studies was to determine the link between a rise in blood glucose concentration and the consequent increase in synthesis and secretion of insulin. The major conclusions were that the sugar exerts its effects via changes in the rate of its metabolism by the cell and that these changes affect rates of insulin production as a consequence of alterations in the activity of specific ion channels in the β-cell membrane. The relevance of these findings to human disease has become apparent in recent years.
Dick Denton is Emeritus Professor of Biochemistry, University of Bristol. He moved to Bristol in 1964 as a research student with Philip Randle, who had become head of the then new Department of Biochemistry. After his PhD, Dick Denton remained in Bristol for the whole of his academic career except for short periods of research with collaborators in the USA, Switzerland and Canada. He was promoted to professor (1987) and became head of the Department of Biochemistry (1995–2000). He was chairman of Medical Sciences and then founder dean of the Faculty of Medical Sciences (2000–2004). His research has concentrated on: the mechanisms whereby insulin regulates metabolism, particularly in fat cells; and the role of calcium ions in the regulation of intramitochondrial metabolism. In 1998, he was elected a Fellow of the Royal Society and became a founder fellow of the Academy of Medical Sciences. He has served on many research committees for Diabetes UK, the Wellcome Trust and the MRC. He was also a member of the MRC Council (1999–2004).

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