Early days: 1964-1968.

At the start of the Department, the study of the regulation of mammalian metabolism was the main focus of research. About one year before he left Cambridge to head up the new Department of Biochemistry in Bristol, Philip Randle and colleagues had written an influential review in the Lancet, entitled “The glucose-fatty acid cycle”. The paper discussed the inter-relationships between the metabolism of glucose and fatty acids in muscle and adipose tissue and their importance in understanding insulin sensitivity and the metabolic disturbances in diabetes. This was the foundation of much of the early research in Bristol within the Randle group and also within that of Peter Garland who moved with Randle from Cambridge to set up his own group and was a co-author of the glucose-fatty acid cycle paper. Initially, some emphasis was on determining the molecular basis of how the metabolism of fatty acids in starvation and diabetes led to the inhibition of the metabolism of glucose at multiple stages in its metabolism including glucose transport, glycolysis and intra-mitochondrial metabolism.

Research in this area in the new Department was funded by two substantial long-term grants which allowed it to be established very rapidly. One was from the Medical Research Council (MRC) which funded the setting up of the MRC Regulation in Metabolism Group. This long-term support for about 6 posts was to Randle and Garland together with Brian Chappell who also moved from Cambridge in 1964. Chappell with his ground-breaking research into the transporters that allowed the transfer of metabolites in and out of mitochondria brought a great deal of expertise relevant to the study of mitochondrial metabolism. The other grant was from the British Diabetes Association (BDA, now called Diabetes UK) and was for a substantial fixed annual sum for five years that could be used flexibly between salaries and running costs. These two funders have remained hugely important in the funding of metabolic research in Bristol over most of the next 50 years. As will become clear in this article, much of this research has been related to diabetes with much focussed on the means whereby insulin regulates glucose utilisation and other areas of metabolism as well as studies into the regulation of insulin secretion from pancreatic beta-cells. Another theme has been the study of the regulation of intra-mitochondrial metabolism (and here there is overlap with the topics covered in the article by Andrew Halestrap).

For the first few months, the groups of Randle, Chappell and Garland were housed temporarily in laboratories on D-floor of the then new Medical School to the west of the main entrance before being moved to new laboratories on the D and C floors when phase 2 (East Wing) of the Medical School was opened. The three research groups all contained research students and ex-research students that were part of the migration from Cambridge.
which was such a characteristic of the beginning of the Department. These included George Schofield, Dick Denton Chris Pogson and Steve Ashcroft with Randle, Tony Crofts and John McGivan with Chappell and David Yates with Garland. All within a few years were to become members of academic staff of the Department. Actually, the third and last phase of the Medical School was now being constructed and contained laboratories that were designed specifically for the groups of Randle, Chappell and Garland. The floor holding the Randle group was essentially a single large laboratory, largely designed by Schofield and Denton with intermittent instruction from Randle. The laboratory had the catchy name of M101 with M referring to the fact it was a mezzanine floor. It was destined to become the centre of metabolic research in the Department until the Integrated Signalling Laboratories opened in early 2001.

Even before the move to M101 and the other phase four laboratories, metabolic research in Bristol had started well. Within the Randle group extensive studies had been carried out in the perfused heart into changes in energy stores and metabolites that accompanied different metabolic fuels and workloads (Randle, England and Denton). These studies contained the somewhat unexpected observation that substantial increases in work by the heart were not accompanied by any apparent changes in the concentration of ATP. The explanation had to wait for an understanding of the role of calcium ions in mitochondrial metabolism as described later in this article. Strong evidence was also obtained that the glucose stimulation of insulin secretion from pancreatic beta-cells required the intracellular metabolism of glucose rather than glucose acting on some receptor, as generally thought at the time (Ashcroft, Hedeskov and Randle; Carl Hedeskov was a visitor from Copenhagen). Schofield developed new techniques for the study of growth hormone secretion from the pituitary and Denton for the study of fat cell metabolism. These latter studies were in part with a visitor from Canada, Mitch Halperin, who returned to Canada to undertake pioneering studies on acid-base balance in humans for which later he was elected a Fellow of Canadian Royal Society.

During this period, Randle became the first winner of the Minkowski Prize of the European Association for the Study of Diabetes (EASD) as well as the Banting Lecturer of the BDA.

Garland and his group, including Yates, carried out a wide range of studies defining the organisation and regulation of fatty acid oxidation within mammalian mitochondria. Garland won the Colworth Medal in 1968. In 1970 was appointed Professor and Head of the new Department of Biochemistry at Dundee University which he developed over the next ten years into one of the best departments in the UK. Subsequently, after a short time with Unilever, he became Chief Executive of the Institute of Cancer Research.


M101 was not the only laboratory in the Department in which the regulation of mammalian metabolism was studied but it was the focus for this research for over 30 years. The small
coffee/tea area of M101 was shared with the extensive washing facilities including for many years acid-baths for laboratory glassware and a noisy “steam-stripper” for the preparation of distilled water. It became the much-loved heart of the laboratory and the site of many discussions and the usually successful completion of the Guardian crossword each day. It was overseen by a series of excellent technicians including Mrs Harris and Mrs Burd who added greatly to the spirit of friendly co-operation. For nearly 25 years, Nigel Edgell, as senior technician, played a key role in ensuring M101 though usually very overcrowded was efficient and safe.

Soon after moving into M101, Denton showed that insulin activated pyruvate dehydrogenase in fat cells as a result of an increase in the proportion of its active unphosphorylated form. The regulation of this important enzyme complex became a major area of research for both Denton and Randle initially with Rick Martin (a student of Denton) and Hal Coore (a visiting Fellow from Jamaica). These studies uncovered a great deal about the regulation of the phosphatase and kinase enzymes involved in the interconversion of the active and inactive forms of pyruvate dehydrogenase. In particular, they led to the recognition that the phosphatase was activated by micromolar concentrations of calcium ions; a finding together with his earlier finding that insulin activated pyruvate dehydrogenase had a substantial influence on the subsequent research of Denton.

Also in M101, Ashcroft continued his work on the link between the metabolism of glucose and insulin secretion. Importantly, he showed that an increase in ATP concentration was involved. Schofield explored the regulation of growth hormone secretion and clarified the role of cyclic-AMP in effects of prostaglandins and somatostatin. Denton and his students concentrated on the actions of insulin on fat cell metabolism. With Andrew Halestrand, it was shown that the insulin stimulation of fatty acid synthesis from glucose involved not only activation of pyruvate dehydrogenase but also the activation of acetyl-CoA carboxylase. England, after a PhD studentship with Randle and a Travelling Fellowship with Ed Krebs (who was to win a Nobel prize in 1992) returned to concentrate on the role of phosphorylation in the regulation of contractile proteins, mainly in the heart. Pogson, spent a few years with the new Molecular Enzymology Group following his PhD with Randle, and then moved to M101 to set up the then new technique of isolated liver cells and used them to study the regulation of gluconeogenesis and associated amino acid metabolism. In 1974, Pogson moved to a Lectureship in the University of Kent and then became Professor and Head of the Department of Biochemistry at Manchester University before completing his career in the pharmaceutical industry.

In 1975, Randle departed to Oxford to become Chairman of the Department of the Department of Clinical Biochemistry. He received many honours for his research work on metabolic regulation carried out mainly in Cambridge and Bristol including FRS (1983), Knighthood (1985) and FMedSci (1995). Ashcroft also moved to Oxford and continued his studies on insulin secretion. These led to the recognition of the key role of the ATP-
regulated potassium channel in glucose stimulated insulin release. He was awarded the Minkowski Prize of the EASD in 1979.

After the departure of Randle and Ashcroft, the research groups of Denton, England, Halestrap and Schofield occupied M101 and research into regulation of metabolism was soon underpinned again by long-term support to Denton from both the MRC and BDA. Halestrap’s research now concentrated mainly on aspects of mitochondrial metabolism including pyruvate transport (and this is described in more detail in his article). Importantly, his work identified the mechanism of action of the most commonly used drug in the treatment of type 2 diabetes, metformin and he and his group went on to carry out many seminal studies on the mitochondrial permeability transition pore. England and his research group working mainly with the perfused rat heart established the role of phosphorylation on the calcium sensitivity of the inhibitor component of troponin and then went on to explore the role of phosphorylation of myosin light chains and C-protein in heart muscle contraction. England left the Department in 1985 to take up a senior research post in SKF (soon to become GSK). Chris Proud was appointed and he quickly established his research into the role of phosphorylation of initiation and elongation factors in the regulation of mammalian protein synthesis in M101. After 10 years he moved to a Chair in Biochemistry at the University of Kent and subsequently in Dundee, Vancouver and Southampton successfully continuing his research in the same area.

In the 1970s, Denton and his group had showed that the stimulation of fat cell pyruvate dehydrogenase by insulin involved the activation of pyruvate dehydrogenase phosphatase. However, it became clear that the mechanism involved was distinct from the activation of this enzyme by calcium ions. The role of the calcium ions activation was to become clear when they showed that two other important intramitochondrial dehydrogenases (NAD-isocitrate dehydrogenase and oxoglutarate dehydrogenase) were also activated by micromolar concentrations of calcium ions. The latter finding was made by Jim McCormack (then a PhD student of Denton) and this was the start of a productive partnership between McCormack and Denton which produced strong evidence that the parallel activation of the three intramitochondrial dehydrogenases by calcium ions was an important means whereby ATP synthesis was enhanced in stimulated cells in many circumstances without the need for any change in ATP concentration. For example, it explained the lack of change in ATP concentration as the work output of hearts increased which had been observed by Randle, England and Denton in the early days of the Department and mentioned above.

McCormack moved to Leeds in 1985 to take up a Lectureship and a Lister Fellowship before continuing his career in the pharmaceutical industry, mainly concerned with the development of new drugs for diabetes and cancer. In subsequent years, Andrew Thomas and Guy Rutter made major contributions to the understanding of the regulation of the calcium-sensitive intramitochondrial dehydrogenases. These included, in a collaboration in the 1990s, some of the earliest measurements of calcium ion concentrations within mitochondria of stimulated cells. Also in the 1990s, Ben Nicholls (a PhD student of Denton
and Len Hall) used molecular cloning to determine the full amino acid sequence of the three subunits of NAD-isocitrate dehydrogenase. It was the only remaining enzyme in the citrate cycle in eukaryotes that had not been sequenced at the time. Nicholls moved to the MRC Laboratory for Molecular Biology in Cambridge where he is now a Group Leader researching into mammalian endocytic pathways.

In 1981, Denton gave the Lawrence Lecture of the BDA. From the early 1980s, it had become evident from the studies of the Denton group that the early actions of insulin on fat cells involved the increased phosphorylation of a number of proteins as well as the expected dephosphorylation of other proteins such as pyruvate dehydrogenase. One of these was acetyl-CoA carboxylase where increased phosphorylation was associated with activation of the enzyme. These studies were largely carried by Roger Brownsey before he obtained a lectureship in the University of British Columbia. He is presently Professor and Head of Department of Biochemistry at this University. Another protein showing increased phosphorylation was recognised by a PhD student, Graham Belsham, and named 22 kDa phosphoprotein at the time because its role was unknown. In fact, many years later Belsham was involved in the identification of this protein as an important regulator of protein synthesis (4E BP1) while he was in the laboratory of Nahum Sonenberg in Quebec. Belsham is currently Professor at the National Veterinary Institute of Denmark. With Jeremy Tavaré, detailed studies were initiated into the early events including the increased phosphorylation of the insulin receptor that followed the binding of insulin to the insulin receptors on the plasma membrane. After a period in the USA on a MRC Travelling Fellowship, Tavaré returned, soon to obtain a BDA Senior Research Fellowship which he held for 10 years from 1991. He and Denton continued their successful collaboration into the mechanism of action of insulin for many years funded largely by long-term support from the MRC. Studies eventually concentrated on the role of insulin-activated protein kinases in which Kelly Moule, Kate Heesom and Gavin Welsh made major contributions and also increasingly on the means whereby insulin stimulated glucose transport. Rutter also had a very successful time during an MRC Travelling Fellowship based in Geneva and returned to set up a group studying insulin secretion and was appointed to a lectureship in 1995. In 1998, Denton was elected to Fellowships of the Academy of Medical Sciences and the Royal Society.

Under the influence of Tavaré and Rutter together with Peter Cullen who was appointed to a lectureship in 1996, the character of research in M101 and associated laboratories rapidly changed with the introduction of a full range of molecular genetic techniques and real-time cell imaging using mainly convocal microscopy. Schofield and Chappell were the first to introduce confocal microscopy into the department. Progress in this area became very rapid following the successful multi-departmental bid (led by Denton) to the MRC which funded the setting up of the Bristol Imaging Facility, with Schofield its first Director. Tavaré took over the Directorship after Schofield retired in 1998 and held this position until 2006. Important advances made at this time in the Department involving real-time imaging
included: following the rapid transfer to the plasma membrane of the glucose transporter and other proteins from intracellular sites in cells exposed to insulin (Tavaré); measurement of changes in mitochondrial calcium ion concentrations in beating heart cells (Griffiths, Rutter), detailed studies on the movement of insulin-containing granules together with associated changes in the concentrations of ATP and calcium ions in pancreatic beta cells initiated by glucose metabolism (Rutter); and investigations into the importance of inositol phosphates such as IP$_3$ and IP$_4$ in intracellular signalling (Cullen).

By the late 1990s, it was clear that M101 after 30 years of intensive use was hopelessly over-crowded and out-of-date. Luckily an opportunity arose to make a large multi-department bid (led by Denton) to the Wellcome Trust to allow the Integrated Signalling Laboratories (ISL) to be built in the space left by the transfer of the teaching laboratories to the refurbished East Wing of Chemistry. The end of M101 as the focus of research into the regulation of metabolism came in 2001 when the groups of Cullen, Denton, Rutter and Tavaré moved into new accommodation within the ISL while the group of Halestrap moved downstairs to the B-floor of stage 4.

**Modern times: 2001-.**

Moule, Heesom and Welsh continued to study insulin activated protein kinases often in collaboration with Tavaré and Denton. But soon their careers changed considerably. Moule became increasingly involved in teaching and the administration of teaching in the Department and Faculty were she is currently Director of Teaching. Heesom, on the other hand, moved in 2002 to Oxford GlycoSciences and into the world of proteomics. In 2004, she returned to the Department to set up the Bristol University Proteomics Facility of which she is still Director. Thus it is fair to say that that one of the important spin-offs from the research into metabolic regulation has been the setting up and development of both the Cell Imaging and Proteomic Facilities within Bristol University. Welsh now holds a Senior Lectureship in the School of Clinical Sciences and concentrates on the study of the regulation of kidney cells. Denton officially retired in 2005 but still does some part-time research. In the last year, he and colleagues have identified the calcium binding site within oxoglutarate dehydrogenase.

Rutter and his group used a remarkable array of imaging and other techniques to analyse the signalling pathways in pancreatic beta-cells. He was awarded the Minkowski Prize of the EASD in 2004. In 2006, he was appointed Professor and Head of Cell Biology at Imperial College, London and he remains at the forefront of research into the regulation of insulin secretion.

Tavaré gave the RD Lawrence Lecture of the BDA in 2000. He has continued to study the signalling pathways involved in the stimulation of glucose uptake by insulin. He and England founded Proxara Biotechnology Limited in 2000, a cancer drug discovery company supported by the Wellcome Trust. In 2010, Tavaré became Faculty Research Director and
then in 2012 the first Director of the Elizabeth Blackwell Institute which focuses on building new interdisciplinary research communities across the University.

Cullen and his group are now world leaders in research into the role of phosphoinositides in endosomal sorting and signalling in particular their role in recruiting proteins such as the sorting nexins to the surface of specific intracellular organelles. Cullen gave the Morton Lecture of the Biochemical Society in 2010.

Although the study of the regulation of metabolism is no longer a major focus of the research within the School, the legacy left from work carried out in this area over the first fifty years of Department/School is, nevertheless, substantial.

Bristol Regulation in Metabolism Group 1989.