# Robert Tattersall, a Diabetes Physician Ahead of His Time

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The clinical and research landscape in the U.K. was dominated in the 1970s and 1980s by clinician scientists. Many worked as full-time employees of the National Health Service rather than universities. During a period when health services were under less pressure than today, they were able to find sufficient time to design clinical studies to answer important research questions that occurred to them while treating their patients. They also inspired a generation of junior colleagues to join their specialty and become clinical researchers themselves. In many ways it was a golden age for clinical diabetes research in Britain. Clinician scientists within the diabetes field who attained international stature include John Ward and Peter Watkins, who made major advances in diabetic neuropathy; Harry Keen, who pioneered the use of insulin pumps and introduced microalbuminuria as a sensitive test for diabetic nephropathy; and George Alberti (1), who demonstrated how low-dose insulin could be used as a practical and effective treatment for diabetic ketoacidosis. But one individual who epitomized the clinician researcher was Robert Tattersall. His contributions were many and varied and led to improved care worldwide, while the diabetes unit he developed in Nottingham came to be recognized as one of the best in the country.

## Early Years

Robert was born in London in July 1943, the only child of Stanley Tattersall and Edith Booth, who were psychiatrists. He was brought up in the grounds of Bucks County Mental Hospital, where his father worked in a senior administrative position. He was educated at Charterhouse School (a private boarding school) and trained in medicine at the University of Cambridge and St Thomas' Hospital, London. After qualification he undertook his first junior post at St Thomas' before moving to Nottingham General Hospital, where he met his future wife, Bridget Jack, while they were both doctors in training. They then moved to London, and Robert started working for David Pyke, a consultant physician at King's College Hospital where he collaborated on the twin studies and concluded that types 1 and 2 diabetes had different etiologies. However, he is best known during his time at King's for his work on what became known as MODY.

*Young Robert's first day at school (1948)*

## Maturity-Onset Diabetes of the Young (MODY)

Robert takes up the story: "On Tuesday mornings at King's we were doing a study of 92 patients who had had diabetes for 40 years or more (2). By chance I saw the only one who was not taking insulin (she had been in the past). I took a very full family history and discovered that others in her family had been able to come off insulin. When I mentioned this to David Pyke he said 'she sounds just like the Mason family.' I trawled through the records at King's and found another patient with this curious type of diabetes—she no longer attended the clinic but I managed to track her down."

At the suggestion of David Pyke, Robert applied for and was awarded a fellowship to the University of Michigan in Ann Arbor, where Stefan Fajans was researching what appeared to be a similar type of diabetes. Their joint work was clearly productive. They published papers describing monogenic forms of diabetes and coined the term "maturity onset *type* diabetes of the young" to

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*Robert and Bridget cutting their wedding cake (1969)*

distinguish it from type 2 diabetes, which in the 1970s was labeled maturity-onset diabetes (3).

In 1974 Robert returned to the U.K. to take up an academic position at St Bartholomew's Hospital as Senior Lecturer, but in 1975 he moved up to the Nottingham General Hospital as a Consultant Physician in medicine and diabetes. It was an exciting time to be working in Nottingham, where there was a new medical school. Tony Mitchell, the Foundation Professor of Medicine, was attracting physicians who were committed to clinical research, and Robert fitted the profile.

## Investigating the Somogyi Effect

Robert went on to pursue a number of different research ideas, some of which were to have a profound influence on clinical practice. He also attracted high-quality fellows to work with him. With his registrar Edwin Gale he set out to explore the cause of overnight rebound hyperglycemia. This had come to be called the Somogyi effect and was firmly established as an important clinical phenomenon. It had been attributed to a sympathoadrenal counterregulatory response during overnight hypoglycemia causing high glucose levels on waking. Thus, the popular, albeit counterintuitive remedy at the time for high glucose values on waking was to reduce the evening dose of insulin to prevent hypoglycemia overnight. This was long before the use of continuous glucose monitoring (CGM), so Edwin and Robert persuaded adults with type 1 diabetes to come into hospital and be studied overnight with regular blood draws to measure glucose, counterregulatory hormones, and insulin levels (4). They found that the 7 of 15 individuals who exhibited raised fasting glucose levels following overnight hypoglycemia had no increase in counterregulatory hormones but had inappropriately low insulin levels, and they concluded that this rather than hypoglycemia was the cause of rebound hyperglycemia. Later, studies at Yale University and elsewhere showed that sympathoadrenal responses are suppressed during sleep. More recent research using CGM has confirmed that with the advent of longer-acting insulin analogs, the concept of rebound hyperglycemia with no intervening meal as a spontaneous response to hypoglycemic episodes is largely a myth.

## Self-Monitoring of Blood Glucose

Arguably the greatest contribution that Robert made to the diabetes field was the first demonstration that people with diabetes could both measure their own blood glucose and use the information to adjust their own therapy to try to maintain glucose levels at target. Clara Lowy, a physician working at St Thomas' Hospital in London had originally used the technique on a pregnant lady, but Robert and Peter Sönksen (who also worked at St Thomas') extended it to others. Patients were provided with bulky, cumbersome machines that had to be connected to power sockets to use at home, but in parallel articles published in *The Lancet*, Sönksen and Tattersall showed clearly that self-monitoring of glucose was not only feasible but led to improved levels of blood glucose and patient satisfaction (5,6). Interestingly, when their ideas were discussed at a British Diabetic Association (BDA) professional meeting, the proposal that patients should both measure their own glucose and adjust insulin doses on the basis of the results was regarded as incredible and even potentially dangerous! In a prophetic comment in the article in *The Lancet* (6), Robert and colleagues included in the abstract the following understatement: "Smaller and more portable machines will make the technique more widely applicable."

The revolution in blood glucose monitoring that followed has probably done more than any other single therapeutic development in equipping people with diabetes with the ability to adjust their own therapy. It has allowed them to achieve the levels of glucose necessary to prevent diabetic complications as well as reduce the risk of hypoglycemia. Without self-monitoring of blood glucose, it would not have been possible to undertake landmark trials such as the Diabetes Control and Complications Trial (DCCT) and develop modern approaches to diabetes management such as flexible intensive insulin therapy. It also demonstrated to professionals that people with diabetes were perfectly capable of managing their own condition expertly if given the opportunity and the appropriate education.

## Brittle Diabetes

I was one of the fortunate trainees who had the opportunity to work on the Tattersall team. I had arrived in Nottingham in 1981 with the firm intention of pursuing a career in cardiology but rotated onto the diabetes team for 6 months initially. It was Robert who persuaded me that a career in diabetes could be both fascinating and rewarding, and it was a choice I have never regretted.

I was able to witness firsthand Robert's insight (related perhaps to the influence of his parents and his wife Bridget Jack, who is a child psychiatrist) into a condition, which in the early 1980s was considered an almost intractable problem. The term idiopathic brittle diabetes was generally used to describe young people, usually adolescent girls, who had extremely unstable diabetes with frequent episodes of diabetic ketoacidosis (DKA). Many of these young patients spent months in hospital while undergoing studies that tried to discover why insulin was ineffective for them when delivered subcutaneously. Since their DKA responded to conventional treatment with intravenous insulin infusion, many believed that those affected had a defect in subcutaneous insulin absorption. Studies were published describing these abnormalities in high-quality journals, including *Diabetes* (7–9).

Yet Robert had formed the opinion very early on that most brittle diabetes was factitious and due to deliberate omission of insulin, which was concealed from the medical staff. He describes conversations he had when working at

King's College Hospital with a doctor, Helen Pond, who told him about the manipulations and subterfuges used to conceal the cause of brittle diabetes. Bridget encouraged him to use family therapy with some of the patients attending the Nottingham Diabetes Unit. He describes one encounter with one patient and her family: "This was a real eye-opener. With the first family I used it, I asked whether anyone had any idea why the girl kept coming in in DKA. One sibling said 'because she doesn't take her insulin,' while a second said 'anyone would want to get away from this family.'"

In a thoughtful and perceptive editorial published in the *British Medical Journal* in 1985 (10), Robert wrote, ". . .diabetologists commonly miss factitious disease, . . .partly from a deep seated reluctance to believe that patients would deceive us wilfully. . . and. . . because we have a stereotyped picture of the sort of patient we would expect to 'cheat,' which often excludes those considered to be 'normal and nice.'" Shortly afterward, David Schade published his own experience of treating these patients in the U.S. and confirmed that virtually all the "brittle diabetes" among the patients he had been referred from across the country was factitious (11). It is noteworthy that nowadays the term brittle diabetes is rarely used, and it is widely recognized that omission of insulin is common, particularly during adolescence.

## Dead in Bed Syndrome, a Seminal Paper

During the late 1980s, the insulin companies had developed genetic engineering techniques to produce insulin of human structure and began introducing it to replace bovine and porcine insulin. Apart from guaranteeing a reliable insulin supply, in other respects it seemed to offer few advantages. Indeed, in some countries, notably Switzerland and the U.K., reports began emerging that some patients had developed impaired awareness of hypoglycemia after switching. These reports began to raise concerns among some people with insulin-treated diabetes. Matters were brought to a head in the U.K. in 1989 when, at an inquest of a young individual with type 1 diabetes, a biochemist stated that he was aware of other deaths among young people with type 1 diabetes who had been taking human insulin. This statement, reported widely by the lay press, turned the concerns into more widespread alarm, and the BDA (the forerunner of Diabetes UK) came under considerable pressure to investigate. Robert, who was chair of the BDA Medical Advisory Committee at the time, undertook this. He and a colleague, Geoff Gill, then set out to investigate deaths of adults with type 1 diabetes under age 50. Their inquiry was extremely thorough. They sought information from clinicians and relatives, studied the medical records and autopsy reports, and gathered as much information as they could. They then published their findings in *Diabetic Medicine* with the title, "Unexplained deaths of type 1 diabetic patients" (12).

In a number of cases they found clear causes of death, such as ketoacidosis, suicide, or hypoglycemic brain death, and in a few they could not assign a cause. However, what caused particular interest was a group of 22 individuals under 40 years old who exhibited a distinct mode of death. Of these 22, 20 were found dead, and where the death could be timed, 17 had died during the night. The scenario was of young people, apparently well, who had retired to bed and were then found in the morning lying dead in an undisturbed bed. Autopsy revealed no obvious cause of death. Most had experienced previous problems with nocturnal hypoglycemia. There was thus strong circumstantial evidence that hypoglycemia had, in some way, contributed to the patients' deaths. In an accompanying editorial, Ian Campbell coined the term "dead in bed syndrome" and the name has stuck (13).

Nearly 30 years later, we remain unsure what led to the deaths of these young people. But over the subsequent years a number of epidemiological studies have confirmed the mode of death; one indicated that sudden death appeared to be 10 times more common than in a population without diabetes. A recently published case history reported a case of dead in bed syndrome in an individual who had had a CGM device attached, and the article contains a chilling figure confirming that the cause of death was profound nocturnal hypoglycemia (14). No cause of death was found at autopsy and it was likely that this 23-year-old man had died an arrhythmic death due to hypoglycemia. Other studies have demonstrated that experimental hypoglycemia can cause abnormal cardiac repolarization and that some individuals develop arrhythmias during clinical episodes of hypoglycemia. Thankfully, fatal episodes remain very rare, while nocturnal hypoglycemia is common. The characteristics that might identify those at increased risk remain elusive; this has prevented a clinical approach that would allow patients with diabetes to be screened and perhaps protected using pacemakers or implantable defibrillators. Nevertheless, the meticulous and logical approach to the problem, the detailed description of the findings, and the thoughtful discussion in the original paper (described by some as seminal) exemplifies Robert's approach to clinical problems.

## Medical Historian

In the early 1990s, Robert had become somewhat disillusioned with the direction that clinical medicine was headed in the U.K. and he returned to another interest that had attracted him while he was at university. With an award from the Wellcome Institute for the History of Medicine, he spent 4 months studying medical history. "Bitten by the history bug," he retired from clinical practice and in the following years wrote a dozen papers on medical history, including two books on the history of diabetes. The first was one of a series of brief historical monographs that was published in 2009 as *Diabetes: The Biography* (15). However, he had collected considerable material that was unused and was encouraged to publish it as well. He went on to write another book, *The Pissing Evil: A Comprehensive History of Diabetes Mellitus* (16). It was well received, and in a foreword to the book, Edwin Gale, his former fellow who himself had pursued an outstanding career as a researcher and Editor in Chief of *Diabetologia*, wrote, "This history of diabetes, many years in the making, is the heavyweight successor to Robert Tattersall's masterly *Diabetes: the Biography*, which came out in 2009. I thought at the time that there was little more to say on the subject, but *The Pissing Evil* shows I was wrong. It is, as it says, a 'comprehensive' history of diabetes, written from the stand-point of the hands-on clinician, although it makes good use of the rare but invaluable glimpses that past victims have given us into the actual experience of diabetes" (16).

*Robert on vacation near the Rongbuk monastery in Tibet with Mount Everest behind him (2005)*

## Final Thoughts

During his career, Robert had recognized that diabetes is an almost-unique disease in that the success of the treatment depends not on the professional carers but on the person with the condition. He encouraged those who worked with him to listen to their patients and ensure that those with the condition were equipped with the complex skills to manage it themselves. Thus, the role of the professional was to support patients in the daunting task of implementing and sustaining these skills on a day-to-day basis. This approach was allied to his ability to identify important questions that could be answered by imaginative clinical studies that changed practice and led directly to improved care.

Robert and Bridget now live in Sheffield in the north of England. They have two daughters (one, a consultant rheumatologist, works in my own hospital in Sheffield) and five grandchildren. Robert has never regretted what many believe was a premature retirement, but his continued influence is reflected in what is now accepted as the modern approach to management of diabetes.

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