An Appreciation of Robert Turner

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Robert Turner (1938–1999) was a remarkable man. Although he is perhaps best known for the groundbreaking UK Prospective Diabetes Study (UKPDS), the breadth and depth of his contributions to diabetes research are remarkable. It is a privilege for us, just a few of his many close friends and colleagues, to be able to review his contributions as a scientist and to remember him as a unique human being. His seminal discoveries spanned three broad areas of diabetes research—namely, the physiology of insulin secretion, the etiopathogenesis of type 2 diabetes, and the clinical management of diabetes. In all of these areas, his combination of intense curiosity, intelligence, indefatigability, and passion for improved patient care led to landmark discoveries that have withstood the test of time.

Robert was a medical student in Cambridge and undertook his clinical training and MD research at the Middlesex Hospital in London with Dr. John Nabarro; his thesis was entitled "Plasma Glucose Control of Insulin Secretion in Man." The interactions of insulin and glucose occupied much of his physiological interests in those early days. His early mathematical examination of insulin delivery rate (1) was rediscovered many years later, and the concepts of feedback control were brilliantly exemplified with fish insulin, which cleared glucose but did not cross-react with insulin assays, thus allowing endogenous insulin to be assayed (2). In these early days, through exposure to scientists such as Roger Ekins, a pioneer of immunoassay, Robert was discovering that lab-based techniques were the window into complex in vivo interactions.

He moved to Oxford in the early 1970s and began to develop the Diabetes Research Laboratory (DRL), which, from humble beginnings, became one of the world's leading centers for diabetes research. The DRL began to hum with activity as the charcoal separation assay developed when Robert was working with Ekins at the Middlesex was further refined and perfected (3). C-peptide assays then came online, and the complex interactions between glucose and insulin began to be delineated and modeled. Robert attracted enthusiastic young clinical researchers such as Rury Holman and David Matthews with a like-minded bent toward mathematical understanding of physiology, and their studies of feedback models of the "liver-β cell loop" (4) and the description of insulin oscillations (5–7) proved to be seminal observations that continue to influence physiological thinking to this day. These were further formalized and delineated in the homeostasis assessment (HOMA) and continuous infusion glucose model assessment (CIGMA) models (8,9) that are now used widely. The original article describing HOMA has been cited >4,600 times (8). Importantly, these observations reflected Robert's philosophical view that diabetes should be considered as an endocrine disorder (indeed, the most important endocrine disease) involving dysfunction of the endocrine cells producing the critical hormone insulin. That may seem obvious now, but at that time, there was a widespread (and entirely false) hierarchical division in the U.K between "clever endocrinologists" who worked on fascinating but relatively uncommon endocrine disorders requiring deep thinking and sophisticated investigation, and seemingly worthy but intellectually pedestrian "sugar doctors" who struggled to look after vast numbers of patients with a common but rather uninteresting disease. Robert once commented that he would not rest until a clinician seeing a patient with diabetes would be fueled by the same desire to understand its mechanisms as was an endocrinologist when seeing a new patient with Cushing's syndrome.

Although Robert was equally interested in improving the clinical care of patients with type 1 or type 2 diabetes, he realized quite early on that he was not an immunologist and that he would be most usefully employed working out why people developed type 2 diabetes. As was so often the case, Robert's views went against the mainstream but turned out to be right. For decades, during which the concept of insulin resistance came to utterly dominate international thinking about the pathogenesis of type 2 diabetes, Robert and his colleagues, with a small but insightful band of international colleagues (including Erol Cerasi, Gordon Weir, and Dan Porte) continued to emphasize the critical importance of inherent defects in pancreatic β-cell function as a key etiological factor in the disease (10). It is sad that he did not live to see the results of the recent genome-wide association studies, which have finally vindicated his view that the principal source of inherited variation predisposing to type 2 diabetes is likely to be in genes involved in islet function (11). Robert's work on the etiopathogenesis of type 2 diabetes can now be seen as a coherent and prescient body of work that was ahead of its time. With Rury Holman and David Matthews, he characterized the nature of the quantitative and qualitative defects in β-cell function in patients at the early stages of type 2 diabetes (4,12). Stephen O'Rahilly joined the team as a research fellow, and together they demonstrated that such β-cell defects were also present in nondiabetic first-degree relatives of patients with type 2 diabetes, suggesting that such defects were inherent to the disease process (13). Robert was never content to restrict himself to physiological observation and wanted to have a

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deeper knowledge of the underlying processes. He was one of the first to administer glucagon-like peptide-1 to individuals with diabetes (14,15), with results that are the cornerstone of much current therapeutic interest. He was never very enthusiastic about animal models and felt that the greatest insights would come from the study of human material. "I'm not very interested in rats," he often said. Anne Clark joined the DRL in 1981 and undertook painstaking and groundbreaking work on the histology of the pancreas in human type 2 diabetes, quantitating and emphasizing the potential importance of the long-neglected islet amyloid that was characteristic of the disease (16). Anne and Robert encouraged Garth Cooper, a research fellow recently arrived from New Zealand, to work with Ken Reid in the Medical Research Council Immunochemistry Unit to see if the protein component of islet amyloid could be isolated and characterized. Cooper's quest was successful, and the discovery of islet amyloid polypeptide/amylin (17) had "spin off" consequences for which long-term effects (if perhaps through circuitous routes) are now having beneficial impacts on patient care through discoveries emanating from Amylin Pharmaceuticals.

Robert was always motivated by the desire to push the science of human diabetes forward and was never constrained by parochial instincts to keep things "in house." Oxford was well placed to exploit the molecular biological revolution of the 1980s, and Robert, realizing that the DRL needed to engage with this field, generously supported Steve O'Rahilly to move to the hematology department at the John Radcliffe hospital, where Jim Wainscoat, a disciple of David Weatherall, the father of U.K. human molecular genetics, was developing his laboratory. Using the family samples that had been collected for physiological studies, O'Rahilly started to undertake some of the first (and very naive) DNA polymorphism–based linkage studies in type 2 diabetes. These studies had the advantage of novelty but the downside of negative results. However, a couple of years later, Andrew Hattersley joined the DRL as a research fellow and, again working in the Wainscoat lab, undertook the linkage study that led to the identification of the glucokinase gene (simultaneously with Philippe Froguel, working in France) as the first defined monogenic disorder leading to human diabetes (18). Diabetes genetics rapidly became an international collaborative effort, and the Oxford lab made important contributions to the discovery of other maturity-onset diabetes of the young (MODY) genes led by Graham Bell in Chicago and Froguel (19).

Robert remained an active clinician throughout his professional life, running a diabetes clinic at the John Radcliffe hospital and participating in the general medical rota at the hospital. His research was always motivated by a passionate desire to improve patient care. He was an international authority on the diagnosis of spontaneous hypoglycemia (2,20,21) and coauthored with George Alberti and Derek Hockaday a seminal paper on the use of low-dose insulin for the treatment for diabetic ketoacidosis (22). Unknown to many people is the fact that, having been intrigued by a toy cash register, he inspired the development of the first automatic lancet for fingerprick blood testing. However, his greatest contribution to the care of patients with diabetes was his demonstration that improved glycemic control of type 2 diabetes resulted in their improved clinical outcome. In 1976, Robert, while feeling unwell in Delhi, had scribbled some notes on a small slip of paper. It was the outline of the UKPDS (23) that he saw come to fruition 21 years later (24–27). The question was conceptually simple, but its answer was to have a profound impact on patient care. Would improved glycemic control in patients with type 2 diabetes convincingly result in improved morbidity and mortality? The answer was yes, and millions of patients now benefit from the implementation of the principles established by this study. Few clinicians outside Oxford know of the superhuman efforts (often appearing Sisiphyean) that Robert made to convince a multiplicity of anxious funders to initiate and continue to support this study. He once calculated, only 10 years into the study, that he had written his own body weight in grant applications. No single agency would fund the study. It was patched together from the Medical Research Council and charitable and industrial sources with invaluable support from the National Institutes of Health, which was imaginative in its international outlook. It lurched from funding crisis to funding crisis, but throughout this purgatory, Robert, when turned down (as he often was), would always say, "They actually didn't mean 'no.' What they meant was, if we come back with this or that alteration, they will give us some money." As well as the simple and clear bottom line results of the UKPDS, this study has generated more than 80 scientific papers, illuminating important aspects of the natural history of diabetes and its associated complications and risk factors (28,29).

In this brief article, we hope we have captured a flavor of the major scientific accomplishments of Robert Turner: a manifestly extraordinary clinician-scientist and mentor. However, impressive as this account is, we felt that we could not put this article to bed without some more personal testaments.

D.R.M.'s comments. On a more personal note, I first met him in my days as a medical student when he was one of the younger clinical staff members undertaking teaching. He took a close interest in the skills of clinical work; he was keen to teach and was friendly and approachable. He became a medical tutor at the Radcliffe Infirmary and wrote a succinct gem of a book, *Lecture Notes on History Taking and Examination* (30), which many of us used as our basic primer of clinical skills. He was a delight to work for clinically, and he and David Weatherall instilled the sense of camaraderie so necessary for a successful "firm." He took over the Regius Professor's laboratory when Richard Doll was the incumbent. Many assays were developed, and large throughput was the order of the day. Insulin-free plasma for the assays was a necessity, and this could be generated from random blood samples, spun down, with the plasma treated with activated charcoal. One day, Melanie Burnett, our longstanding, long-suffering assayist, showed me a centrifuge cuvette of compacted red cells and supernatant plasma. The red cells occupied only a small proportion. The sample turned out to be from Robert. A tour through the labs revealed that everyone was using him as a ready source of plasma. His hemoglobin turned out to be the wrong side of 10 g. He had to go on iron, and we had to enforce a moratorium. No one was to bleed the boss!

Research meetings were a great forum and a wonderful training arena. Anyone could say anything and challenge anything—and did. Robert used to love it. He would think and change his mind and debate and turn ideas over. He was passionately interested in diabetes and its causes and its physiology.

The UKPDS bit into Robert's patience and demonstrated that he was a man of true and unstoppable determination. It was planned as a 10-year study in total, but with progressive recruitment and attrition, it took 20 years. There were many naysayers, and one always heard grumblings that, because money had been given to the UKPDS, other important work had not been funded—the important work in question always and unaccountably belonging to the complainant. Robert orchestrated the triumphant success of the UKPDS at the European Association for the Study of Diabetes (EASD) meeting in 1998 and tragically died the next year while visiting the U.S. to present more results there.

Those of us who worked with Robert for decades will always be deeply grateful to him. He had an insatiable enthusiasm for research, a broadness of mind, exuberance under challenge, a humorous banter in debate, and an unstoppable determination. He was generous, clever, self-effacing, and kind. He is still much missed.

G.C.W.'s comments. It is most unusual for a postdoctoral fellow to serve as the key mentor of a younger postdoctoral fellow, but of course Robert was most unusual. My initial research assignment in the Diabetes Unit at Massachusetts General Hospital was to work on insulin-stimulated glucose transport, but my rescue from that fate was facilitated by this charming, energetic Englishman. Robert's fascination with islets and insulin secretion captivated me. His project was to stimulate the growth of new β-cells, building on the hypothesis that "intermediate cells" in pancreatic ducts could make new islets when rats were fed soybean meal, which inhibited trypsin activity. Sadly, his prescient efforts on what is now the hot topic of neogenesis did not lead to much—except lab nooks and crannies full of soybean meal and appreciative cockroaches. Within a short time, Robert's infectious nature took hold of me, and I was allowed by my generous lab chief, Donald Martin, to work on islets, in particular, the glucagon section. Paying attention to Robert's lessons about rigorous approaches to radioimmunoassays and using his charcoal striping method, I stumbled into finding that Roger Unger's glucagon assay results with the famous 30K antibody were much too high because of an interfering factor. This impudent assertion provoked considerable consternation but turned out to be correct.

That time was the beginning of a treasured friendship between Robert, Jennie, Susan Bonner-Weir, and myself, which led to wonderful times skiing in France and meeting for vacations at our country house in Vermont and in Scotland, Oxford, and Boston. This was enhanced by their two sons and our daughters being of similar age. I still can't believe that Robert and I found double black diamond ski runs for which neither of us had the skill; yet, somehow we survived. Anyone familiar with Robert and Jennie can appreciate the range of our conversations on every conceivable subject. Among all of this were countless discussions about our mutual favorite subject, diabetes. For us, the primacy of the β-cell in the pathogenesis of type 2 diabetes was obvious from the beginning, but we frequently talked long into the night about virtually everything having to do with diabetes. A dominant theme was the patient with diabetes. Not only did he speak affectionately about individual patients under his care, but his research was always directed toward something that would improve their lives. I have been privileged, along with Rury, David, and a few others, to follow in detail the entire progression of the UKPDS. Robert's single-minded tenacity and passion in the face of seemingly insurmountable obstacles astonished me. It was so fortunate that he lived to see his success. One of our most special times together was in the spring before he died; he and Jennie followed his time as Joslin's Marble Visiting Professor, with a visit to see us in Vermont for a weekend. Susan and I miss him terribly.

S.O.R's comments. In 1983, I took an afternoon off from my clinical duties as a senior house officer (resident) at the Hammersmith Hospital in London to see Robert, having been advised by a fellow senior house officer who had been his intern that he was a "really nice and interesting bloke!" I was an Irish medical graduate, with few connections in the U.K., absolutely no research experience, and a vague notion that "doing some research" might be important if I wanted to be a good hospital physician. Given my status as a scientific tyro, there was absolutely no chance that I could obtain any competitive funding to do research, but Robert spotted something in me and committed to funding me for a year out of his "back pocket" with a vague aspiration that we would see where things might go. The following 5 years in Oxford changed my life. The excitement of lab meetings where Robert, David Matthews, Rury Holman, Anne Clark, and lots of bright fellows would "ping-pong" ideas for hours on end was thrilling. After 6 months of this, I reflected on the fact that someone was paying these people a living wage for having fun. I decided I wanted a piece of this action, and my career aspirations changed dramatically and irrevocably. Robert's intellectual and personal generosity was hugely inspiring. On many a Saturday morning, when I had convinced an entire family to come to Oxford for CIGMA tests, Robert, knowing the skeleton staff we had, would just "appear" to help

with phlebotomy. Throughout my time in Oxford, Robert and Jennie made their home a welcoming haven for me and many other waifs and strays from all over the planet. Robert had another long-lasting effect on my life. Suzy Oakes, who administered the UKPDS from its early days with a passionate commitment inspired by Robert, was inexplicably diverted from this vocation in 1990 to join me in Boston, where we married.

Conclusions. We now live in an era in which "translational research" has finally taken center stage in the world of biomedical science. There is widespread concern about the global dearth of academic clinicians who can understand and illuminate the fundamental biology of disease and also translate that understanding into clinical benefit. Such rare individuals are now nurtured and treasured like ineffectually breeding pandas. It is tragic that Robert's premature death occurred at precisely the time when this realization had dawned on the world leaders of biomedical science who had perhaps been temporarily blinded by the beauty of "pure" science to the importance of focusing on human suffering and its alleviation. It is inexpressibly sad that Robert did not live to see the full and formal appreciation of his remarkable contributions to diabetes research and to his mentorship of the next generation of leaders in this field. Internal and external accolades such as his professorship at Oxford and distinctions bestowed by international organizations came at an inexplicably late stage in his career. Had he still been with us, he would have been increasingly seen as a unique exemplar of clinical science and been garlanded with many more glittering prizes. Knowing Robert as we did, however, it would have been of much more importance to him to have "made a real difference." This he certainly did—to the lives of innumerable patients with diabetes living today and to the improved care of future patients through the work of clinicians and scientists on whom he has had a profound and irrevocable influence.

REFERENCES

1. Turner RC, Grayburn JA, Newman GB, Nabarro JD: Measurement of the insulin delivery rate in man. *J Clin Endocrinol Metab* 33:279–286, 1971
2. Turner RC, Johnson PC: Suppression of insulin release by fish-insulin-induced hypoglycaemia: with reference to the diagnosis of insulinomas. *Lancet* 1:1483–1485, 1973
3. Albano JD, Ekins RP, Maritz G, Turner RC: A sensitive, precise radioimmunoassay of serum insulin relying on charcoal separation of bound and free hormone moieties. *Acta Endocrinol (Copenh)* 70:487–509, 1972
4. Turner RC, Holman RR, Matthews D, Hockaday TD, Peto J: Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. *Metabolism* 28:1086–1096, 1979
5. Lang DA, Matthews DR, Peto J, Turner RC: Cyclic oscillations of basal plasma glucose and insulin concentrations in human beings. *N Engl J Med* 301:1023–1027, 1979
6. Matthews DR, Naylor BA, Jones RG, Ward GM, Turner RC: Pulsatile insulin has greater hypoglycemic effect than continuous delivery. *Diabetes* 32:617–621, 1983
7. Matthews DR, Lang DA, Burnett MA, Turner RC: Control of pulsatile insulin secretion in man. *Diabetologia* 24:231–237, 1983
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
9. Hosker JP, Matthews DR, Rudenski AS, Burnett MA, Darling P, Bown EG, Turner RC: Continuous infusion of glucose with model assessment: measurement of insulin resistance and beta-cell function in man. *Diabetologia* 28:401–411, 1985
10. O'Rahilly SP, Nugent Z, Rudenski AS, Hosker JP, Burnett MA, Darling P, Turner RC: Beta-cell dysfunction, rather than insulin insensitivity, is the primary defect in familial type 2 diabetes. *Lancet* 2:360–364, 1986
11. Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, Timpson NJ, Perry JR, Rayner NW, Freathy RM, Barrett JC, Shields B, Morris AP, Ellard S, Groves CJ, Harries LW, Marchini JL, Owen KR, Knight B, Cardon LR, Walker M, Hitman GA, Morris AD, Doney AS, Wellcome Trust Case Control Consortium (WTCCC), McCarthy MI, Hattersley AT: Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* 316:1336–1341, 2007
12. Holman RR, Turner RC: Maintenance of basal plasma glucose and insulin concentrations in maturity-onset diabetes. *Diabetes* 28:227–230, 1979
13. O'Rahilly S, Turner RC, Matthews DR: Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. *N Engl J Med* 318:1225–1230, 1988
14. Rachman J, Gribble FM, Barrow BA, Levy JC, Buchanan KD, Turner RC: Normalization of insulin responses to glucose by overnight infusion of glucagon-like peptide 1 (7-36) amide in patients with NIDDM. *Diabetes* 45:1524–1530, 1996
15. Rachman J, Barrow BA, Levy JC, Turner RC: Near-normalisation of diurnal glucose concentrations by continuous administration of glucagon-like peptide-1 (GLP-1) in subjects with NIDDM. *Diabetologia* 40:205–211, 1997
16. Clark A, Wells CA, Buley ID, Cruickshank JK, Vanhegan RI, Matthews DR, Cooper GJ, Holman RR, Turner RC: Islet amyloid, increased A-cells, reduced B-cells and exocrine fibrosis: quantitative changes in the pancreas in type 2 diabetes. *Diabetes Res* 9:151–159, 1988
17. Clark A, Cooper GJ, Lewis CE, Morris JF, Willis AC, Reid KB, Turner RC: Islet amyloid formed from diabetes-associated peptide may be pathogenic in type-2 diabetes. *Lancet* 2:231–234, 1987
18. Hattersley AT, Turner RC, Permutt MA, Patel P, Tanizawa Y, Chiu KC, O'Rahilly S, Watkins PJ, Wainscoat JS: Linkage of type 2 diabetes to the glucokinase gene. *Lancet* 339:1307–1310, 1992
19. Stoffel M, Patel P, Lo YM, Hattersley AT, Lucassen AM, Page R, Bell JI, BellGI, Turner RC, Wainscoat JS: Missense glucokinase mutation in maturity-onset diabetes of the young and mutation screening in late-onset diabetes. *Nat Genet* 2:153–156, 1992
20. Turner RC, Oakley NW, Nabarro JD: Control of basal insulin secretion, with special reference to the diagnosis of insulinomas. *Br Med J* 2:132–135, 1971
21. Turner RC: The diagnosis of insulinomas and other causes of fasting hypoglycemia. *Horm Metab Res Suppl* 6:40–45, 1976
22. Alberti KG, Hockaday TD, Turner RC: Small doses of intramuscular insulin in the treatment of diabetic "coma." *Lancet* 2:515–522, 1973
23. UKPDS Group: UK Prospective Diabetes Study VIII: study design, progress and performance. *Diabetologia* 34:877–890, 1991
24. UKPDS Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–854, 1998
25. UKPDS Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
26. UKPDS Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 317:703–713, 1998
27. UKPDS Group: Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 317:713–726, 1998
28. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR: Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *Br Med J* 321:412–419, 2000
29. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ (England)* 321:405–412, 2000
30. Turner R, Blackwood R: *Lecture Notes on History Taking and Examination.* Oxford, U.K., Blackwell Scientific, 1991