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A life in balance: wandering the pathways of control

S. A. Amiel

RD Lawrence Professor of Diabetic Medicine, King’s College London, UK

Correspondence to: Stephanie A. Amiel. E-mail: Stephanie.amiel@kcl.ac.uk

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Abstract

‘To keep in equilibrium’, one of the Oxford English Dictionary’s many definitions of balance, is a desirable target for any life, but has special meaning for the life of a person with diabetes. Achieving balance—between hypo- and hyperglycaemia; between energy intake and energy consumption; between insulin action and insulin secretion; between attention to diabetes and attention to everything else—remains challenging, but progress has been made over the last three decades both

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in our understanding of how nature achieves balance and in the tools we have to try to reproduce the actions of nature in disease states. In particular, the role of the brain in controlling diabetes, from glucose sensing to decision making, has been investigated. Physiological and neuro-imaging studies are finally being translated into patient benefit, with the aim of improving, as Dr Banting put it, the provision of ‘energy for the economic burdens of life’.

Introduction

In 1921, a team comprising Banting, Best, Collip and Macleod demonstrated that a protein extractable from the pancreas was the missing element in people with Type 1 diabetes and that replacing that element would lower the blood glucose. They purified the protein, creating a revolutionary and life-saving treatment for the otherwise fatal disease. Their discovery and its implementation were little short of a miracle. Insulin has remained the sole effective treatment for Type 1—and much of Type 2—diabetes, but its use is not without problems and research continues to try and address these.

The Oxford English Dictionary defines ‘balance’ as ‘to keep in equilibrium’ [1]. ‘Balance’ thus is key to the life of the person with insulin-deficient, insulin-dependent diabetes—balance between energy intake and energy expenditure, eating and exercising, fasting and resting (Fig. 1). Self-managing insulin treatment in insulin deficiency is like being a juggler trying to keep many balls in the air all at once. It is not surprising that sometimes even the most expert and experienced person drops one such ball, resulting in one or other of the two acute problems of diabetes therapies—hypoglycaemia and weight gain. Our research has addressed both of these dropped balls. It started in the investigation of the problem of hypoglycaemia in insulin therapy. That work and the needs of our local population, where obesity and Type 2 diabetes are rife, led us on to the investigation of appetite control and weight gain in diabetes, obesity and insulin resistance. The ‘pathways’ of my title refer to the pathway of my research experience, the brain pathways that we have investigated.
in the course of that research and the pathways we have created for patient care listed there in
opposite order from their priorities.

**Hypoglycaemia in Type 1 diabetes, part 1: a syndrome of impaired awareness**

Hypoglycaemia—low blood glucose concentrations—was early recognized as a complication of
exogenous insulin therapy. One’s first experience of hypoglycaemia is very symptomatic, as the body
mounts a stress response that results in a drive to eat as well as a drive to endogenous pathways of
recovery of the blood glucose concentration. With time, and repeated exposure, subjective
awareness of hypoglycaemia changes and episodes with loss of personal cognitive control and even
loss of consciousness are a major worry for everyone using insulin. Most recently, we have started to
investigate the impact of hypoglycaemia on the family and friends of those who experience it. The
words of the partner of a man with recurrent severe hypoglycaemia describe the enormity of the
problem more than any scientific description. Speaking of herself, to researchers David Rankin and
Julia Lawton, she said ‘...I feel guilty. I’m not the kind of character that finds joy in mothering another
adult that I loved and respected as a male, you know, responsible being. I’m not, I want a proper
partner...’ [2]. It is clear that more needs to be done to protect our patients—and their relatives—
from hypoglycaemia during insulin therapy.

The year 1978 can be considered the birth of the modern insulin era. In that year, Harry Keen,
George Alberti, John Pickup and John Parsons, working in London, published the first description of
the clinical use of continuous subcutaneous insulin therapy—insulin pump therapy—for the better
control of Type 1 diabetes [3]. They used the Mill Hill infuser (XXXXXX, XXXXX, XXX), then being used
by Parsons for preclinical experiments in calcium metabolism. Simultaneously, but independently, an
American team, led by Robert Sherwin and William Tamborlane at Yale University, also developed an
insulin pump, based on the pumps used to infuse desferrioxamine for the treatment of iron overload
in children with thalassaemia [4]. The London and American teams had competed over the first
publication on insulin pump therapy, but they quickly came to collaborate on the Kroc study, an

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early study of the impact of tighter diabetes control administered by pump on the progression of diabetes complications—specifically retinopathy and microalbuminuria [5]. Funded by a grant from the founders of Macdonald’s, the Kroc study demonstrated an initial deterioration in retinopathy with tight control [5] but, bravely continuing, a later improvement [6]. Microalbuminuria improved. The Kroc study demonstrated the feasibility of conducting a randomized controlled trial of intensified vs. conventional insulin therapy in people with Type 1 diabetes and was the forerunner of the American Diabetes Control and Complications Trial—the study that has demonstrated the benefits of tight glycaemic control applied early in the evolution of Type 1 diabetes, to reduce risks of both microvascular [7] and, eventually, also macrovascular disease [8]. But the methods of lowering mean blood glucose during the Diabetes Control and Complications Trial were not optimal even then and the lower glycated haemoglobin of improved diabetic control was met not only by reduced risk of retinopathy, but also by higher—much higher—risk of severe hypoglycaemia. Especially in those people achieving their glycaemic control with intensive therapy—at any given HbA1c, the risk of severe hypoglycaemia was higher in those in the active treatment arm of the study [9].

At Guy’s Hospital, Professor Keen had noted that his pump patients seemed less symptomatic of low blood glucose concentrations than before pump. At the time, this was thought to have potential benefit, enabling the patients to achieve more stable blood glucoses at lower concentrations than heretofore. The term ‘hypoglycaemia tolerance’ was suggested. At Yale, a single research study had been carried out to examine the impact of intensive insulin treatment and tighter diabetes control on hypoglycaemia responses. Anticipating a restoration of the glycogen response to hypoglycaemia, known to be defective in Type 1 diabetes, the Yale team had instead found a lesser hormonal response to a controlled fixed hypoglycaemic challenge [10]. We tested this further by infusing low-dose insulin into three groups of people—those without diabetes, patients with diabetes on conventional therapies and patients with diabetes on intensified therapy [11]. We found that, while the subjects without diabetes and the less-well-controlled subjects with diabetes were able to arrest
the glucose fall, the intensively treated patients with Type 1 diabetes could not. Four required intravenous glucose supplementation to enable them to complete the 3-h study safely. Yet when we measured their catecholamine responses to the hypoglycaemia, they were at least as high as in the other groups.

In order further to investigate this, we needed a controllable hypoglycaemic challenge that could be applied reliably and reproducibly across individuals and across groups. Working with Ralph DeFronzo, we developed a modification of the hyperinsulinaemic glucose clamp. Originally designed as a euglycaemic study to measure whole body insulin sensitivity, we used it to deliver a slow, stepped reduction in plasma glucose, which would allow us to define the hierarchy as well as the magnitude of the physiological responses to hypoglycaemia [12]. We presented the preliminary results of our first study with the stepped hypoglycaemic clamp to the London meeting of the European Association for the Study of Diabetes in 1984. Later, with the clamp technique established, we were able to demonstrate in a longitudinal study that the application of strict glycaemic control as then practised was associated with a defect in the counter-regulatory hormone responses to hypoglycaemia—the responses began at lower glucose concentrations and were less at any given hypoglycaemic concentration after tight control [13]. Was this a good thing? Returning to England, we found our intensively treated patients with diabetes to be more prone to hypoglycaemia-induced changes in the electroencephalogram [14]. Then at Guy’s, supported by Ian Macdonald from Nottingham, we added an ability to measure cognitive function during our hypoglycaemic clamps. Alberto Maran found that, while the glucose concentration for the subjective awareness and catecholamine responses was much lower in people with intensively treated Type 1 diabetes, the glucose concentration for deteriorated performance of the four-choice reaction time was not (Fig. 2) [15]. Examining the symptomatic and counter-regulatory hormone responses, we found these started at a higher blood glucose and before the onset of detectable cognitive dysfunction in the less-well-controlled patients, and at lower blood glucose and after the onset of cognitive change in the intensively treated patients, all of whom had a history of problematic and/or severe
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regionality of the brain’s responses to metabolic change. Infusion of β-hydroxybutyrate delayed the onset of the counter-regulatory hormone response to hypoglycaemia [23]. Diarmuid Smith found that infusing lactate could delay both cognitive impairment and subjective awareness [24] (and later used neuroimaging to show that the human brain would use lactate to support its metabolism even during euglycaemia [25]); Mark Evans showed that elevating circulating non-esterified fatty acids by heparin and intralipid infusion delayed only the perception of symptoms and hormonal responses, with no impact to protect cognition [26], although infusing the essential amino acid alanine had impact only on the cognitive responses [27].

In order to investigate the role of regional brain function in hypoglycaemia and hypoglycaemia unawareness, we moved to neuroimaging. Working with Paul Marsden at the positron emission tomography imaging centre at St Thomas’ Hospital and Steve Williams and Mick Brammer at the Institute of Psychiatry, we used positron emission tomography to look at regional changes in glucose metabolism and perfusion, and functional magnetic resonance imaging (MRI) to address the questions of regional brain responses to hypoglycaemia in people with diabetes, with and without impaired awareness of hypoglycaemia and defective counter-regulatory stress responses.

The hypothesis underlying metabolic neuroimaging is that activation of neurones in task performance results in a regional increase in metabolism and in perfusion. These processes can be imaged using positron emission tomography for metabolism (for example, using positron emitting glucose tracers such as \(^{18}\text{F}\)fluoro-deoxyglucose) and perfusion (using labelled water); functional MRI using arterial spin labelling for perfusion or the change in magnetic signal from increased oxygenation of an active area, using blood oxygen label-dependent imaging. In a recent study using water positron emission tomography to image regional changes in perfusion as a surrogate marker for regional neuronal activation, we were able to image the evolution of the regional brain responses to hypoglycaemia and its recovery [28]. Ming Ming Teh and Joel Dunn observed early activation in brain regions involved in interception and sympathetic activation (e.g. anterior

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cingulate cortex) and the pulvinar in the thalamus, with deactivation in brain regions involved in memory formation such as the posterior parahippocampal gyrus (Fig. 3). This was followed by increasing anterior cingulate cortex activation, and visible activation of the insular and ventral striate cortices and hypothalamic–pituitary brain regions, correlating with adrenaline release. Following resolution of hypoglycaemia, there was persistent engagement of the anterior cingulate cortex and deactivation of the pulvinar. Many of these brain responses are translatable into clinical features of hypoglycaemia, such as the anterior cingulate cortex activation with a symptomatic stress response [29] and reduced activation of brain regions involved in memory formation [30], which could account for such phenomena as the known failure to make or consolidate memory during hypoglycaemic events [31,32].

**Metabolic neuroimaging and Type 2 diabetes**

At this point, our research branched off into investigations of regional brain activation in insulin resistance, obesity and Type 2 diabetes. There is a growing literature on abnormalities of the brain’s response to food cues in obesity and Type 2 diabetes, and increasing interest in the role of the brain in controlling body weight. In 2008, we had started a collaboration with local general practitioners and their primary care practices to recruit people with newly diagnosed Type 2 diabetes into an observational cohort study that has as its primary aim the investigation of the impact of depression at diagnosis on diabetes-related biomedical outcomes at 2 years. In collaboration with Khalida Ismail, Professor of Diabetes and Mental Health at King’s College, we created a team to recruit almost 2000 people from the local community into the research (the South London Diabetes Study; SOUL-D). Public interest was high. Of our recruits, nearly 40% are of African or Caribbean ethnicity, mirroring the composition of the local population with established Type 2 diabetes and reflecting not only the increased risk of people from these ethnicities for diabetes (only 20% of the local population is of black ethnicity), but also their willingness to engage in research (Fig. 4) [33]. Notably, as elsewhere in the world, people from non-white backgrounds are presenting approximately
10 years earlier than the white population, although with fewer complications than reported for older studies of new-onset diabetes such as the UK Prospective Diabetes Study (UKPDS). We are probably detecting diabetes earlier in its evolution now—a high proportion of our new-onset cohort had no symptoms of hyperglycaemia at diagnosis and many were found by screening. Obesity is greater and is an important feature of the diabetes in the whole study cohort.

We had already taken a look at the impact of insulin resistance on regional brain activation. When we began to investigate the regional brain responses to hypoglycaemia using insulin clamp techniques during neuroimaging, we needed to establish the impact of euglycaemic hyperinsulinaemia on estimates of global and regional brain glucose uptake, as estimated using glucose positron emission tomography. As others had before us, we found no impact on the global cerebral metabolic rate for glucose when we used insulin infusions in different concentrations, supporting the axiom that brain glucose uptake is insulin independent [34]. However, when Emma Bingham removed insulin (with somatostatin) and replaced it only at low levels, we found that approximately 20% of the cerebral metabolic rate for glucose was insulin dependent [35]. Correcting for differences in global brain glucose uptake, we found that insulin was increasing regional brain glucose metabolism in specific brain areas, including the ventral striate, insular and orbitofrontal cortices, and reducing it in the amygdala. The former brain regions are involved in food seeking, reward pathways and hedonic perception; the latter is activated in anxiety. Repeating the study in people with peripheral insulin resistance, Karen Anthony found that the effect of replacing basal insulin was only approximately half that seen in those who are insulin sensitive [36]. More cogently, the impact of insulin on neuronal activation in the appetite and reward pathways was reduced, while deactivation in the amygdala remained similar to that in the insulin-sensitive study. These data are compatible with the explanation that, in insulin resistance, the hypoeinsulinaemic responses to food may be less satisfying, but at least as calming in those with insulin resistance—a recipe to encourage continued eating. This was a first demonstration that the brain pathways involved in appetitive motivation and response to food and feeding may be altered in people with insulin
resistance in ways that might encourage further eating. Insulin resistance in brain pathways may contribute to the link between insulin resistance and risk of obesity. Others have investigated this issue and we reviewed the literature in this area in 2012 [37]. Working with Fernando Zelaya, Yee Cheah has recently shown a correlation between non-obese insulin resistance and the regional brain response to food ingestion in the anterior cingulate cortex and orbito-frontal cortices using arterial spin labelling functional MRI: there was a correlation between insulin sensitivity within the normal range and these responses [37]. He has also found an impact of aging, independent of obesity, on the brain’s response to food cues, which we would like to suggest as a contributor to ‘middle-aged spread’ [38]. Kate Hunt is also dissecting out the impact of insulin resistance from obesity or diabetes on the brain’s response to food ingestion. Using $^{18}(F)$ fluoro-deoxyglucose–positron emission tomography, she and Joel Dunn have are also investigating the impact of bariatric surgery on these responses [39]. Sarah Lee and Yashi Nathan have found that insulin-resistant subjects with diabetes have brain responses to food cues in the fed state that more closely resemble the non-obese non-diabetic fasted state, and that a single dose of the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide may help restore the fed response [40].

**Hypoglycaemia in Type 1 diabetes, part 2: the impact of a neuroimaging study on restoring hypoglycaemia awareness in practice**

We continued to work on the problems of hypoglycaemia during intensified insulin therapy in people with Type 1 diabetes. During the running of the Diabetes Control and Complications Trial there had been vigorous transatlantic debate about the inevitability of the link between lowering HbA$_{1c}$ (and risk of vascular complications) and increased frequency of severe hypoglycaemia. A programme devised in Dusseldorf, Germany, claimed to be able to achieve both lower HbA$_{1c}$ and, simultaneously, lower risk of severe hypoglycaemia—with lasting benefit after a single intervention [42]. Researchers from King’s College London, Sheffield and North Tyneside went to see what the German intervention was. It turned out to be a 5-day inpatient structured education programme,
based on principles of both insulin pharmacodynamics and of adult education. With the help of Michael Berger, the charismatic leader of the Dusseldorf programme, and his team, we translated the German curriculum into English and brought it back to test in the UK. The first trial was a success, showing a XX mmol/mol (1%) reduction in HbA1c after a 6-month randomized controlled trial [43], with no increase in the rather low rate of severe hypoglycaemia. In later studies, we were able to demonstrate a fall also in hypoglycaemia [44]. The North Tyneside team was led by Sue Roberts, who later became England’s National Director for Diabetes. With initial support of the Department of Health, the Dose Adjustment for Normal Eating (DAFNE) programme was rolled out to other UK centres. A national coordinating committee and an office were set up for the provision of training for healthcare professionals in delivering DAFNE, to provide (and keep updated) educational materials for the courses, to establish a national quality assurance and audit programme. We have trained new centres not just across the UK (nearly 30,000 UK residents with Type 1 diabetes have now participated in DAFNE and the patient group has created its own website and provides input into new research in the area) and in South Africa, Ireland, Kuwait and Australia. Oz-DAFNE has trained a centre in Singapore.

In the UK, David Hopkins examined the database and found that, in the UK’s clinical programme, 40% of people undertaking DAFNE have impaired awareness of hypoglycaemia, suggesting preferential referral of people with problematic hypoglycaemia, as the usual stated prevalence of impaired awareness of hypoglycaemia is approximately 25% [16]. One year after DAFNE training, 43% of those reporting impaired awareness of hypoglycaemia at entry reported restored awareness. Parenthetically, almost all the residual severe hypoglycaemia in the programme was in those who remained or had developed impaired awareness. We can assume that the 43% who recovered awareness did so because using DAFNE principles had reduced their exposure, in frequency and/or duration, to mild and moderate hypoglycaemia and allowed them to regain awareness to occasional episodes. Some years earlier, Iain Cranston had studied 12 people with Type 1 diabetes and hypoglycaemia unawareness and demonstrated a convincing restoration of symptomatic
hypoglycaemic responses after a period of scrupulous avoidance of exposure to home blood glucose measurements of 3 mmol/l (54 mg/dl) in a research setting [45]. It is worth noting that half his study participants were people using intensive insulin therapy with very tight glucose control, while the others were people with long-standing Type 1 diabetes not well controlled, and the restoration worked equally well in all. This was in contrast to our initial hypothesis, which had been that only in those who were tightly controlled would the unawareness be driven by recurrent hypoglycaemia exposure and reversible by hypoglycaemia avoidance. We thought the long-duration poorly controlled patients would have a more resistant unawareness syndrome, perhaps associated with organic neuropathy. We were wrong.

If DAFNE helps people achieve better diabetes control (which must by definition include less exposure to hypoglycaemia), what makes 57% of people with impaired awareness of hypoglycaemia retain it after its education in flexible insulin therapy? And, importantly, what can we do to help them? One possibility is to offer improved technology in either glucose sensing and/or insulin delivery to reduce their hypoglycaemia exposure. We were expecting the introduction of real-time glucose sensing to help patients avoid extremes of blood glucose. Pratik Choudhary has led the King’s College contribution to this research, testing new systems and investigating the ability of real-time glucose sensing to restore hypoglycaemia awareness. We have been unable to document this benefit. However, use of real-time glucose monitoring associated with pumps in clinical practice, as in research trials, has helped reduce hypoglycaemia exposure in those most prone to it [46] and severe hypoglycaemia can also be reduced by its use [47]. Some of the benefit in the last study may have related to a number of systems including an automated suspension of insulin delivery, which occurs if the sensor detects a low blood glucose and no evidence that the user has taken any corrective action. A very recent randomized controlled trial has shown a reduction in severe hypoglycaemia with real-time monitoring and automated insulin suspension in hypoglycaemia, although there has been no evidence for restored awareness [48]. Perhaps the system simply replaces endogenous sensing and prevents prolonged hypoglycaemia.

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The introduction of the automated temporary insulin suspension may be one more step towards a fully closed loop system, in which insulin delivery is always driven by measured blood glucose—a bionic replacement of glucose-responsive insulin delivery. These types of system struggle with issues such as anticipatory insulin delivery and time lags between blood glucose change, its detection by a subcutaneous sensor and the integration of the sensor signal and the pharmacodynamics of subcutaneously delivered insulin. We have been fortunate in collaborating with Roman Hovorka in Cambridge, whose algorithms for closed loop insulin delivery have already demonstrated superior overnight glucose control in children and adults with Type 1 diabetes when compared with conventional open loop pump insulin delivery [49,50]. Together with Helen Murphy, we have started testing such systems in women with pregnancy and Type 1 diabetes [51].

While waiting for the perfection of a bionic pancreas, the diabetes world has not lost sight of the efficiency of the system nature provided in the pancreatic islet. In 1998, in collaboration with the King’s Liver Transplant Unit, and particularly Professor Nigel Heaton and Mr Parthi Srinivasan, we investigated the potential for developing human islet isolation at King’s. I had in mind that restoring endogenous insulin secretion by transplantation would be an ultimate treatment for people with really intractable hypoglycaemia problems, although I believed that clinical cell therapy was a long way off. Indeed, when we created the King’s human islet isolation programme, funded by Dixons Charitable Trust, we told its Chairman, Sir Stanley Kalms, that we would not move into patient treatment within the 5 years of the grant. We were setting the programme up to allow King’s islet researchers to work on human tissues. We were right—but only just. Guo Cai Huang came to set up our islet isolation programme. Shortly after his publication of the first successful islet transplants in clinical practice [52], James Shapiro from Edmonton was part of an inspection of the Dixons funded programme at King’s. Impressed by the quality of Guo Cai’s islets, James told us we should be putting them into people with diabetes, rather than just ‘wasting them’ on basic research. Always obedient, we complied. Supported by Anil Dhawan, a paediatrician with a viable human hepatocyte isolation programme, and with Dixons support, we were able to open a Clinical Grade human cell
isolation facility at King’s. The King’s transplant coordinators, led by Wendy Littlejohn, worked with both donor families and with the recipient programme and in 2001 we performed the UK’s first islet transplant using the Edmonton protocol for the indication of intractable recurrent hypoglycaemia. Diabetes UK was an enthusiastic supporter of the clinical programme—indeed our second recipient, Richard Lane OBE, became President of the charity and has been a source of inspiration to us. In collaboration with the islet isolation programme at Oxford, and with four other transplant centres in the UK, we formed the UK Islet Transplant consortium. In one of the fastest translational programmes in recent years, the National Health Service became and remains the only state-run health service to provide islet transplantation as a treatment for intractable hypoglycaemia in Type 1 diabetes [53]. We acknowledge the work of Jim Shaw in Newcastle, Edmund Jessop of the then National Commissioning Board, UK Transplant and the UK’s pancreas transplant surgeons for making islet transplantation at least in theory accessible to any patient of the National Health Service (NHS) who cannot stop severe hypoglycaemic events with exogenous insulin therapy [53].

But while cell replacement therapy remains dependent on a donated pancreas, means of expanding islet populations in vitro are still embryonic and our understanding of the immunosuppression needed to prevent both rejection and recurrence of the diabetes, and progress towards a bionic pancreas, is incomplete. We need alternative strategies to help patients with hypoglycaemia unawareness and severe hypoglycaemia—and their families. To advance this, we looked again at the research data. We knew that avoidance of exposure to periods of blood glucose under 3 mmmol/l could restore awareness to occasional episodes [45]. To drive home that message, Diabetes UK (then the British Diabetic Association) promulgated the slogan ‘Make 4 the floor’, one of the first coordinated attempts to ensure that people with diabetes were given lower as well as upper limits for their glucose targets. We assume that reduced exposure to moderate hypoglycaemia underlies the partial success of DAFNE in helping people regain hypoglycaemia awareness. But one of the patients who recovered symptomatic counter-regulatory responses to hypoglycaemia in Iain Cranston’s study was unable to sustain that improvement and tragically died in hypoglycaemia.

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2 years later while travelling in India. What was it that made him able to avoid hypoglycaemia during the study, and not when not involved in research? The obvious answer was that, in the study, Iain worked very closely with the patients, contacting them frequently to review their control and discuss with them insulin dose adjustments. By now we knew that even after 9 years of intensive educator support in the Diabetes Control and Complications Trial, patients in the intensive arm could not sustain the degree of control they achieved in the trial [56]—one of the bones of contention between the Diabetes Control and Complications Trial and the Dusseldorf programme that seemed to have more lasting effect. The HbA1c benefits of DAFNE are clearly prolonged if appropriate healthcare professional follow-up is added [57]. But if we do now provide ongoing support in DAFNE, why do over half of people entering DAFNE with impaired hypoglycaemia awareness remain in that state 1 year later?

Our neuroimaging data gave the first clue. Joel Dunn, reworking 18(F)fluoro-deoxyglucose–positron emission tomography data from our earlier studies, found not just that being unaware was associated with reduced activation of brain regions associated with the generation and perception of sympathetic stress responses (amygdala, anterior cingulate cortex, brainstem and cerebellum), but unexpectedly with lesser reduced activation of the lateral orbitofrontal cortex, another part of the reward pathways and involved in hedonic perception. In some of our hypoglycaemia unaware patients, this brain region had more rather than less 18(F)fluoro-deoxyglucose uptake during the induced hypoglycaemia [58]. Observing these analyses, Laurence Reed, an addiction psychiatrist with experience in neuroimaging, became interested in our work in hypoglycaemia, not only because hypoglycaemia was a good model for other physiological stressors, but also because of the evidence in the 18(F)fluoro-deoxyglucose analyses of central habituation to a stress [59]. Could it be that impaired awareness of hypoglycaemia involves not just unawareness of the hypoglycaemia itself, but also of the dangerous and unpleasant nature of the event? If the person having an unpleasant experience does not realize its unpleasantness, perhaps there is no real motivation to avoid it in future?
In support of this hypothesis, Charlotte Smith, then a medical student, looked at the records of all the people attending our intensive therapy clinic, a weekly clinic set up originally to provide intensive support for people with problematic hypoglycaemia complicating their Type 1 diabetes, and expanded to support most of our patients with Type 1 diabetes needing help to achieve tight glycaemic targets. Looking at the extent to which people were using treatment regimens suggested in one clinic visit when they returned for the next, and also the number of people who were using that advice, she found that people with hypoglycaemia unawareness (as recorded in the clinic notes and letters) were much less likely to be ‘adherent’ to regimen change [60].

Helen Rogers used semi-structured interviewing and formal qualitative methods to find recurrent themes in the hypoglycaemia experiences of our hypoglycaemia unaware patients [61]. Of the whole group, 13 patients had thoughts about their hypoglycaemia that might be expected to interfere with their ability fully to engage with strategies for hypoglycaemia avoidance. The main themes were: fear of the consequences of hyperglycaemia; a desire to avoid a sickness role; an underestimation of the consequences of hypoglycaemia; and an acceptance that hypoglycaemia was a ‘normal’ part of life with diabetes. This investigation was part of our National Institute for Health Research (NIHR) programme looking at non-pharmacological (essentially psychological and educational) interventions to improve diabetes outcomes. We were also involved in the NIHR programme investigating how to improve outcomes from the structured education programme DAFNE, led by Simon Heller in Sheffield. In collaboration with Sheffield, Nicole deZoysa, our NIHR-funded clinical psychologist, with Helen and the patients, doctors and educators from our respective clinical DAFNE programmes, devised a curriculum to help patients improve their hypoglycaemia awareness by adding strategies to help them recognize and address not just hypoglycaemia, but also their own barriers to managing it. The curriculum would be delivered in outpatient sessions, some full-day group sessions, others conventional one-to-one clinic visits, over 6 weeks, by DAFNE educators whom Nicole trained and supported in the use of psychological therapeutic approaches—specifically motivational interviewing and cognitive behavioural therapy—in the context of hypoglycaemia. The course also included
revision of the DAFNE training on hypoglycaemia prevention and treatment and exposure to new information about the pathophysiology of hypoglycaemia unawareness. It drew on other educational programmes designed to increase glucose awareness—most notably, the Blood Glucose Awareness Training of Dan Cox and Linda Gonder-Frederick and colleagues, who were active in supporting the development of our course [62]. We called it DAFNE—for DAFNE—and HART for Hypoglycaemia Awareness Restoration Training.

We have conducted one pilot of the programme. Twenty-four patients undertook DAFNE Hypoglycaemia Awareness Restoration Training in four courses, run two in Sheffield and two at King’s. An early analysis of the data (at 3 months’ post course) shows significant reductions in severe and moderate hypoglycaemia, improvement in scores representing hypoglycaemia awareness and changes in behaviour or worry around hypo- and hyperglycaemia [63]. This is obviously just a start and now requires formal testing but, to use a metaphor from the course, it is a green shoot that certainly merits nourishing. For me, sitting in the back of one of the Hypoglycaemia Awareness Restoration Training sessions, it was a joy to watch the translation into treatment of research that had started in the clinical diabetes service at Guy’s, gained momentum using clamp technology at Yale, and moved through the brain scanners of King’s to achieve a new treatment strategy with the potential to improve the quality of life of people with diabetes and their families. There cannot be many career opportunities that can deliver that.

A last word

I hope it will be obvious from the above that whatever has been achieved in the last 30 years has been a team effort. My mentors, Harry Keen, Arnold Bloom, Bob Sherwin, Bill Tamborlane, Edwin Gale, GianCarlo Viberti and Peter Watkins, started me on my path; my teams of nurses, junior doctors, imaging scientists, research students and most recently psychiatrists and psychologists and my colleagues in primary care have supported—or even carried out—the work; my funders, including Diabetes UK, the Juvenile Diabetes Research Foundation International, the Medical
Research Council, the Wellcome Foundation, the Diabetes Foundation, the National Institute of Health Research, Dixons Charitable Trust, the King’s College Hospital Charity, the Royal Society, the Diabetes Research and Wellness Foundation and industry partners including NovoNordisk, the Eli Lilly–Amylin collaboration, and Medtronic have made our research possible. My clinical colleagues have kept me grounded and my research relevant. Most of all, of course, the people with Type 1 and Type 2 diabetes, their families and the healthy people who have provided control data, including particularly the people of Camberwell and those living on the route of the number 68 bus—without whom this work would not be necessary and for whom I hope, in a small way, we have helped to make things better. The last word, of course, belongs to Banting. After he and his team discovered insulin over 90 years ago, he is recorded as describing it as providing ‘energy for the economic burdens of life’. I hope that, in a small way, the work I have been able to do has made the costs of that energy a little bit lower.

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Competing interests

None declared.

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54. Shaw UKITC

55. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and


59. Stress desensitization


**Figure 1** ‘Balance’ thus is key to the life of the person with insulin-deficient, insulin-dependent diabetes—balance between energy intake and energy expenditure, eating and exercising, fasting and resting.

**Figure 2** The adrenaline response to a controlled hypoglycaemic challenge in adults with Type 1 diabetes (solid squares, solid line) is delayed in onset and reduced after intensification of insulin therapy, as achieved in the 1980s, when it was associated with increased risk of severe hypoglycaemia (open circles, dotted line). The glucose concentration at which reaction times

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became impaired (solid black arrow) did not change, so that this response to hypoglycaemia followed the onset of the symptomatic stress response prior to intensification therapy but preceded it afterwards. Such an altered hierarchy to hypoglycaemia in clinical experience explains the syndrome of impaired hypoglycaemia unawareness. The figure is adapted from Amiel et al. (1988) with permission from Xxxxxxxx [13] using data from Maran et al. (1995) [15].

Figure 3 Statistical parametric maps projected onto a magnetic resonance brain image showing changes in regional perfusion in response to hypoglycaemia in healthy volunteers. The colours indicate the statistical significance that can be attached to the signal change in the region: orange for activation, blue for reduced activation. Activation of the anterior cingulate cortex. During hypoglycaemia, there is successive engagement of medial thalamus and pulvenar; orbitofrontal cortex; anterior cingulate cortex; ventral striate; anterio-inferior insular cortex; and deactivation of hippocampus and parahippocampal gyri. In recovery, thalamic areas become deactivated and anterior cingulate cortex activation remains elevated. See text for the functional correlates. Data are reported in The et al. (2010) [28] and the image adapted from one used in Cheah and Amiel (2012) with permission from Xxxxxxxx [37].

Figure 4 The ethnic background of our local community (top right) is predominantly white European (white), with 20% of people of black African and Caribbean ethnicity (dark grey) and just over 13% of other ethnicities. However, local people enrolling in a study of new-onset Type 2 diabetes (bottom left) the South London Diabetes Study (SOUL-D) have a much higher percentage of people from the Black African and Caribbean community, nearly 40% of the total, reflecting their high risk of diabetes. Data are from Winkley et al. [33].