Brainstorming in diabetes
The 2008 Diabetes UK Arnold Bloom Lecture

SA Amiel*

Introduction
Dr Arnold Bloom was consultant physician to the Whittington Hospital in North London. A trawl through Medline shows his contribution as a scientist; he tested the early sulphonylureas, and biguanides; he contributed to informing the world about the new entity of impaired glucose tolerance (introduced by the World Health Organization [WHO] in 1979); and he was instrumental in setting up the National Register of Newly Diagnosed Diabetic Children, which was one of the early studies to show the seasonal variation in the incidence of type 1 diabetes. But his publication record also shows the characteristic for which those who worked with him and for him most appreciated: his compassionate care for his patients. He worked hard for the introduction of disposable syringes for patients needing insulin, an eventually successful campaign which ended the discomfort, and the inconvenience of the boilable glass syringe and bluntable reusable needle that had been part of taking insulin injections heretofore.

Dr Bloom coined many aphorisms, which encapsulated in a few words important clinical truths.

‘Diabetes is a disease for the intelligent’
By this remark, Dr Bloom was well ahead of his time – in an era when the physician was a very paternal figure, he was acknowledging the critical importance of involving the person with diabetes in his or her self-management, knowing that without patients knowing what to do, they could not possibly achieve success with their diabetes. In this article, a rather different interpretation of the words is made. It will explore the role of the brain in the control of central metabolism, initially in the arena of hypoglycaemia and hypoglycaemia unawareness and later in the control of appetite in insulin resistance and obesity.

The 1990s was the era of the Diabetes Control and Complications Trial (DCCT). The now much-quoted mirror image rise in risk of severe hypoglycaemia (episodes where the patient is too incapacitated to self-treat) and the fall in risk of retinopathy with intensified insulin therapy and reducing HbA1c was not yet known. However, already people working with the then-experimental insulin pump therapy (continuous subcutaneous insulin infusion [CSII]) were noticing that the treated patients were experiencing more profound hypoglycaemia without any of the usual stress symptoms and were, indeed, unaware of their hypoglycaemic state. Prof Harry Keen at Guy’s called this ‘hypoglycaemia tolerance’ and it was thought to be a useful contributor to lower average blood glucose concentrations and HbA1c. An early demonstration that normal glucose homeostasis might be deficient in the intensively treated patients of the DCCT and the early patients experimenting with CSII was published in 1987, when we showed that the ability to arrest a fall in plasma glucose in response to a three-hour low-dose insulin infusion was significantly reduced in the type 1 diabetic patients on intensified therapy, despite a similar stress hormone response (albeit in the face of a deeper hypoglycaemia). At Yale, we developed the stepped-hypoglycaemic insulin clamp, in which the fall in plasma glucose in response to a higher-dose insulin infusion was brought under the control of the investigator, using five-minute bedside blood glucose testing and variable rate glucose infusion. This allowed us to apply a comparable...
hypoglycaemic challenge to all subjects in any circumstances, and in an early application we showed that the glucose concentration triggering the catecholamine and symptom responses to this hypoglycaemic challenge was significantly lower in diabetic patients after intensifying glucose control (Figure 1). Later, we used the same methods to show that the glucose concentration at which cognitive impairment was first detectable was not lowered in tightly controlled hypoglycaemia-prone diabetes, providing the first clear explanation for hypoglycaemia unawareness. We showed that the protective gap between the onset of symptomatic stress responses to hypoglycaemia and the onset of cognitive impairment was closed and even reversed in the hypoglycaemia unaware – as the plasma glucose falls, the first event is slowing of cortical function, not subjective awareness. The patient has no chance to take action to stop the glucose fall.

Heller and Cryer performed the definitive experiment by measuring responses to a controlled hypoglycaemic challenge in healthy volunteers who had been rendered hypoglycaemic or kept at normoglycaemia the afternoon before. Their demonstration that defective counterregulation could be induced acutely by antecedent hypoglycaemia inspired a series of studies, including ours, where restoration of awareness to the hypoglycaemia unaware was attempted by the strict avoidance of exposure to a blood glucose of <3mmol/L in daily life. In our study, we were able to restore awareness to two groups of people: the ‘typical’ intensive therapy patients with hypoglycaemia unawareness and the equally common patient with intermittent severe hypoglycaemia despite very poorly controlled diabetes and high HbA1c. This research was translated into practice in the then British Diabetic Association’s ‘Make 4 the Floor’ campaign. Importantly, this was not to suggest that any blood glucose reading under 4mmol/L was hypoglycaemia: it was to stress the critical importance of providing a lower limit to the glucose targets we encouraged patients to achieve – one that provided some protection from falling below the dangerous level of 3mmol/L.

Throughout the 1990s, Michael Berger and his team in Dusseldorf had been describing a method of improving HbA1c while lowering the risk of severe hypoglycaemia. With teams from North Tyneside and Sheffield, we went to see what was happening in Dusseldorf and found a five-day structured education programme during which patients with type 1 diabetes really did learn how to use their insulin and their home glucose testing to adjust their insulin doses around their chosen dietary intake and exercise patterns. Supported by Diabetes UK, we spent a year translating the curriculum and teaching aids into English, revising, or learning, the principles of adult education and constructing an English version of the Dusseldorf curriculum, peer review and quality assurance programme. A recent routine clinical audit of patients entering DAFNE in the year 2005 has shown impressive results in terms of improved mental health and, relevant to this paper, substantial falls in severe hypoglycaemia rates. Of people entering the programme with hypoglycaemia unawareness, 48% had regained awareness at the one year audit point. What of the remaining 52%? And why, if we can reverse the defective counterregulation of hypoglycaemia unawareness so readily in research studies, was one of the patients in our original study dead of hypoglycaemia two years later? Recent neuroimaging data may throw some light on this question and offer a

**Figure 1.** The adrenaline response to a controlled and identical hypoglycaemic challenge started at a lower glucose concentration and was diminished at any glucose concentration in a group of young people with diabetes after a few months of intensified insulin therapy. The data shown in blue are from the study conducted before intensification of insulin therapy, and the red data from the same subjects after a few months of intensified insulin therapy. The arrow below the x axis shows the blood glucose values at the start and end of the clamp. (Figure adapted from Amiel et al. with permission of the editors of Diabetes)
new therapeutic strategy for those who cannot throw off the burden of recurrent hypoglycaemia.

Using glucose-based positron emission tomography (PET) and single step hypoglycaemic clamping, we have studied the regional brain responses to acute hypoglycaemia. With the PET Imaging Centre at King’s, we have demonstrated that glucose metabolic rate rises in the cortex of the aware diabetic patient, while it falls during hypoglycaemia in the unaware – the lack of rise associated with the failure to generate or perceive symptoms. We are currently using water PET further to investigate this. In a recent new analysis of regional differences in the uptake of \textsuperscript{18}fluoro-deoxyglucose during hypoglycaemia, we have found other regional differences in the brain response between the hypoglycaemia aware and unaware (Figure 2). In the aware, there was greater activation of areas such as the amygdala (activated by fear, vigilance and anxiety), brain stem (involved in hypoglycaemia detection and the hypothalamic-pituitary-adrenal axis) and anterior cingulate cortex (involved in interoception – the monitoring of the body’s internal state, including the degree of sympathetic activation). All this is consistent with the reduced stress hormone response to the hypoglycaemia and the subjective awareness of it. But the aware also showed reduced activation of the orbito-frontal cortex – a brain region activated by perception of pleasurable stimuli and involved in seeking reward. This did not happen in the unaware – in some of whom there was even activation of the region.

A similar pattern of activation and de-activation is seen in animals repeatedly exposed to a single stress stimulus and is described as ‘stress desensitisation’. If confirmed as a feature of hypoglycaemia unawareness, adaptation of current treatment modalities that tackle other recurrent performance of health-harming procedures such as smoking, alcohol or other addictive behaviours, might be needed in addition to purely educational strategies to help patients with hypoglycaemia unawareness avoid exposure to hypoglycaemia in future. In order to see whether there is any clinical evidence to support our hypothesis, we have recently audited our intensive insulin therapy clinic. We find evidence for significantly less compliance with suggested treatment changes made for patients categorised as hypoglycaemia unaware than in those patients categorised as aware. We hypothesise that patients with complete hypoglycaemia unawareness have, in addition to counterregulatory deficit, failure of the biological signals that should be telling them that the hypoglycaemia is dangerous and needs to be avoided in future, making it much more difficult for them to adopt avoidance strategies in ongoing self-management.

**Figure 2. Differences in regional changes in brain \textsuperscript{18}fluoro-deoxyglucose uptake, measured during controlled hypoglycaemia using PET. The intensity of colour shows the strength of the statistical differences in uptake between diabetic subjects with and without awareness of hypoglycaemia. Yellow shows brain regions where there was greater uptake during hypoglycaemia in the aware, blue shows brain regions where there was a fall in brain glucose uptake in the aware which did not occur in the unaware. (The full study is published in Dunn et al.\textsuperscript{21})**

**‘The most sensible thing to do with a diet sheet is eat it!’**

Dr Bloom’s statement was made in response to the news that dietary fibre had benefit in people with type 2 diabetes, but also shows his perception of the difficulties that people have in adhering to dietary (and other lifestyle) advice that seems restrictive. The American Diabetes Prevention Program showed definitively that people with impaired glucose tolerance could lose weight and maintain weight loss, and increase physical activity and sustain that over the period of the trial when given lifestyle advice and support, incidentally reducing the incidence of new diabetes. Yet most weight reduction strategies, except surgery, fail to work in the long term and the world’s populations are all growing fatter and heavier, despite widespread knowledge of the health risks.

We have begun to apply the techniques used to investigate hypoglycaemia unawareness to the problems of appetite control and obesity. It began almost by chance. We had needed to establish whether the hyperdynamic metabolic state induced by insulin clamping altered the calculations of glucose cerebral metabolic rate using PET. We, like others, found no change in global cerebral metabolic rates of glucose (CMRglc), with high- and higher-dose insulin infusions. However, when we removed basal insulin with somatostatin, we did find that global...
Figure 3. At low doses of insulin, brain regions – including the orbito-frontal cortex, insular cortex and ventral striate – respond to insulin with increased rates of glucose metabolism (CMRglc) but this effect is reduced in people with insulin resistance, as represented by the broken yellow arrow. Glucose metabolic rate in the amygdala falls with insulin (green) and this effect is preserved in those with insulin resistance, as suggested by the broken blue arrow. (Adapted from data in Bingham et al.27 and Anthony et al.28)

The ultimate treatment

I would like to conclude by returning to the clinical problem that brought us into this field of investigation at the beginning – recurrent severe hypoglycaemia and hypoglycaemia unawareness.

When a patient presents with problematic hypoglycaemia, we define the problem, eliminate (or treat) intercurrent diseases that may be increasing the predisposition to hypoglycaemia (primary defects in counter-regulatory hormones, problems of food absorption etc), offer structured education, with or without extra psychological assessment and therapies, and, in the absence of improvement with these strategies, offer insulin pump therapy, with its improvement with these strategies, structured education, with or without counterregulatory hormones, problematic hypoglycaemia, we treat intercurrent diseases that may be increasing the predisposition to the clinical problem that brought us into this field of investigation at the beginning – recurrent severe hypoglycaemia and hypoglycaemia unawareness. (Figure 3). These data remain to be confirmed and we are currently using functional magnetic resonance imaging for this.

CMRglc fell by almost 20%.27 In a further small study, we found that in men with systemic insulin the removal and replacement of basal insulin concentrations had much less effect on global CMRglc – about 7% only.28 The insulin was increasing CMRglc particularly in brain regions involved in appetite regulation – insular cortex, resistance compared with seven men of high insulin sensitivity, including ventral striate, orbito-frontal and insular cortices. Insulin reduced CMRglc in the amygdala. The effect of insulin in the former group was significantly reduced in the insulin-resistant group, while insulin’s ability to reduce CMRglc in the amygdala was not affected. We hypothesise that the insulin-resistant person may therefore gain less satisfaction from eating but a greater comfort sensation, because of the normal amygdala response to the post-prandial hyperinsulinaemia of insulin resistance (Figure 3). These data remain to be confirmed and we are currently using functional magnetic resonance imaging for this.

Conclusions

Research into hypoglycaemia unawareness led to observations that changed clinical practice, in particular the stress on the importance of a lower limit to glucose targets suggested to people with diabetes as goals for their therapy and the ability of structured education to reduce frequency of severe hypoglycaemia while improving overall diabetic control. Using neuroimaging to investigate the problems of hypoglycaemia unawareness has suggested that, at least for some people, abnormalities of the cortical response to acute hypoglycaemia may interfere with their ability to maintain behaviour changes that minimise risk of further hypoglycaemia, known to restore awareness of intermittent episodes and reduce risk of severe hypoglycaemia. These data suggest that interventions that target behavioural modification, in addition to educational strategies, may be more successful in helping patients regain or retain awareness in the long term. Application of neuroimaging techniques to investigate the brain’s response to food ingestion may be able to shed similar light on the pathogenesis of appetite dysregula-

Pract Diab Int May 2008 Vol. 25 No. 4

Copyright © 2008 John Wiley & Sons
tion in some forms of obesity. Meanwhile, strategies to bring us closer to biologic glucose-stimulated insulin delivery and, for a small number of patients, transplantation of pancreatic islets or even whole pancreas, may also bring us closer to achieving our goals of normalising blood glucose control in people with diabetes, with less risk and fear than has been possible heretofore.

Acknowledgements
I would like to thank my mentors, Prof Harry Keen, Dr Arnold Bloom, Prof Robert Sherwin, Prof William Tamborlane, Prof Edwin Gale, and Prof GianCarlo Viberti for their support and encouragement; the fellows and nurses who carried out most of the later studies; my collaborators in neuroimaging, particularly Paul Marsden, Steve Williams, Mick Brammer, Fernando Zelena, and the scientists who worked with the data; my colleagues in transplantation and islet research; and the many volunteers and patients who helped us do these studies.

Conflict of interest statement
The work reported in this lecture has been funded by Diabetes UK, the Wellcome Trust, the Juvenile Diabetes Research Foundation, the Diabetes Foundation, the King’s College Hospital Charity, the Diabetes Research and Wellness Foundation, Dixon’s Charitable Foundation, and the Novo Nordisk UK Clinical Research Foundation.

References
17. The DAFNE Study Group. A randomised, controlled trial of training in flexible, intensive insulin management to enable dietary freedom in people with Type 1 diabetes: the DAFNE (Dose Adjustment For Normal Eating) trial. BMJ 2002; 325: 197–204.