Personal practice

Management of diabetes mellitus

D I JOHNSTON

Children's Department, University Hospital, Queen's Medical Centre, Nottingham

It is a privilege to introduce insulin treatment to a newly diagnosed diabetic child and to witness the restoration of normal vigour. The daunting task is to impose and sustain a lifelong discipline dedicated not just to the relief of immediate symptoms but to the less tangible goal of improved health some decades later.

We are at a disconcerting phase in our ability to understand and manage insulin dependent diabetes mellitus (IDDM). The disease is occurring with increasing frequency in our young and yet we still know little of its environmental causes. Evidence relating quality of control to late complications continues to accumulate, but we lack the treatment strategies that allow most diabetic children to achieve desired targets of control. The laboratory can provide us with the measures of diabetic control but who are to be judged? Are patients and their families at fault for not being prepared to adjust their lifestyles sufficiently, or are we at fault for setting them unrealistic goals without providing adequate skills and equipment? There are no easy solutions to these dilemmas. There is, however, an obligation to monitor our service as carefully as we monitor an individual's diabetes. We have to steer a careful path, selecting those developments that are appropriate to our young patients but reserving judgment on those that emerge in a wave of enthusiasm but have not been adequately subjected to informed scrutiny.

This paper attempts to select issues of importance in two main areas: aetiology and management. It describes practice within our diabetic clinic, not to emphasise areas in which we feel secure, but to stimulate debate as to the way in which we should evolve.

Aetiology and prevention

It is now established that IDDM results from fluctuating autoimmune injury to the beta cells over months and years before clinical symptoms emerge.¹ Genetic susceptibility is an essential precondition

but as yet ill defined environmental factors play the major part in determining which individuals develop IDDM. It has been estimated that while heredity contributes 5–40% of the risk, the environment contributes 60–95%.²

Genetic susceptibility is largely, but not entirely, associated with HLA-DR3 and or DR4 on chromosome six. Ninety five percent of white people with IDDM carry DR3 or DR4. These types occur in about 50% of the general population, however, and are therefore of too limited specificity to permit population screening. Closer linkage occurs with the DQ subregion, and it has still to be established whether other genetic markers, for example on chromosome 11, will facilitate prediction. Tarn *et al* have used HLA-DR3, DR4 typing to calculate risk rates in families of index cases.³ HLA identical relatives have a 16% risk of developing IDDM by age 25 years; haploidentical relatives have a 9% risk, and those not sharing HLA types have almost zero risk. This is a valuable research exercise but has to be seen in the context of only 12–15% of newly diagnosed diabetics having an affected first degree relative.

Although cellular immunity is predominant in causing insulinitis and disruption of insulin production, plasma concentrations of islet cell antibodies and complement fixing islet cell antibodies provide markers of the damage. Islet cell antibodies are present in about 80% of newly diagnosed diabetics. Prospective studies within families of index cases have established that islet cell antibody concentrations fluctuate for months and years before diagnosis. The appearance of low titres does not necessarily predict clinical diabetes; however, the detection of high titres of islet cell antibodies or complement fixing islet cell antibodies does suggest more advanced insulinitis. Tarn *et al* have estimated the potential yield of screening for islet cell antibodies as being one in 270 per year for first degree relatives, and one in 4000 per year for the general population.³ The justification for such screening may emerge if properly designed studies establish

that we can alter the early natural history of IDDM to provide worthwhile longterm benefit. The measurement of islet cell antibodies does not have a role in forecasting the natural history of established IDDM.

Insulin autoantibodies occur in 18–20% of new diabetics before insulin treatment. They appear to denote susceptibility to autoimmune injury rather than parallel the severity of insulinitis.

The nature of the environmental factors remains elusive despite their crucial role and the enormous research effort focused upon them. The increasing incidence of IDDM within the same genetic pool and the social class gradient are two of the findings suggesting the importance of infectious or dietary exposure. The long evolution of IDDM has stimulated interest in slow virus infection. Recent studies point towards cytomegalovirus,⁴ and reovirus⁵ as being capable of infecting beta cells and provoking hyperexpression of class 1 major histocompatibility proteins.

The role of diet, and in particular cows' milk, remains largely speculative but it is intriguing that minimal cows' milk exposure precipitates beta cell immune damage and diabetes in the BB rat.⁶ Behavioural stress is also a trigger factor in the BB rat.

Management at diagnosis

Prompt recognition of diabetic symptoms by families and primary care staff, together with immediate referral to appropriate facilities, has made ketoacidosis at presentation relatively uncommon. The diabetes team can now anticipate the advantage of a relatively well child and a family not overwhelmed by life threatening illness. It is essential that this first encounter between family and diabetes team be carefully planned. Initial explanations and the teaching of practical procedures have a critical role in determining the future motivation and involvement of children and their parents. Ward, clinic, and community based members of the diabetes team must coordinate teaching to ensure that injections are demonstrated in an agreed and uniform manner. Our team has produced a small handbook that encompasses this plan as well as catering for the guidance needed by a new family. There are a number of excellent commercially sponsored handbooks that can be adopted for this purpose.

Our usual practice is to offer a brief admission so that the child and family can benefit from intensive involvement with the team. The emphasis is on the child or parents, or both, performing the injections and capillary blood tests from the outset. The family are also introduced to the principles of good nutrition and a balanced carbohydrate intake. Our

diabetes liaison health visitor supervises the transition to home and school. She updates an education checklist and arranges revision in the major areas. We do not provoke hypoglycaemia before discharge, but do emphasise measures to prevent and treat such episodes.

We introduce new diabetics to twice daily insulin injection based on a medium duration human insulin, calculating the initial dosage around 0.5 units/kg/day and dividing it 60% before breakfast and 40% before the evening meal. This alone is sufficient for those presenting with mild metabolic imbalance. In those with greater weight loss and appreciable ketonuria we add short duration insulin equivalent to 0.25 to 0.5 units/kg/day. Children, particularly those with big appetites while restoring body weight, may require initially higher total insulin dosage: 1.0 to 1.5 units/kg/day. With the return of normal activity and appetite we plan downward titration of the dosage guided by symptoms of hypoglycaemia, capillary blood glucose profiles, and concentrations of glycated haemoglobin (HbA_{1c}). The early phase of diabetes management is currently attracting great attention and we are conscious of the emerging evidence that may dictate radical change in our strategy. The evolution of IDDM is such that residual beta cells may retain the ability to produce endogenous insulin for weeks, months, or years after diagnosis. This residual function is responsible for the complete or partial remission phase of early IDDM. Complete remission enables the patient to cease insulin treatment while achieving good control: fasting blood glucose concentration under 7.8 mmol/l, a postprandial concentration under 11 mmol/l, and HbA_{1c} within the normal range. Complete remission is rare in our experience, and the literature suggests a figure of only 2–3% for paediatric clinics compared with up to 18% in adult series. Recognition depends on how actively clinics pursue insulin reduction.

There is no agreed definition of partial remission, although good control on an insulin dose of no more than 0.25 units/kg/day seems appropriate. Partial remission is common in young diabetics (30–60%) but the duration of remission is very variable: weeks to several years. The younger the child at diagnosis the less likely is sustained remission, probably reflecting more aggressive autoimmune injury or the continuation of provoking environmental influences. Young children are more likely to have HLA-DR4, severe metabolic disturbance at presentation, and evidence of a provoking viral infection.⁷

The residual beta cell mass can be estimated using radioimmunoassay measurement of C peptide concentrations in either plasma or urine. Prospective studies show a trend towards early recovery of beta

cells after correction of the initial metabolic disturbance, followed by a progressive decline over months or years. Several studies in adult diabetics have linked persistence of detectable C peptide production to better metabolic control and the slower evolution of microvascular complications.^{8,9} This relation has been less easy to show in children,¹⁰ and it appears that beta cell function decays more rapidly in children and adolescents.

There is obviously a strong case for exploring treatments that might protect and even allow the regeneration of beta cells. With current insulin regimens the reduced beta cell mass is exposed to the chronic stimulus of hyperglycaemia. This glucotoxicity and the rate at which it is corrected may be key factors in future management. More vigorous treatment at onset is reported to produce a higher rate of remission.¹¹ What degree of intensive insulin treatment is justified in a newly diagnosed child? There are advocates of prolonged insulin infusion and frequent monitoring after diagnosis.^{12,13} Children randomised to continuous subcutaneous insulin infusion treatment from diagnosis, however, showed only modest prolongation of partial remission as compared with those receiving conventional treatment.¹⁴ Those of us who aim for less dramatic early intervention and for prompt home management remain to be convinced.

A range of drugs capable of modifying the immune system are being explored in IDDM. At present the most attractive is cyclosporin. It acts mainly on T cell mediated immunity, and delays the onset of diabetes in BB rats and NOD mice. Two major controlled studies of cyclosporin treatment are underway. An initial report showed that in adults it prolonged the complete remission phase in a fifth of patients.¹⁵ Another French study is examining the value of cyclosporin in children.¹⁶ In a preliminary study using historical controls, 27 out of 40 patients were able to discontinue insulin treatment. Half still did not need insulin at 12 months. It is interesting that the response of young diabetics should appear to be more dramatic than that seen in the parallel adult study. Children were more likely to enter remission if they had shorter duration of symptoms, less weight loss, and milder metabolic disturbance. Response to cyclosporin showed no relation to either HLA types or immune markers.

While these reports are exciting, they should not be regarded as a licence for the widespread use of cyclosporin in diabetic children. There are still important issues to be resolved, and only carefully structured protocols will provide much needed answers. The essential question is whether cyclosporin treatment produces sufficient improvement

in the longterm course of IDDM to justify potential drug toxicity? It would be anomalous to expose young diabetics to the risk of cyclosporin induced nephrotoxicity while attempting to prevent the onset of diabetic nephropathy in 30–40% of them. Hopefully the unravelling of the immune mechanisms responsible for IDDM, combined with biotechnology, will enable the development of more specific and safer drugs.

The management of established diabetes

In the prepubertal child we continue to favour treatment based on a twice daily injection of mixed short and medium duration insulins. We pay attention to the total dose and avoid exceeding 0.8 units/kg/day; an apparent requirement for greater dosage often points to errors in the balance of insulins used or to other problems of management. The varied lifestyle of young children demands individual and flexible titration of insulin regimens. Some children under 8 years benefit from a bedtime injection of medium duration insulin instead of the pre-evening meal injection.¹⁷ We disagree with the claims that effective control, after the partial remission phase, can be achieved using a single daily insulin injection. Twice daily insulin permits more active insulin adjustment and response to blood glucose monitoring. Our experience is that informed parents of both infants and children elect to use twice daily injection. The more frequent injection regimen enables them to react better to the often unpredictable events and dietary intake of the average child. Information available from long term studies is limited but tends to support the belief that two injections provide better control as judged by the avoidance of late complications.¹⁸ There is also some logic in the argument that the more frequent the injections, the better the preparation for multiple injection regimens that are now being promoted in later life.

The physiological and behavioural adjustments of adolescence combine with diabetes to pose one of the greatest challenges that we face. It is well recognised that insulin requirements tend to rise, often to around 1.5 units/kg/day.¹⁹ Increased growth hormone secretion rather than sex steroids accounts for this phase of increased insulin resistance.²⁰ Our clinical impression is that girls are more difficult to control, but this may reflect gender differences in exercise and eating behaviour rather than pubertal events. Girls are certainly more susceptible to obesity, and some recognise that the energy loss of poorly controlled diabetes and glycosuria helps them stay slim. These problems have to be anticipated and avoided by sympathetic, realistic dietary

guidance. Left unchecked obesity will fuel loss of confidence, disinterest in diabetic control, and more substantial eating disorders.

We are promoting more intensive insulin regimens in teenagers but appreciate that success is dependent on whether we can modify our clinic style to generate interest among these, the most severe of our critics. Our established child and family orientated clinic lacks the necessary flexibility and scope for group participation. We are now offering adolescents the alternative of an early evening open clinic within our local diabetes centre. For those of us who find relating to teenagers in our own family a struggle, the prospect of motivating groups is awesome! Hopefully the task will be shared with young leaders who have emerged from our clinics and attended the Youth Diabetes Project based at Firth-Loch Tay. The adolescent clinic will also provide a better interface with our colleagues providing a similar service for young adults.

Monitoring control

Most children adjust to the demands of capillary blood glucose monitoring. We recommend a minimum of three to four tests per day twice a week, or one per day the time being varied in an attempt to construct a profile over the week. Naturally enthusiasm wanes with duration of diabetes. Families who are able to make management decisions as the result of these tests are better motivated to persevere. It is important therefore to see the tests as a tool for the instruction of the family rather than as a criterion used by doctors and nurses to make judgments about control. Families can be guided through problem solving exercises—for example, the recognition of potential nocturnal hypoglycaemia or the adjustment of the evening insulin dosage to reduce fasting hyperglycaemia. A few children develop a phobia to capillary punctures. If the answer does not lie with switching to an alternative finger pricking gadget, we have to accept a phase of urine glucose testing. Others falsify tests in an attempt to disguise overeating, or in the belief that the diabetes team will then leave them in peace. Discrepant HbA₁ results and some spot checks at home usually expose falsification. We are beginning to introduce glucose meters equipped with memories for such youngsters but recognise that they will continue in their attempts to outwit us. The real solution lies with our strategies for promoting education and motivation.

Determination of HbA₁ remains the gold standard of diabetes control. Capillary blood is suitable for the assay, and allows regular measurement in clinic or at home visits. Our results are not available in the same clinic but are reviewed a few days later

at a follow up meeting of the diabetes team. High and rising values allow us to target our diabetes liaison health visitor's time to greatest effect. The size of our task is shown by the clinic mean HbA₁ concentration that fluctuates between 11.0 and 11.5% (normal range up to 8.0%). We find that the mean rises with age and duration of diabetes. Audit of these clinic values has to take account of the number of adolescents within the children's service.

Serum fructosamine is being promoted as a further index of integrated glycaemia. The assay has the attractions of speed, reproducibility, and reduced cost. The measurement reflects total serum protein, mainly albumin, glycation. It has a shorter half life and is more sensitive to brief hyperglycaemic excursions.²¹ These are potential disadvantages in the interpretation of control in childhood, and we do not plan to convert to fructosamine measurement until these doubts have been resolved.

More intensive insulin regimens

Although the relation between long term diabetes control and the development of complications remains a topic of active debate, most of us are sufficiently convinced by the accumulating evidence to wish to promote optimal control. The issue facing paediatricians is whether currently available techniques of diabetes management can be applied to children with sufficient intensity to bring about near normal control within the constraints of an acceptable lifestyle, and without the disruption of repeated severe hypoglycaemia. How near does near normal control have to be to produce real benefit? It is unlikely that there is any simple answer to this question; a different combination of genetic and environmental factors probably determines the threshold of susceptibility to tissue damage in any one individual. Only long term early intervention prospective studies, such as that mounted by the Diabetes Control and Complications Trial Research Group,²² will resolve this crucial issue. The logistical problems of mounting this study in adult diabetics have been such that it is difficult to entertain such a protocol for young diabetics. Given that microvascular disease is 'programmed' by metabolic conditions early in diabetes, is the prepubertal child relatively protected? There is some evidence to support this. Microalbuminuria, an index of renal glomerular damage, is less prevalent in diabetics under age 12 years compared with those aged over 12 years matched for duration.²³ What this means in the context of setting targets for control before, during and after puberty is unknown. The reality is that we aim for the best control that the child, family

circumstances, and available treatment strategies permit.

Continuous subcutaneous insulin infusion has theoretical attractions and it is confirmed that it can produce near normal glycaemic control, at least within the structure of supervised research protocols. It is less certain whether it can be applied with the same good results to the generality of patients in the average clinic setting, and there are certainly major obstacles in its application to children and adolescents.²⁴ We have had only limited experience in the application of continuous subcutaneous insulin infusion but see our clinic resources as better directed to the promotion of multiple injection regimens based on pen injection devices (NovoPen and NovoPen II). In usual diabetic clinic conditions the control achieved with multiple injection treatment is similar to that while using continuous subcutaneous insulin infusion, but neither is normal.^{25 26}

We are actively promoting NovoPen based regimens among older children and adolescents. Short duration insulin is administered before main meals according to simple guidelines. Fifty to sixty percent of the total insulin dose is given as either medium or long duration insulin injected at bedtime. We have used either Monotard or Ultratard, others favour an isophane insulin. The combination of potentially improved control and a more flexible strategy has appeal, but the results are not uniformly successful. Some patients maximise the benefits and sustain improved HbA₁ concentrations. Others exploit the flexibility by embarking on further dietary non-compliance, and add increasing obesity to their problems. Success, as with any regimen, is dependent on motivation and informed use of regular home blood glucose monitoring.

Some of the problems

Hypoglycaemic attacks are an inevitable component of adequately controlled diabetes. There is little data on their incidence in children. Surveys within adult clinics show that 10–15% of patients experience at least one severe episode each year. Attempts at gaining optimal control are accompanied by a two to threefold increase in the frequency of episodes.²² Although families must be educated to recognise and prevent 'at risk' situations, it is sometimes the case that severe nocturnal attacks occur without warning. Parents should be equipped with the means of raising the blood sugar, glucose gel for buccal mucosa absorption (Hypostop), and glucagon injection. The greater problem is rationalising the threat of recurrence so that parents still retain the target of good control. They can be reassured that acute accidental hypoglycaemia does not cause brain

damage even if it manifests as an epileptiform attack. Late evening blood tests particularly after a day of increased physical activity give fairly reliable warning of nocturnal hypoglycaemia. Attention to the total insulin dosage should avoid chronic hypoglycaemia which can be debilitating. Severe hypoglycaemia despite appropriate precautions raises the possibility of intentional overdosage.

Fasting hyperglycaemia and an exaggerated glycaemic response to breakfast is a well recognised problem,²⁷ and one which generates considerable confusion for families achieving otherwise satisfactory control. Faced with low or normal blood tests at bedtime and at midnight there seems no easy solution. This rise in blood glucose concentration has several causes; a transient decrease in hepatic insulin sensitivity occurring in the early morning hours, a waning of the insulin available from depot preparations, and exaggerated counter regulation provoked by nocturnal hypoglycaemia. The term 'dawn phenomenon' has been coined to describe the early morning rise in blood glucose. Nocturnal surges of growth hormone, which are higher in patients with IDDM, correlate with the changes in hepatic glucose production. Studies with continuous subcutaneous insulin infusion have confirmed the need for a low rate of insulin infusion between 2300 and 0300 hours followed by a phase requiring about 30% increased dosage. Hormonal and neural mechanisms triggered by nocturnal hypoglycaemia (Somogyi phenomenon) add to this process but probably do not play as large a part as was previously thought.

Measures that we use to combat morning hyperglycaemia include delaying the evening mixed injection and meal within the limits tolerated by child and family, and splitting the evening injection so that the medium duration insulin is given as a third injection at bedtime. Neither is consistently effective. Multiple injection regimens incorporating ultralente insulin have a theoretical attraction but do not always succeed. The answer may lie in the development of new delayed release or proinsulin like formulations. For the present we have to accept the problem, avoiding the temptation to make inappropriate upward adjustments in the evening insulin dosage.

Brittle diabetes

At any one time our clinic population of over 200 children and adolescents contains one or two children who require frequent admission because of ketoacidosis. The disruptive nature of their diabetes effects mood, confidence, growth, and education. Their families become trapped within a spiral of

uncertainty and anxiety. The diabetes team finds itself devoting increasing efforts in an attempt to help the child and family but sometimes without apparent reward. The problems posed by brittle diabetics have been vividly reviewed.²⁸ The causes fall into three main categories: diabetes management, coincidental illness, and child-family dynamics. In our experience the first two show themselves relatively easily. Our diabetes health visitor is the key person in exposing and correcting mismanagement in the home. Many adolescents fail to keep to recommended guidelines, and have raised blood glucose and HbA_{1c} concentrations to reflect this. Almost all claim to be in excellent health, however, and do not admit to disruption of lifestyle. Among the long list of coincidental disorders that may interfere with diabetic stability, we have encountered chronic pyelonephritis, coeliac disease, inflammatory bowel disease, chronic active hepatitis, autoimmune hypothyroidism, and Addison's disease. Careful clinical review together with selected investigations usually shows the problem without there being confusion with personality based brittle diabetes.

We are constantly impressed how well most families faced with conspicuous financial and social adversity cope with diabetes. Brittle diabetics appear to emerge within families that appear at a superficial level to be contented and united. A typical example is an adolescent girl who has required 10 hospital admissions in the last two years. Each episode is precipitated by ketoacidosis that evolves rapidly, and which is readily controlled after admission. Despite acceptable blood glucose control in the ward outpatient control is erratic and punctuated by symptomatic ketosis and resulting days off school. The girl and her mother perform frequent monitoring in their attempts to avert ketoacidosis. No fault can be found in injection technique, and there is no evidence of dosage omission or manipulation. It emerges that child and mother are closely bonded almost to the exclusion of father and other siblings. This enmeshed relationship focuses upon and amplifies the potential threats created by diabetes. Glycaemic excursions become an obsession, and body language is so highly tuned that formal blood testing is hardly required to fuel their anxiety. The mother may already have been conditioned to health awareness by her own or another relative's chronic illness. The father appears as a peripheral figure, working hard to support his family but avoiding the tensions generated by his daughter. Such a scenario reinforces the importance of the diabetes service having ready access to the skills of family therapy. Diagnosis is complex. Treatment is difficult and time consuming. Success is by no means guaranteed even with adequate resources. Fortu-

nately most such girls have a relatively good medium term prognosis for overcoming this chaotic period. Maturity and increasing autonomy make them more resilient.

It is our impression that boys are less likely to have such an enmeshed relationship, and that devious manipulation is the greater factor. For a small number of these difficult diabetics, the solution lies with carefully selected semiresidential schooling.

Complications of diabetes

The natural history of insulin dependent diabetes is such that paediatricians are largely divorced from the problems created by retinopathy, nephropathy, neuropathy, and large vessel disease. Less sophisticated colleagues have a curious misconception that this gap denies us an essential insight into diabetes and its management. The reality is that children's diabetes services are actively mobilising themselves to pursue increasingly good control during the phase of life when it is most difficult to achieve. Most families are only too well aware of the potential threats facing their child. They are regularly exposed to advertisements and media revelations highlighting the likelihood of blindness, amputation, and heart attacks. It requires considerable delicacy to explore these issues with youngsters and their parents.

Our current strategy for detecting complications is relatively conventional but it has the advantage of a computer based patient record system that ensures regular procedures. These include annual eye examination (with dilatation if duration of diabetes is 10 years or more), annual blood pressure measurement, urine screening for infection and proteinuria, skin state, liver size, and assessment of finger joint flexion deformity. We do not plan to screen for microalbuminuria until there is clearer guidance on optimal procedures for sample collection and measurement.

Transfer to the adult diabetes service

We usually arrange to transfer patients between 16 and 18 years of age but remain sensitive to the wishes of those who prefer earlier promotion. Those whose experience of life is rapidly outpacing their carers in the children's service clearly need prompt handover! A common approach to diabetes management and shared support staff facilitate transfer. The computer based record system ensures continuity of documentation and permits us to follow the progress of our ex-patients. The establishment of a local diabetes centre and adolescent clinics will give us an opportunity to explore whether structured

handover clinics offer any additional advantage. The unacceptable drop out rate after transfer reminds us that paediatricians and diabetologists must work closely together to ensure that clinics become more attractive to young adults so that the investment of care during childhood is not squandered.

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Correspondence to Dr D I Johnston, Children's Department, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH.