RECENT ADVANCES

Advances in childhood onset diabetes

J P H Shield, J D Baum

There is evidence that the incidence of childhood onset insulin dependent diabetes mellitus (IDDM) continues to rise in Western Europe.¹ While the cause of this increase remains elusive, our understanding of both the aetiopathological basis and subsequent long term complications of IDDM has progressed significantly over the last five years.

Heterogeneity of childhood diabetes

Childhood onset diabetes is an autoimmune disorder in the majority of cases: however, the aetiopathogenesis of several well known rare variants has recently been clarified, thereby establishing the diverse nature of the disease. These include maturity onset diabetes of the young caused by glucokinase abnormalities (MODY 2), Wolfram's syndrome (DIDMOAD), Rabson-Mendenhall syndrome, and maternally inherited diabetes and deafness (MIDD).

MODY 2 is a dominantly inherited, relatively benign condition presenting with mild hyperglycaemia in childhood. Its cause lies in mutations of the gene on 7p (short arm of chromosome 7) encoding for the hexokinase enzyme glucokinase which acts as the pancreatic β cell "glucose sensor".²

Wolfram's syndrome—diabetes insipidus and diabetes mellitus, optic atrophy, and deafness (DIDMOAD)—is usually inherited in an autosomal recessive manner (although some cases may have a mitochondrial basis³). An extensive United Kingdom survey has further characterised it as non-autoimmune diabetes, usually manifest in the first decade in association with optic atrophy, to be followed in the second decade by diabetes insipidus and deafness, with multiple neurological abnormalities developing in the early fourth decade leading to premature death.⁴

Rabson-Mendenhall syndrome is a severe diabetic disorder with inherited insulin resistance. It is caused by mutations in the insulin receptor leading to uncontrolled hyperglycaemia and early death from either ketoacidosis or rampant microvascular disease.⁵ Various mutations have been described, including the replacement of a serine residue by leucine at position 323 of the receptor protein leading to defective binding capacity.⁶ Although the syndrome is exceedingly rare, its investigation has increased our understanding of insulin receptor activity and has led to a theoretical model of treatment for this condition using

monoclonal antibodies acting as a substitute for the normal ligand, thereby activating the defective receptor.⁷

MIDD is of interest as it is caused by a single point mutation in mitochondrial DNA (the 3243 mutation). It can be manifested as either insulin dependent or non-insulin dependent diabetes in association with varying degrees of deafness.⁸ The precise nature of the cellular defect resulting from the mutation is unknown, but the same mutation is found in MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes).

The wealth of information that may be obtained by studying these rare variants of childhood onset diabetes has a scientific significance far outweighing the frequency of these conditions in clinical practice.

The genetics of classical childhood onset IDDM

There is little argument that classical IDDM is a disease which is environmentally triggered in genetically susceptible individuals. Recent evidence has strengthened the position of genetic susceptibility in the development of the disease.

In 1995 Kyvik *et al* estimated an adjusted probandwise risk for IDDM monozygotic unaffected twin partners from birth to age 35 years at 0.7 (95% confidence interval 0.45 to 0.95), a higher level than previously suggested.⁹ Further confirmation of the importance of genetic factors is presented in a recent epidemiological study from the Lazio region of Italy, which defines a fourfold risk of IDDM in children of full Sardinian ancestry (Sardinia having a very high incidence of 34/100 000/year, compared with ~8/100 000/year in mainland Italy) compared with the indigenous population, and an intermediate risk for those with only one parent from Sardinia.¹⁰

The last five years have witnessed a barrage of information identifying susceptibility loci (regions within chromosomes) associated with autoimmune related IDDM, confirming the complexity of its polygenic inheritance. There are currently 12 such loci mapping to various chromosomes (IDDM 1-10, GCK, and CTLA-4; table 1), the biggest contribution coming from IDDM1 which imparts approximately 35% to genetic susceptibility in the United Kingdom.¹²

IDDM 1, mapping to 6p21, encompasses the major histocompatibility complex (MHC)

Institute of Child
Health, St Michael's
Hill, Bristol BS2 8BJ
J P H Shield
J D Baum

Correspondence to:
Dr Shield.

Table 1 Known IDDM susceptibility loci and their chromosome locations (from reference 11)

Locus name	Chromosome location
IDDM 1	6p21
IDDM 2	11p15
IDDM 3	15q
IDDM 4	11q13
IDDM 5	6q25
IDDM 6	18q
IDDM 7	2q31
IDDM 8	6q27
IDDM 9	3q21-25
IDDM 10	10p11.2-q11.2
Glucokinase	7p
Cytotoxic T lymphocyte associated 4	2q33

*p short arm, q long arm.

and is therefore an obvious candidate gene for a condition with an autoimmune basis. Within the MHC region, the strongest association with IDDM has been with class II DQ alleles, specifically the DQB1 polymorphism. Non-charged amino acid residues at position 57 of the DQ β chain of the DQ heterodimer are positively associated with IDDM, while a charged residue (aspartate) is protective.¹³

IDDM2 is also of great interest, lying as it does within the insulin gene region and mapping to 11p15, which encompasses genes for tyrosine hydroxylase, insulin, and insulin-like growth factor II (IGF II).

Currently it seems that the susceptibility locus actually lies within a variable number tandem repeat sequence (VNTRs—short identical DNA sequences which multiply repeatedly in a tandem row), 5' (upstream) to the insulin gene.¹⁴ This is a highly polymorphic (variable) region composed of tandemly repeated 14–15 base pair sequences. The number of repeats can be divided into three discrete classes, class I (26–63), class II (average 80; rare in whites), and class III (141–209). In general, class I alleles are associated with IDDM while class III alleles are protective.¹⁵ The mechanism by which polymorphisms within this site predispose to IDDM is as yet unknown. The next few years will undoubtedly witness the identification of further gene mutations within the susceptibility loci, further improving our overall understanding of the fundamental problems in IDDM.

Prediabetes and diabetes prevention

IDDM in childhood often has a prolonged preclinical phase of months or years, with evidence of autoimmune processes associated with progressive pancreatic β cell destruction.¹⁶ If the trend towards an increasing incidence of IDDM in Europe is to be reversed, the disease must be capable of preclinical identification and effective treatment in this phase. Such interventions would obviously be a major advance.

Much work has centred on IDDM prediction or risk analysis in first degree relatives of cases with IDDM, where the increased risk can be calculated. However, no one specific test reliably identifies those at risk of developing diabetes, even within this small selected group (only 10% of those developing IDDM have a first degree relative with IDDM).¹⁷ Using a

“multiple marker” strategy—combining auto-antibody analysis (islet cell antibodies (ICA), insulin autoantibodies (IAA), 37 kDa fragment of glutamic acid decarboxylase (GAD), and protein tyrosine phosphatase-like molecule IA-2) with genetic HLA markers for diabetes susceptibility and metabolic pointers such as a blunted or delayed first phase insulin response to intravenous glucose (FPIR)—some investigators claim to be able to predict the majority of first degree relatives liable to develop clinical diabetes.^{18, 19} However, once the same methodology is extended to the general population, within which the vast majority of new cases develop, the positive predictive value of tests such as ICA positivity is greatly reduced. For instance, 2.8% of a healthy cohort of schoolchildren in the Oxford/Windsor area were recently identified with ICA concentrations ≥ 4 JDF (Juvenile Diabetes Foundation) units,²⁰ although the majority of these children would not be expected to develop diabetes given the prevalence of IDDM in the general population of approximately 0.1–0.2%.²¹ Using multiple risk criteria, including autoantibody analysis and MHC and non-MHC defined genetic susceptibility, it may be possible to identify more accurately those in the general population at greatest risk of developing IDDM and thereby target preventive treatment.

Various treatments designed to prevent IDDM in its prediabetes stage are currently under evaluation in “at risk” first degree relatives of IDDM cases. Nicotinamide, a soluble B group vitamin and precursor of nicotinamide adenine dinucleotide (NAD), appears to protect pancreatic β islet cells from immune mediated damage²² and is currently under evaluation in high risk first degree relatives of IDDM cases within the European Nicotinamide Diabetes Intervention Trial (ENDIT). The interim statistical review of the trial will be performed in late 1998.²³ Other trials are also currently under evaluation, such as subcutaneous (DPT1) and oral insulin inducing “immune tolerance” in prediabetes.²⁴

These trials represent secondary preventive approaches in which the aim is to control disease progression before the development of overt disease. However, one trial currently under way in Finland is aimed at primary prevention, whereby a putative “trigger” to disease induction—in this case the early introduction of cows’ milk proteins into the diet—is avoided in one group of genetically susceptible infants while a conventional diet is followed in a genetically similar control group.²⁵ This trial is based on observations made in various studies, in the latest of which a highly significant difference in T lymphocyte proliferation to β casein (a cows’ milk protein) was observed in those patients with recently diagnosed IDDM compared with normal controls and those with autoimmune thyroid disease.²⁶

An understanding of the natural history of childhood IDDM represents a major advance, permitting the development of screening methods, identifying those at risk, and setting the stage for effective interventions aimed at

preventing clinical disease onset. These studies may ultimately change the whole perspective of childhood diabetes.

The Diabetes Control and Complications Trial (DCCT)

In September 1993, the DCCT reported its findings on the effects of improved glycaemic control on the development of microvascular disease²⁷; a subsequent report²⁸ focused on a subset of the study population in the adolescent age range (13 to 17 years). This landmark study leaves no doubt that improving glycaemic control will reduce the long term risk of diabetic microvascular, and in all probability, macrovascular disease. However, simple methods by which glycaemic control can be improved remain elusive, while the incorporation of the DCCT's intensive management regimen into normal practice would be prohibitively expensive.²⁹ Furthermore, it should be noted that the adolescent group of volunteers was unable to achieve the same improvement in glycaemic control as their adult counterparts, despite a disproportionate resource input. The DCCT did not address the question of diabetes control in children under 13 years of age, nor the implications of the increased risk of major hypoglycaemic events associated with improved control.³⁰ The authors did observe, however, that "the specific goals of near metabolic normality should be reserved at this time for adolescence."³¹ Unfortunately this prepubertal phase cannot be regarded as a period protected from the ravages of persistent hyperglycaemia.³²⁻³³ It is an increasingly difficult task steering our patients between stricter control with its long term health advantages and over control with the risk—certainly in preschool children—of repeated severe hypoglycaemia and consequential neurocognitive dysfunction.³⁴

Other areas of advance

RECOMBINANT IGF-I TREATMENT

Abnormalities in the insulin-like growth factor 1 (IGF-I)/growth hormone axis in IDDM have been clearly shown to be linked to poorer glycaemic control in adolescence.³⁵⁻³⁶ Initial studies had suggested that administration of recombinant IGF-I might prove to be a useful adjunct to current insulin regimens improving insulin sensitivity and glycaemic control.³⁷ However, a recent study showed improved glycaemic control only in the first three months of treatment, raising questions as to whether initial improvements can be sustained.³⁸ Further placebo controlled studies are needed to define the limits of practicability in the clinical reality of the lives of the teenagers concerned; however, the theoretical basis for such an intervention is now established and certainly offers potential benefits.

TRANSPLANTATION

Cure by transplantation is naturally the dream of many diabetic children and their parents. From studies in adult patients, the procedure remains disappointing and potentially hazardous. Transplantation or implantation of pan-

creatic islet cells directly into the hepatic system has major advantages over whole gland pancreas transplants which, because of the operative risks and significant levels of organ rejection,³⁹ should only be conducted in subjects with end stage renal failure while undergoing renal transplantation.⁴⁰ Unfortunately, the results of islet cell transplants are currently not encouraging, with only 28 (16%) of 180 patients transplanted between 1989 and 1994 remaining insulin independent for more than one week.⁴¹

INSULIN DELIVERY SYSTEMS AND ANALOGUES

The notion of giving insulin pernasally has naturally excited interest among families with diabetes. Unfortunately, because of its limited bioavailability (especially covering meal time insulin requirements⁴²) associated with a high rate of therapeutic failure, intranasal treatment "is not a realistic alternative to subcutaneous insulin injections."⁴³

The insulin analogues are likely to generate more prolonged interest. One such example is Lispro, a "designer insulin," in which the positions of the amino acids B28 (proline) and B29 (lysine) have been interchanged, leading to a novel insulin molecule which is more rapidly absorbed from injection sites and has altered antigenic properties.⁴⁴⁻⁴⁵ Early results among adolescent subjects, while not achieving improvements in long term glycaemic control, have shown other advantages, allowing a reduction in the time between injection and eating, with fewer hypoglycaemic events and lower peak postprandial levels of glucose.⁴⁶ However, it remains to be seen whether, in the clinical arena, the new insulin analogues will significantly influence glycaemic control.

Conclusions

The last five years have seen great strides in our appreciation of many aspects of IDDM from prediabetes susceptibility to the prevention of long term microvascular disease. The rapid expansion in our understanding of the basis of insulin secretion and action has opened up many new avenues of treatment. The real challenge over the next five years will be to translate the knowledge gained in the laboratory into improved treatment in the clinical setting.

- 1 Bingley P, Gale EAM. Rising incidence of IDDM in Europe. *Diabetes Care* 1992;12:289-95.
- 2 Hattersley AT, Turner RC. Mutations of the glucokinase gene and type 2 diabetes. *Q J Med* 1993;86:227-32.
- 3 Rotig A, Cormier V, Chatelain P, et al. Deletion of mitochondrial DNA in a case of early-onset diabetes mellitus, optic atrophy, and deafness (Wolfram syndrome, MIM 222300). *J Clin Invest* 1993;91:1095-8.
- 4 Barrett TG, Bunday SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DID-MOAD) syndrome. *Lancet* 1995;346:1458-63.
- 5 O'Rahilly S, Moller D. Mutant insulin receptors in syndromes of insulin resistance. *Clin Endocrinol (Oxf)* 1992;36:121-32.
- 6 Krook A, Kumar S, Laing I, Boulton AJM, Wass JAH, O'Rahilly S. Molecular scanning of the insulin receptor gene in syndromes of insulin resistance. *Diabetes* 1994;43:357-68.
- 7 Krook A, Soos MA, Kumar S, Siddle K, O'Rahilly S. Functional activation of mutant human insulin receptor by monoclonal antibody. *Lancet* 1996;347:1586-90.
- 8 Maassen JA, Kadowaki T. Maternally inherited diabetes and deafness: a new diabetic subtype. *Diabetologia* 1996;39:375-82.
- 9 Kyvik KO, Green A, Beck-Nielsen H. Concordance rates of insulin dependent diabetes mellitus: a population based study of young Danish twins. *BMJ* 1995;311:913-17.

- 10 Muntoni SA, Fonte MT, Stoduto S, *et al.* Incidence of insulin-dependent diabetes mellitus among Sardinian-heritage children born in Lazio region, Italy. *Lancet* 1997;349:160-2.
- 11 Gough SCL. Genetics of insulin-dependent diabetes mellitus. *Baillieres Clin Paediatr* 1996;4:593-608.
- 12 Todd JA. Genetic analysis of type 1 diabetes using whole genome approaches. *Proc Natl Acad Sci USA* 1995;92:8560-5.
- 13 Gough SCL. Genetics of insulin-dependent diabetes mellitus. *Baillieres Clin Paediatr* 1996;4:593-608.
- 14 Bennett ST, Lucassen AM, Gough SCL, *et al.* Susceptibility to human type 1 diabetes at IDDM 2 is determined by the tandem repeat variation at the insulin gene microsatellite locus. *Nature Genet* 1995;9:284-92.
- 15 Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. *N Engl J Med* 1994;331:1428-36.
- 16 Bennett ST, Todd JA. Human type 1 diabetes and the insulin gene: principles of mapping polygenes. *Annu Rev Genet* 1996;30:343-70.
- 17 Christie MR, Tun RYM, Lo SSS, *et al.* Antibodies to GAD and tryptic fragments of islet 64K antigen as distinct markers for development of IDDM: studies with identical twins. *Diabetes* 1992;41:782-7.
- 18 Bingley PJ, Bonifacio E, Gale EAM. Can we really predict IDDM? *Diabetes* 1993;42:213-20.
- 19 Bonifacio E, Genovese S, Braghi S, *et al.* Islet autoantibody markers in IDDM: risk assessment strategies yielding high sensitivity. *Diabetologia* 1995;38:816-22.
- 20 Bingley PJ, Bonifacio E, Shattock M, *et al.* Can islet cell antibodies predict IDDM in the general population. *Diabetes Care* 1993;16:45-50.
- 21 Betts P, Buckley M, Davies R, McEvilly E, Swift P. The care of young people with diabetes. *Diabetic Med* 1996;13:S54-9.
- 22 Pozzilli P, Browne PD, Kolb H. The Nicotinamide Trialists. Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. *Diabetes Care* 1996;19:1357-63.
- 23 Gale EAM. Theory and practice of nicotinamide trials in pre-type 1 diabetes. *J Pediatr Endocrinol Metab* 1996;9:375-9.
- 24 Pozzilli P. Prevention of insulin-dependent diabetes. *Baillieres Clin Paediatr* 1996;4:577-92.
- 25 Akerblom HK. Diabetes and cow's milk. *Lancet* 1996;348:1656-7.
- 26 Cavallo MG, Fava D, Monetini L, Barone F, Pozzilli P. Cell-mediated immune response to β casein in recent-onset insulin-dependent diabetes: implications for disease pathogenesis. *Lancet* 1996;348:926-8.
- 27 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
- 28 The Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 1994;125:177-88.
- 29 Shield JPH, Baum JD. Prevention of long-term complications in diabetes. *Arch Dis Child* 1994;70:258-9.
- 30 American Diabetes Association. Implications of the Diabetes Control and Complications Trial. *Diabetes* 1993;42:1555-8.
- 31 Drash AL. The child, the adolescent, and the Diabetes Control and Complications Trial. *Diabetes Care* 1993;16:1515-16.
- 32 McNally PG, Raymond NT, Swift PGF, Hearnshaw JR, Burden AC. Does pre-pubertal duration of diabetes influence the onset of microvascular complications? *Diabetic Med* 1993;19:906-8.
- 33 Donaghue KC, Fung ATW, Hing S, *et al.* The effect of pre-pubertal diabetes duration on diabetes: microvascular complications in early and late adolescence. *Diabetes Care* 1997;20:77-80.
- 34 Rovet J, Alvarez M. Attentional functioning in children and adolescents with IDDM. *Diabetes Care* 1997;20:803-10.
- 35 Dunger DB. Insulin and insulin-like growth factors in diabetes mellitus. *Arch Dis Child* 1995;72:469-71.
- 36 Dunger DB, Cheetham TD. Growth hormone insulin-like growth factor 1 axis in insulin-dependent diabetes mellitus. *Horm Res* 1996;46:2-6.
- 37 Cheetham TD, Holly JMP, Clayton K, Cwyfan-Hughes S, Dunger DB. The effects of repeated daily recombinant human insulin-like growth factor I administration in adolescents with type 1 diabetes. *Diabetic Med* 1995;12:885-92.
- 38 Acerini CL, Patton CM, Savage MO, Kernell A, Westphal O, Dunger DB. Randomised placebo-controlled trial of human recombinant insulin-like growth factor I plus intensive insulin therapy in adolescents with insulin-dependent diabetes mellitus. *Lancet* 1997;350:1199-204.
- 39 Stratta RJ, Weide LG, Sinhi R, Sudan D, Jerius JT, Larsen JL. Solitary pancreas transplantation. Experience with 62 consecutive cases. *Diabetes Care* 1997;20:362-8.
- 40 American Diabetes Association [position statement]. Pancreas transplantation for patients with diabetes mellitus. *Diabetes Care* 1997;20(suppl 1):S54.
- 41 Secchi A, Soggi C, Maffi P, *et al.* Islet transplantation in IDDM patients. *Diabetologia* 1997;40:225-31.
- 42 Danielsen GM, Drejer K, Langkjaer L, Plum A. New routes and means of insulin delivery. In: Kelnar CJH, ed. *Childhood and adolescent diabetes*. London: Chapman and Hall, 1995:571-84.
- 43 Hilsted J, Madsbad S, Hvidberg A, *et al.* Intranasal insulin therapy: the clinical results. *Diabetologia* 1995;38:680-4.
- 44 Ter Braak EW, Woodworth JR, Bianchi R, *et al.* Injection site effects on the pharmacokinetics and glucodynamics of insulin Lispro and regular insulin. *Diabetes Care* 1996;19:1437-40.
- 45 Lahtela JT, Knip M, Paul R, Anttonen J, Salmi J. Severe antibody-mediated human insulin resistance: successful treatment with the insulin analog Lispro. *Diabetes Care* 1997;20:71-3.
- 46 Garg SK, Carmain JA, Braddy KC, *et al.* Pre-meal insulin analogue insulin Lispro vs Humulin R insulin treatment in young subjects with type 1 diabetes. *Diabetic Med* 1996;13:47-52.