which will include ventilation, circulatory support, treatment of seizures, monitoring and treatment of raised intracranial pressure, broad spectrum antibiotics, antivirals, and often immune modulators such as steroids.

If one could predict which children will develop severe influenza virus associated encephalopathy before the onset of encephalopathic symptoms, there is a chance that early or different treatment strategies might ameliorate the outcome. The former has been achieved by Hosoya and colleagues.¹³ They measured plasma and serum concentrations of putative predictors (cytokines, cytochrome *c* oxidase, and markers of haematological, hepatic, and renal function) before and after the onset of the encephalopathic symptoms in children with influenza virus associated encephalopathy. They then examined the sensitivity, specificity, and cut-off concentrations of each putative predictor by constructing receiver operating characteristic (ROC) plots. Here, for each value of the putative predictor, the proportion predicting one outcome (the true positive rate (sensitivity); in this case death or neurological sequelae) is plotted against one minus the proportion predicting the alternative outcome (the true negative rate (specificity); in this case recovery). The area under the ROC curve is a measure of diagnostic accuracy and can be compared among the different putative predictors, the value at the upper left corner of the curve is the most discriminative cut-off level (giving the maximum likelihood ratio) and the sensitivity and specificity for this threshold level can be determined. Hosoya and colleagues found that pre-encephalopathy serum concentrations of cytochrome *c* oxidase had the greatest

diagnostic accuracy, and the threshold value of 45 ng/ml or more predicted a poor outcome in influenza virus associated encephalopathy with a sensitivity of 93% and a specificity of 100%. This is clearly a very important finding, although, as the authors point out, it needs confirming.

The next question is whether being able to predict a poor outcome in influenza virus associated encephalopathy can lead to better treatment. That cytochrome *c* oxidase proves to be the most accurate predictor suggests that already the proposed pathogenic sequence is well underway and that endothelial apoptosis has occurred. It thus seems that severe influenza virus associated encephalopathy is inevitable. However, reduction of circulating cytokines (perhaps by plasma exchange or anti-cytokine antibodies) might limit the vascular damage and prevent the encephalopathy, procedures to prevent the cerebral oedema (such as fluid restriction, perhaps brain cooling, and thiopentone to reduce cerebral metabolism) might also be helpful and finally, acute endothelial repair might become possible using infusions of endothelial precursor cells.

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Diabetes

The great weight gain experiment, accelerators, and their implications for autoantibodies in diabetes

T J Wilkin

Perspective on the paper by Reinehr *et al* (see page 473)

Cause and effect can generally be established only by an intervention in which all extraneous variables are controlled. Usually, this means creating the artificial conditions of a

randomised trial. Occasionally, the intervention comes about naturally.

For more than 50 years, mankind has been the subject of one such natural experiment—an intervention of

unprecedented scale which has proved both a serious threat to health and an unexpected source of fundamental new understanding. The intervention has been that of extreme weight gain, amounting in adults to some 9 kg over the past generation.¹ The corresponding increase in children has been even greater.² The gains have not been in bone, muscle, or water, but in fat. Body fat—most particularly visceral fat—leads to insulin resistance, and insulin resistance to increasing demands on β -cell reserve.³

Diabetes is a disorder of β -cell failure in which insulin reserves are no longer sufficient to meet demand.⁴ The rise of insulin resistance in contemporary society has served both to increase the incidence of diabetes and to accelerate its onset, so much so that type 2 diabetes, a disorder of middle age just

a generation ago, now ranks among the fastest growing disorders of paediatric practice across the industrialised world.⁵ The impact has been extraordinary, but it is not confined to type 2 diabetes. There has been a parallel increase in the incidence of type 1 diabetes,⁶ and an acceleration of its onset corresponding to that observed in type 2.^{7,8} Most striking has been the convergence of their phenotypes, making it increasingly difficult for paediatricians to distinguish the types at presentation.⁹

Thirty years ago, type 1 diabetes seemed distinct from type 2. It was predominantly a disorder of childhood, acute in onset, insulin requiring from the start, associated with high susceptibility MHC (HLA) genes and usually seropositive. Type 2, in contrast, affected adults, was slow in onset, unrelated to MHC genes, and seronegative. This tidy distinction, however, may have had more to do with registers than with reality. Paediatricians kept records, whereas adult diabetologists did not, and for some decades missed the fact that type 1 diabetes could present at any age—nearly half after the age of 30 years.¹⁰ It was nevertheless recognised early on that some adult diabetics, apparently type 2, were seropositive.¹¹ Confusingly, such antibodies also predicted future insulin dependency—by definition type 1 diabetes, not type 2.¹² Man is master at rationalising what seems irreconcilable, so antibody positive diabetes in the adult was given a name—“latent autoimmune diabetes in adults” (LADA). Once named, LADA became an entity, and PubMed currently cites more than 260 articles describing the behaviour and associations of this new “disease”. As the phenotypes have converged, so have attempts to classify childhood diabetes also run into trouble. “Type 1½” diabetes,¹³ “double” diabetes,¹⁴ and “hybrid” diabetes are all attempts to reconcile the apparent coexistence of two types of diabetes in the same child.

The article by Reinehr and colleagues in this issue of *Archives* examines the place of β -cell autoantibodies in the classification of contemporary childhood diabetes.¹⁵ They investigated 7050 children and adolescents with diabetes, of whom 128 were classified on standard criteria as type 2. Of these, 36% carried at least one β -cell autoantibody, but did not differ from the rest in terms of age, gender, body mass, metabolic status, or—importantly—subsequent need for insulin. Similar observations have been made in American children,^{16,17} but never before in Europeans. However, having established the clinical and serological characteristics of a relatively large cohort of contemporary European diabetic children, the authors propose, for no apparent reason, yet another layer to the

already over-burdened taxonomy of diabetes. To LADA, which itself has no pathogenic basis, they add LADY—“latent autoimmune diabetes in youth”.

We now have type 2 diabetes, gestational diabetes, type 1a diabetes, type 1b diabetes, LADA, LADY, and MODY 1–6 (maturity onset diabetes of the young). While the classification of MODY is justified on the grounds of discrete single gene defects in the glucose sensing pathways of the β -cell, the remainder are descriptive terms without any clear pathogenic distinction. Given the failure of the terminology to offer any better understanding of type 1 diabetes, convergence of the diabetic phenotypes, and now doubt over the very meaning of autoantibodies, there seems good reason to halt any further fragmentation of a classification that has never worked well, and ask whether there are common threads which might better help understand the underlying cause of diabetes and its changing behaviour.

The accelerator hypothesis is an attempt to unify the basis for type 1 and type 2 diabetes, to reconcile the observations from the Great Weight Gain Experiment into a common understanding of events, and to offer a common approach for prevention of both types of diabetes.¹⁸ Starting with the observations that type 1 and type 2 diabetes have both increased in parallel with rising body weight,¹⁹ and that autoantibodies are increasingly detected in what clinically appears to be type 2 diabetes, the hypothesis proposes that “type 1 and type 2 diabetes are the same disorder of insulin resistance set against different genetic backgrounds”.

Autoimmunity has always been regarded as the result of a dysregulated immune system, but there is no evidence for dysregulation, and the accelerator hypothesis views insulinitis, and the islet related antibodies associated with it, as predictable and physiological responses to the upregulation of β -cells that results from the increased demands of insulin resistance. Immune responses are controlled by HLA genes, so it should not be surprising that those carrying the genes which encode the most intense immune response generally develop diabetes earliest in life. This, the hypothesis argues, is childhood diabetes or, more accurately, diabetes accelerated into childhood. Those carrying HLA genes which encode a less intense response take longer to exhaust their β -cell reserve, and present with diabetes later in life as a result. The accelerator hypothesis revolves around the notion of tempo, modulated jointly by insulin resistance and the genetically controlled immune response to it.

The rise in body mass over the past 30 years has increased insulin resistance as

much in children as it has in adults,²⁰ and there is a clear relationship between body mass and insulin resistance in children as young as 5 years.²¹ The secular rise in body mass is likely to have been sufficient in itself to increase the incidence of type 1 and type 2 diabetes, but there is a more subtle interaction between insulin resistance as the environmental determinant of risk and HLA genotype as the genetic determinant of susceptibility. Each contributes a proportion (its attributable proportion) to the ultimate probability of developing disease and, as the contribution from one increases, so the contribution from the other must decrease. Consequently, a rising proportion attributable to insulin resistance must inevitably mean a falling proportion attributable to HLA genes.^{22,23} At the same time, increasing upregulation of the β -cells consequent on rising insulin resistance will render them more antigenic. Accordingly, as the childhood population gains weight, the incidence of diabetes rises, age at onset falls, the role of HLA genes diminishes, and—crucial to the issues surrounding LADA, LADY, and the traditional criteria used to classify diabetes—an increasing number of patients with type 2 diabetes become seropositive. The slower tempo among those of lesser genetic susceptibility, who nevertheless remain seropositive because of β -cell upregulation, throws the traditional criteria for type 1 diabetes into confusion. Nature’s grand experiment has created conditions into which these criteria no longer fit, suggesting they were always conditional in the first place—and therefore likely to have been spurious.

Hypotheses need mechanisms, and the accelerator hypothesis relies on insulin resistance both as an accelerator of β -cell loss in own right, and as a driver of the immune response to β -cell antigens. It predicts that the rise in type 1 diabetes should parallel that of weight gain in the population and that children who go on to develop type 1 diabetes should be heavier than their peers as toddlers. Both have been amply demonstrated.^{24–26} Importantly, it predicts that fatter children should develop type 1 diabetes younger—true acceleration. There are now five studies reporting this inverse relationship in cohorts of children with type 1 diabetes,^{27–31} and a sixth to show that the conversion rate to type 1 diabetes among children at risk is dependent on their level of insulin resistance.³² There are also two studies showing a secular rise in BMI at diabetes onset, suggesting that the proportion attributable to body mass needed to explain the mechanisms proposed is indeed increasing.^{28,29} Autoantibodies—confined to a genetically high responder subgroup of diabetes for as long as insulin resistance made little

contribution—are now widespread, driven by the ever increasing antigenicity of a β -cell upregulated to accommodate ever increasing demands on its function.

The mounting epidemic of obesity has done more than merely test the resources of nations to contain it. By disturbing the control systems that regulate blood glucose—by conducting what amounts in endocrine terms to a population-wide stress test—the Great Weight Gain Experiment has exposed responses that are not consistent with the conventional model of type 1 diabetes. It is not, of course, a perfect experiment, for it lacks the control arm necessary to exclude confounders. But if the changing behaviour of autoantibodies is to be accommodated within a meaningful taxonomy, and the proliferation of “neo-diseases” stemmed, we should maybe think of switching the type 1 diabetes paradigm from immune dysregulation to one of insulin resistance.

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Community child health

Balancing biomedical, care, and support needs in the technology dependent child

D W Vickers, L C Maynard

Perspective on the paper by Sullivan *et al* (see page 478)

In this issue, Sullivan *et al* report on their findings of a study of gastrostomy feeding in children with cerebral palsy.¹ This study is part of a larger examination of the impact of this intervention on children. Their key findings are that there is no increase in respiratory

morbidity following gastrostomy insertion and indeed a reduced need for antibiotics or hospital admission in the 12 months following the procedure for children with cerebral palsy. As they point out, there are a number of reports in the literature that have suggested the

reverse finding, an increase in mortality following gastrostomy. A recent systematic review highlighted the continued paucity of evidence on the risks and benefits of this intervention, in particular noting an excess of deaths in the gastrostomy fed group with cerebral palsy, observing however that this may reflect differing levels of disability in the intervention and control groups.²

Clearly there are risks in any surgical procedure, but this paper goes some way to provide reassurance that the medical risks are small. This paper is therefore useful in providing further information for professionals working with children and families to be clearer about the biomedical risks and benefits of this procedure.

This study reports on experience in specialist multidisciplinary feeding clinics for children with neurological disabilities which is likely to mean that they are