THE ACCELERATOR HYPOTHESIS – AN EVOLVING CONCEPT

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Abstract. *Clinical trials designed to prevent type 1 diabetes (T1D) based on the autoimmunity paradigm have proved disappointing, and have not so far translated into patient benefit. Meanwhile, the incidence of T1D continues to rise. The accelerator hypothesis explores the role of weight gain in childhood diabetes, as both islet cell immunity and T1D are associated with BMI. Insulin resistance, which results largely from weight gain, increases insulin demand, and demand puts stress on beta cells, which accelerates their apoptotic loss. An immune response to the stress in those who are genetically predisposed ('autoimmunity') hastens the loss further, and may explain by default why autoimmunity is a feature of diabetes in the young. The accelerator hypothesis was proposed in 2001 and, like most hypothesis, has evolved over the years.*

Key words: *Accelerator hypothesis, type 1 diabetes, clinical trial, insulin resistance,classification of diabetes, tempo in diabetes, hybrid diabetes*

Historical Reports of Insulin Resistance in Diabetes

Himsworth was the first to describe insulin resistance in diabetes nearly 80 years ago but not, as is often thought, so as to distinguish adults from juveniles with the disease – insulin resistance was noted in both [1, 2]. Others repeated Himsworth's observations using simple insulin-glucose tolerance tests [3–5], until a more sophisticated measure of insulin sensitivity, the glucose clamp, provided direct evidence that impaired insulin action is '…..a common feature of T1D' [6]. Indeed, while conceding it was possible to separate patients according to insulin sensitivity, Elliott Joslin concluded that testing for it was of little use because the overlap in clinical phenotype was so great [7]. Insulin resistance was associated with diabetes from earliest times, in both young and old, and posed no threat to its oneness.

The Categorisation of Diabetes

Diabetes remained one until the 1970's, when three observations made largely in children (lymphocytic insulitis [8], islet cell antibodies 9] and HLA genotype [10]) were interpreted by opinion leaders at the time to mean that childhood diabetes, unlike adult diabetes, was caused by dysregulation of the immune system (autoimmunity). A previously single disorder was now deemed to be two categorically distinct entities of different aetiology, and the autoimmune paradigm has been deeply rooted since. Importantly, however, the classification was based on observation, and not on experiment. Indeed, some 20 human trials using immunotherapy to test the autoimmunity paradigm since have proved unsuccessful [11], and none has translated into patient benefit. Interest in the relationship of insulin resistance to autoimmunity emerged only because of mounting concern that the original interpretation may not have been correct [12]. Autoimmunity is clearly present in T1D, but its primacy in the sequence of events is being questioned. Rather than the driver of beta cell loss, could autoimmunity be an immune response to islets which are stressed by the demands of insulin resistance?

Experimental Basis for Autoimmune Diabetes

The experimental data cited in support of the autoimmunity hypothesis for T1D is substantial, but drawn largely from prevention studies in animals [13]. Such trials are often successful, but animals are not human, and biomedical research is frequently confronted with hypotheses that work in animals, but not in man. In the case of T1D, the models are not just animals, but animals abnormal to the point where they fail to develop diabetes unless their environment is rigidly controlled. The models most used, the NOD mouse and Biobreeding rat, are inbred for immununogenetic anomalies that are essential to the model, but not part of the human disease. The models show that the immune system *can* destroy the beta cells of inbred rodents, but say little about the

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mechanisms responsible for T1D in outbred man. The ongoing TRIGR study using hydrolysed protein formula (Nutramigen) in human infants has an impressive pedigree, and will report in 2017, but care must be taken with confounders in its interpretation. Nutramigen, like breast-milk, may be associated with slower growth rates than cow's milk and breast-milk is associated with a lower incidence of T1D [14].

The Doctrine of Immunological Tolerance

Any suggestion that autoimmunity might be a response to beta cell stress, rather than its cause, must first confront one of the pillars of immunology – tolerance to self antigens. The issue was addressed by the author some 25 years ago [15], in the wake of Pierre Grabar's construal of the immune system's primordial role as the body's housekeeper, clearing up the detritus of apoptotic (and, where needed, necrotic) cell death [16]. Being shape-specific and clonal, the immune system was ideally adapted to expand and contract in response to specific housekeeping need. What to others before him had been a canon of absolute tolerance to self antigens, was to Grabar the absence of a technology sufficiently sensitive to detect a natural process of waste removal – until it was intense, when it was given the label 'autoimmunity' in order that it should comply with the tolerance paradigm [17]. Grabar's great contribution was to breach the doctrine of self-tolerance that had previously obliged autoimmunity to be a pathology. Autoimmunity is nevertheless inflammatory, and may be expected to further accelerate apoptotic death of the troubled beta cell [18].

Orphan Observations

'Orphan observations' are facts which don't fit, and which tend to be ignored as a result. Concerns over the duality of diabetes first emerged through epidemiology, though few noted their significance at the time. Yemenite immigrants to Israel in the 1950's suffered very little diabetes but, after 25 years in a land of plenty, experienced a 40-fold increase in its prevalence. Intriguingly, it wasn't just T2D – the proportion of insulin dependency among the new diabetics was similar to that among Israelis of European origin [19]. The observation is a classic orphan, but fundamentally important because it suggests a common driver for both major forms of diabetes. Again, it is seldom remarked upon, but clearly documented, that wherever in the world there has been a rise in T2D, there has been a corresponding increase in type 1 [20], and many studies report how the frequency of T1D among the relatives of those with type 2 is many times greater than that in the general population [21, 22]. Most recently, Hussen et al report how having a parent with any type of diabetes increases the risk of T1D in the child [23]. More fundamental still is the changing status of islet autoantibodies. Sero-positivity was always the exclusive

hallmark of T1D, but reports of isle-related autoantibodies in people T2D have posed serious taxonomic difficulty [24]. Finally, there is now evidence for insulin resistance, not just in those with type 1 disease, but in those at-risk as well [25–27]. When weighed together, orphan observations can shape a new paradigm, and the notion that T1D may be T2D accelerated into childhood by a reactive genotype is an example.

The Accelerator Hypothesis

Insulin resistance, largely (but not always) the result of excess weight gain, is generally believed to drive type 2 diabetes. The metabolic up-regulation of the islets, and the glucotoxicity and lipotoxicity that result from the metabolic disturbance associated with insulin resistance, are thought to stress the beta cell and hasten its apoptosis [28–30]. Excess weight gain is a feature of childhood over recent time, and it has been known for 40 years (though little mentioned) that children who develop T1D are on average heavier as toddlers than their peers who do not [31]. The observation resurfaced during the 1990's [32–34], and in 2001 the accelerator hypothesis formalised an alternative paradigm to autoimmunity – that *Type 1 and type 2 diabetes are the same disorder of insulin resistance, set against different genetic backgrounds* [35]. Beta cell stress, according to the hypothesis, provokes an immune response (autoimmunity) which is particularly intense in the small proportion of the population that carries reactive HLA genotypes, and a recent meta-analysis found in all the studies it reviewed that people with T1D showed greater weight gain during the first year of life compared with controls [36]. Crucially, if the immune reaction (the autoimmunity of T1D) is the response to beta cell stress, rather than the driver, it is arguably not the appropriate target for prevention. Evidence for the hypothesis has been set out in a number of reviews [37–42], and its early predictions have held firm in several reports worldwide [43–46], though not in all [47–49], and for diverse reasons [50–52]. The hypothesis anticipates that measures to reduce insulin demand will reduce the incidence of T1D but it does not dismiss autoimmunity. Rather, autoimmunity is regarded as a response to beta cell stress, not its cause, but inflammatory in its own right. The hypothesis is conceptually simple, but important if it resets the target for prevention of childhood diabetes from the immune system to insulin demand.

Tempo – the Central Concept Underlying the Accelerator Hypothesis

Diabetes is ultimately a disorder of beta cell loss [53], and the accelerator hypothesis is concerned with variation in the tempo of the loss. Beta cells are lost progressively over a lifetime [54], but the loss is of no consequence for most, given the substantial reserve [55]. However, if for whatever reason the loss is accelerated, it may become critical, and the age at presentation of diabetes will
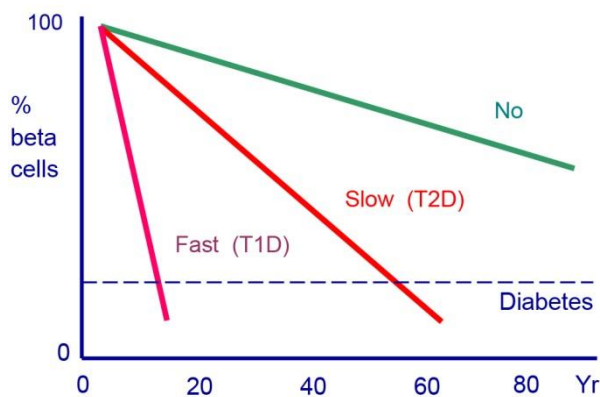
Fig. 1. The concept of tempo as it applies to diabetes. A single process advancing at different rates.

depend on the degree of acceleration (Figure 1). Rather than categorise diabetes into types 1 and 2 (or indeed 1½ [56], LADA [57], hybrid [58], or double diabetes [59]), the accelerator hypothesis sees a continuous spectrum – a single process of beta cell loss which progresses at different rates, from 'no' diabetes during the lifetime of most people, through 'slow' diabetes in adulthood to 'fast' diabetes in childhood. The probability of developing diabetes is defined by an infinitely variable interaction between level of demand and immune response. The variation in diabetes is one of tempo, not of type. Only tempo can explain how T2D, that a generation ago was confined to middle age and beyond, has now become the fasting growing chronic disorder of childhood and how T1D, for decades a disorder of adolescence, is now rising fastest in the under 5's [60].

Testing the Accelerator Hypothesis

No evidence is complete without a randomized controlled trial, and no hypothesis is complete without a mechanism. If the accelerator hypothesis is to progress beyond speculation, it will be necessary to demonstrate that beta loss is slowed (and the incidence of T1D reduced) by protecting the beta cell against stress, and that beta cell rest is indeed the mechanism that drives the immune response that we call autoimmunity. Glucose is the principal stressor of the beta cell, and metformin is a recognized hypoglycaemic agent that is safe in children.

The editor-in-chief of this journal was the first to test the ability of metformin to slow the progression of beta

cell loss in a pilot study of 21 children recently diagnosed with T1D [61]. There were 26 control children on insulin alone. Six of the metformin-treated group entered complete insulin remission for 12 months or more, and their C-peptide at the end of the study was significantly higher than that of the control group. It is not clear whether the metformin was simply re-sensitising the children to their own residual insulin, or preserving beta-cell function (the higher C-peptide might suggest true preservation), but the study provided impetus to the planning and ultimately funding by JDRF of the autoimmune diabetes Accelerator Prevention Trial (adAPT) currently recruiting in the UK. adAPT will expose children at high risk of T1D (double antibody positive) to metformin for five years in order to establish whether beta cell protection can reduce the incidence of diabetes. Mechanistic studies involving T cells (B. Roep, Leiden) will also seek to determine whether beta cell rest reduces immune reactivity to specific beta cell antigens.

adAPT (Eudract # 2015-000748-41) is currently seeking youngsters throughout Scotland and the North of England who are the siblings or offspring age 5-16y of people who developed T1D before the age of 25y. The 4-5% who are double antibody positive have a 40% chance of developing T1D over the course of the trial [62], and will be invited to join a three stage randomised controlled trial of metformin. Stage 1 (four months, Pilot study) will validate the protocol, and establish the numbers that may ultimately be needed to achieve a reliable result. Stage 2 (36 months, Proof of principle) will indicate whether the rate of beta cell loss is slower in the treated group. C-peptide levels measured during the course of a multi-point mixed meal tolerance test will provide the outcome measure, but a subgroup will also be invited to participate in 7-day studies of continuous glucose monitoring. Stage 3 of adAPT (60 months, T1D incidence) will compare the numbers who develop T1D in the active and placebo groups. adAPT will not report fully until 2022.

adAPT is testing a new paradigm in type 1 diabetes. Where the immune activity in T1D has been looked upon previously as an immune attack by a dysregulated immune system, adAPT views it as a normal, if intense, response to beta cell stress caused by metabolic overload in people carrying a particular immunogenotype. A successful outcome to the trial may lead towards a safe, cheap and universally available approach to the prevention of type 1 diabetes.

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