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EDITORIAL

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Spring harvest? Reflections on the rise of type 1 diabetes

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The rising tide

Childhood diabetes appears to have been a relatively rare disorder in Europe and North America in the first half of the 20th century, with incidence rates comparable to those seen in some Asian populations today. The incidence began to rise around the middle of the twentieth century, and an increase has been documented since then in many populations around the world [1]. For example, between 1989 and 1998, there was an overall year-on-year rise of 3.2% across Europe, equivalent to a doubling time of 25 years, and the most rapid relative increase was in children under the age of 5 years. Central and Eastern Europe, previously regions with a low incidence, now showed a rapid increase, suggesting a possible catch-up phenomenon [2]. A change of this magnitude in relatively stable populations cannot be explained by the increased transmission of diabetes susceptibility genes from one generation to the next, and strongly suggests some form of environmental influence.

A finger on the trigger

The intuitive inference is that children have recently become exposed to new environmental agents that are causing the condition to develop. This seems highly plausible, given the sweeping changes in lifestyle that have affected post-industrial civilisation, the association of type 1 diabetes with an affluent Western style of life, and the increase in prevalence observed in populations migrating from countries with a low incidence to countries with a higher incidence, for example, Asian immigrants to the UK [3]. Since type 1 diabetes is known to have a long prodrome, potential environmental triggers must be sought early in life, and the 'usual suspects' include prenatal or postnatal viral exposure, breast-feeding or other aspects of infant nutrition, and vaccination. The search for these initiating factors has largely directed epidemiological investigation to date, and has resulted in the first attempts at primary avoidance of the condition [4].

Attractive though the trigger factor concept might seem, there are powerful objections to it. Most reported associations with viral infection or early nutrition are relatively weak and have been poorly replicated. Interpretation is complicated by a host of potential confounders, and such associations, if confirmed, could at best account for a small proportion of new cases. New initiating factors would be expected to produce epidemics or other abrupt shifts in incidence, whereas the increase observed in many populations has been linear. This in itself makes a role for vaccination programmes unlikely, and is hard to reconcile with the major variations in breast-feeding and infant nutrition that have taken place over the past 50 years [1]. The proposal that enteroviruses such as coxsackie B4 cause type 1 diabetes faces the paradox that exposure to these viruses is declining in Western populations, and the hypothesis has therefore come to rest on the assumption that the *absence* of maternal antibodies or early exposure increases the diabetogenic potential of encounters with the virus later in life [5].

Given that candidate environmental influences remain elusive after more than 30 years of investigation, more complex interactions have been considered. An environmental influence might initiate a disease process, for example, or alter its rate of progression, or both. Multiple or repeated exposures might be necessary, and timing may also be crucial. Complex models such as these may rescue the concept of environmental trigger factors, but at the cost of diminishing utility, since the explanation easily becomes so elastic as to be incapable of disproof.

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Predisposition or cause?

The alternative possibility is that trigger factors have played little role in the increase in childhood type 1 diabetes. This does not exclude a role for the environment, however, since the same effect could be produced by the *loss* of environmental influences that were previously ubiquitous [6], or by other non-specific changes that promote expression of the disease. It is therefore interesting to note that investigators with an interest in type 1 diabetes have tended to look for specific causes, whereas those working with type 2 diabetes focus upon predisposition. The assumption in type 2 diabetes is that a spectrum of genetic susceptibility exists, which requires exposure to a 'diabetogenic' environment—for example, one that offers easy access to food with little requirement for physical exertion—before it can be fully expressed. In such an environment, the population as a whole gains weight, obesity spreads to the young, and type 2 diabetes develops earlier and earlier, to the point where it reaches the paediatric clinic. The rising incidence of childhood type 2 diabetes thus reflects the response of a genetically susceptible subset of the population to an environment that is no longer protective against the development of diabetes. Could a similar process—not necessarily driven by the same mechanisms—be responsible for the rise of type 1 diabetes? If so, we should expect to find evidence that the condition is presenting earlier in life, which would, in turn, imply the existence of a pool of individuals with more slowly progressive immune-mediated diabetes within the adult population. If these conditions are satisfied, we could then focus our attention on environmental influences that might promote progression of the underlying disease process and thus accelerate its clinical onset.

Environmental anticipation

The concept of accelerated onset was first proposed by Kurtz et al. in 1988 [7]. Previous analysis of three UK birth cohorts had shown an estimated prevalence at age 11 years of 0.1 per 1,000 for children born in 1946 as against 0.6 per 1,000 for children born in 1958 and 1.3 per 1,000 for children born in 1970. Kurtz went on to show that the prevalence at age 10 years in the 1970 cohort equalled that in the 1958 cohort at age 13 years and in the 1946 cohort at age 18 years. This suggested that the rising trend might be due to earlier disease onset, rather than to a change in lifetime risk of diabetes. Two subsequent studies have offered direct evidence of a left shift in the median age of onset of type 1 diabetes, such that the increase in children has been matched by a reduced incidence in young adults. A Belgian study of the incidence of type 1 diabetes presenting up to the age of 40 years found that the rising incidence in children over the period from 1989–2000 was balanced by a reduced incidence in the older age group such that that the overall incidence from 0–39 years was unchanged [8]. Equally, analysis of two Swedish registries of type 1 diabetes covering the 0–34 year age group showed a rising incidence of type 1 diabetes in children over the period from 1983 to 1998, but no overall increase for the age group as a whole; the median age at diagnosis fell by 2.5 years in males and 1.5 years in females [9]. Longer-term data from Norway show that diabetes was more common in the 15–29 year age group than in the 0–14 year age group in the 1930s; by the 1950s, the balance was roughly equal, and by the 1970s, diabetes was more common in children than in young adults [1]. There was, however, an overall increase in incidence in the 0–29 year age group over this much longer period of observation.

Genetic analysis is also consistent with the hypothesis of a left shift in the age of onset of type 1 diabetes. The distribution of HLA susceptibility haplotypes is inversely related to age at onset, and studies from Finland and the UK have shown that the relative frequency of high-risk HLA haplotypes in children with type 1 diabetes has diminished over the past 50 years [10, 11]. In Finland, the incidence of childhood diabetes increased 2.5-fold over the period from 1966 to 2000, and was associated with a reduction from 25.3 to 18.2% in the proportion of affected individuals carrying the highest risk genotype, together with an increase from 6.0 to 13.2% in those carrying protective genotypes [10]. A comparable increase in incidence has occurred in the UK, although less well-documented, and the proportion of children under 15 years carrying the HLA genotype *DR3-DQ2*/*DR4-DQ8* fell from 47% in 50-year survivors to 35% in recently diagnosed children, although there was no increase in those carrying protective genotypes [11]. In Finland, the proportion of affected children with the highest risk genotypes is small relative to that in countries with lower incidence rates, and suggests that the latter may be at an earlier stage of the same environmental process [12]. This implies that the influence of environmental change upon progression to diabetes within genetically susceptible subsets of the population can be tracked in space as well as over time. Taken together, these studies suggest that the proportion of affected children with high-risk HLA genotypes has fallen over the course of decades, matched by a compensatory increase in intermediate-risk haplotypes, while the proportion of children with low-risk haplotypes has either risen slightly [10] or remained unchanged [11]. This tells us that the increasing incidence of childhood type 1 diabetes has been largely confined to a genetic subset of the population, and is also consistent with the view that children at all levels of genetic risk are now getting the condition earlier.

The population reservoir

The concept of accelerated progression implies a population reservoir of individuals with a more slowly progressive form of the same disorder. Type 1 diabetes is commonly perceived as a disease of childhood, for reasons that are easy to understand: affected children have a distinctive phenotype, are highly visible within the health care system, and are readily available for study. Childhood diabetes is, nonetheless, only one end of a spectrum of

disease, the main problem being that the other end of the spectrum—immune-mediated diabetes in adult life—is so poorly defined [13]. Easiest to identify are those adults who present in much the same way as children, with ketoacidosis or an immediate requirement for insulin. Traditional criteria such as these suggest that 63% of individuals with type 1 diabetes will have presented by the age of 19 years [14], but broader criteria, correlating well with immunogenetic markers of type 1 diabetes, were used in a larger Danish study that found that 44% of all type 1 diabetes presented after the age of 30 years. The authors argued that differences in rates of childhood diabetes within Scandinavia could be explained by differences in the median age of onset rather than by differences in lifetime risk, and estimated the cumulative lifetime incidence of type 1 diabetes in Denmark to be around 1% [15]. This might even be an underestimate, given that 5–10% of those who present with clinical features of type 2 diabetes have islet autoantibodies and are therefore considered to have a form of autoimmune diabetes [13]. Immune-mediated diabetes is therefore relatively common in later life, which means that a small increase in the rate of progression from subclinical to clinical disease could produce a steady rise in the number of affected children.

Keeping it in the family

This being the case, and given the genetic background of the condition, we should expect to find slowly progressive immune-mediated diabetes in the parents and grandparents of children with type 1 diabetes. The parents of affected children are known to have an increased risk of 'classic' type 1 diabetes, but type 2 diabetes is also reportedly more common among these individuals. But is it really type 2 diabetes? Earlier studies classified diabetes according to the need for insulin treatment, but clinical analysis backed by antibody testing has revealed that the apparent excess of type 2 diabetes is due to an atypical (non-insulin requiring) immune-mediated form of diabetes [16]. Nor does the story end here, for one child in four with type 1 diabetes has a grandparent with overt diabetes [17]; immune-mediated diabetes is common in this generation, and preferential transmission of HLA haplotypes from the affected grandparent to the affected grandchild can be demonstrated. A *forme fruste* of classic type 1 diabetes is present in older relatives of affected children.

Footprints of disease

The available evidence supports the concept that more rapid disease progression, rather than more frequent disease initiation, is driving the rise of childhood type 1 diabetes. This hypothesis can be examined more directly. Type 1 diabetes is heralded by the appearance of islet autoantibodies, and rarely develops in their absence. If initiating factors determine the difference in diabetes incidence between one population and the next, the prevalence of islet autoantibodies in the background population should reflect this difference. Conversely, a lack of difference in antibody prevalence would favour differential rates of progression. Although a number of groups have examined autoantibody prevalence in healthy schoolchildren, comparative studies based in the same laboratory have been rare. One such study noted that schoolchildren from Lithuania and the UK had very similar levels of high-risk autoantibody combinations, despite a 2.5-fold difference in the incidence of childhood diabetes [18], which would support the progression hypothesis. Large, well-designed central laboratory analyses of autoantibody prevalence in children from countries with high and low incidence rates of childhood type 1 diabetes should allow the question of initiation versus progression to be resolved beyond dispute.

The rock and the tide

In summary, evidence that trigger factors have driven the rise of early-onset type 1 diabetes is lacking. In contrast, there is direct epidemiological evidence of earlier presentation, the proportion of children with intermediate-risk HLA haplotypes has increased, and immune-mediated diabetes, not necessarily requiring insulin therapy, is prevalent in older members of the general population and in the predecessors of affected children. These observations are consistent with the view that the major role of the environment is to modulate the rate at which the disease is expressed. It can be noted that this accords well with animal models such as the non-obese diabetic mouse, in which specific trigger factors have not been identified. It is also consistent with our experience of other common organ-specific immune-mediated disorders. In these, as with type 1 diabetes, immune markers of progression appear years or even decades before end-stage organ failure. Autoimmune thyroiditis, for example, may take longer than a lifetime to develop. Here also we tend to regard disease development as a matter of predisposition rather than specific cause, with the important exception of coeliac disease. This does indeed have an undoubted environmental trigger in the form of dietary gluten, but—given that children routinely encounter it in early life—a salient feature of the condition is that decades may pass before exposure to this well-recognised initiating factor gives rise to overt clinical symptoms. Disease progression thus remains the key determinant of the incidence of this disease.

The expression of type 1 diabetes within a population might be pictured as a rock projecting from the sea (Fig. 1), a rock that is progressively exposed as the tide recedes. First to be exposed are those with the highest level of genetic susceptibility, a proportion of whom will express the characteristic disease phenotype in early childhood. Increasing age represents the fall of the tide, which uncovers lower levels of genetic susceptibility. This can be seen in a diminishing contribution from high-risk HLA haplotypes in older patients, together with an increasing

prevalence of haplotypes that protect against early-onset diabetes. Further down the rock, we dimly perceive a mass of individuals who present in later life with clinical features that resemble (or are continuous with) type 2 diabetes. In a protective environment the water level starts high, which means that childhood-onset diabetes is restricted to those with the strongest genetic predisposition, and is correspondingly rare. In a less protective environment the water level is lower, a more diverse spectrum of people get the disease, and they get it younger.

This model implies a relatively large reservoir of susceptible individuals within the population. Their immune system has been alerted to islet antigens, yet refrains from attacking them: they exist in a state of 'armed neutrality'. In some, this persists longer than a lifetime, while in others the beta cell mass erodes to the point at which diabetes develops. A further inference is that immune-mediated diabetes need not be a 'new' disease. Historically, it may have resembled other autoimmune disorders, which typically present in middle or later life. This, incidentally, is a fair description of the current situation in Japan, where classic type 1 diabetes is rare in childhood (although increasing in the pubertal age group), but a slowly progressive form of immune-mediated diabetes is relatively common in adults [19]. It could explain why genes predisposing to early-onset diabetes—a lethal trait—have not been purged from the population by evolutionary selection.

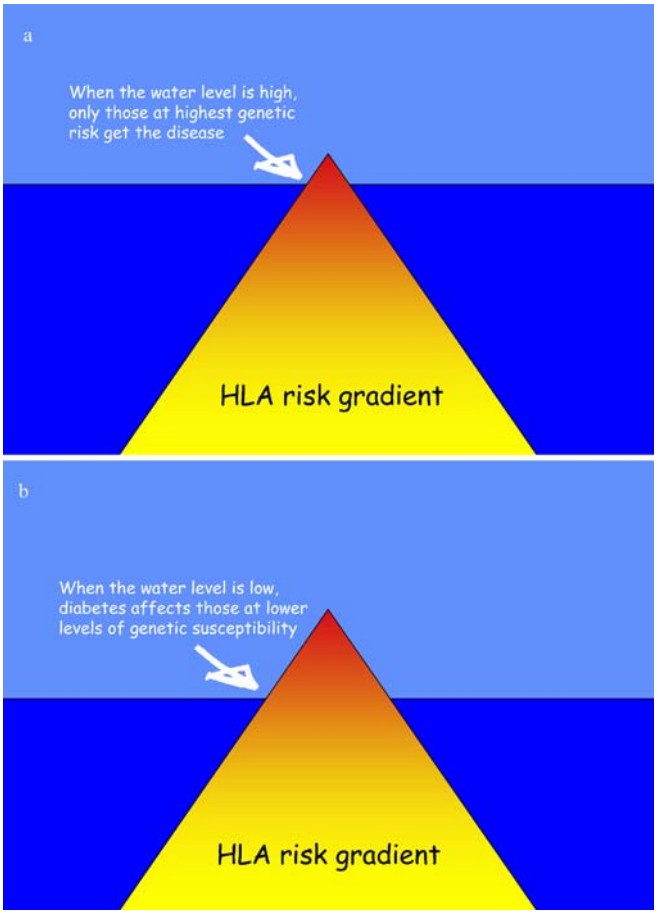

Fig. 1 The spectrum of genetic susceptibility to type 1 diabetes is depicted as a rock projecting from the sea. The water level represents the protective effect of the environment. When the water level is high, as in childhood, risk is largely confined to those at the highest levels of genetic susceptibility (**a**). With increasing age, environmental protection recedes, exposing those at lower levels of susceptibility (**b**). Evidence that the baseline 'water level' has fallen over the past 50 years is discussed in this article

According to this hypothesis, stochastic factors largely determine who develops potentially harmful immune responses and who does not [20]. Further progression is modulated by the environment, which influences both the early development and orientation of the immune system and the metabolic challenge faced by a diminishing beta cell mass. What might these environmental influences be?

Last tango in pancreas

Two well-recognised changes within our population have influenced the incidence of early-onset type 1 diabetes. Increasing maternal age at delivery increases the risk of diabetes in the offspring, and the trend for women to defer pregnancy can account for a small fraction of the observed increase, perhaps 10% over 30 years [21]. Another accelerator has been the decreasing age of puberty, with its associated endocrine and metabolic changes, which might explain why the peak age of onset of diabetes in girls has fallen by about 4 years in Norway since the 1930s [22]. Other potential influences could operate either by encouraging more rapid evolution of immune processes that threaten the beta cell, or by rendering the beta cell more vulnerable.

Environmental changes sufficiently sweeping as to influence the pathogenesis of type 1 diabetes might be expected to influence a range of disease processes, and it is therefore worth noting that other immune-mediated disorders of childhood, such as childhood asthma, have risen in parallel. Despite their opposing T helper cell orientation (Th1 for diabetes as against Th2 for atopic disorders), the rise of both types of disorder might represent a common failure in T cell regulation. We should keep an open mind as to the possibility that the loss of traditional 'educators' of our immune repertoire is responsible for the emergence of a number of immune-mediated disorders in the latter part of the 20th century, childhood type 1 diabetes among them [6].

Environmental change might also mean that the beta cell has become more exposed to attack. Wilkin drew attention to this view with his 'accelerator hypothesis' [23], which extends the proposal of earlier investigators that childhood type 1 diabetes is presenting earlier because of more rapid growth and increased obesity in childhood [24]. The paper by Knerr et al. in this issue of *Diabetologia* adds further support for this argument [25]. The consequence of more rapid growth is insulin resistance, increasing the load on residual beta cells, which respond by becoming more active, and in consequence offer more of a target to the immune system. The accelerator hypothesis further proposes that type 1 and type 2 diabetes represent a disease

continuum (albeit with different genetic determinants) rather than two distinct diseases, and that the rise of childhood obesity has driven the increase in both [23]. Children have indeed grown faster over the course of the past century, and final height has increased at a rate of around 1 cm per decade in some populations. In the 1920s, Elliott Joslin and Priscilla White found that children with diabetes were 3–4 cm taller than their peers, causing Joslin to remark that 'overheight was more frequent a precursor of diabetes in children than was overweight in adults' [26]. In the 1950s, investigators considered that this effect on height might be due to overproduction of growth hormone, which would thus promote both increased stature and diabetes. Modern variants of this notion reverse the argument by proposing that increased linear growth, nutritionally driven, promotes the onset of diabetes by (among other things) enhancing the production of growth hormone. Linear growth apart, increasing adiposity—especially when centrally distributed—will increase the burden upon the beta cell, and hyperglycaemia will present earlier (i.e. in the presence of a larger beta cell mass) than in a lean individual. Not surprisingly, measures of insulin sensitivity enhance prediction of diabetes onset when added to measures of insulin secretion alone [27].

Growth is complicated, representing as it does the net outcome of a range of biological and environmental influences, and apparently simple observations can give rise to a baffling array of secondary questions. High birthweight increases the risk of diabetes, for example, but it would be premature to assume that this is due to maternal nutrition, since HLA haplotypes predisposing to type 1 diabetes are also associated with increased birthweight [28]. Rapid early growth is a further risk factor, but possible genetic influences upon this may also need to be considered. Other important questions remain unanswered. Breast-fed babies grow less rapidly, but is this why they are slightly less likely to develop diabetes? Why should social class have influenced linear growth more strongly than it appears to have influenced risk of diabetes? And how do we disentangle linear growth from adiposity—itself inversely related to social class? These are important questions to examine further, but there is at present a big logical leap between the observation that children with diabetes grow more rapidly in the years preceding diagnosis and the argument that the rise of childhood type 1 diabetes is driven entirely by increased growth and adiposity. Equally, there are good general grounds for interventions designed to reduce childhood adiposity, but it is premature to conclude that these will have a major influence upon the development of type 1 diabetes. The useful concept of acceleration should therefore not be restricted to what may prove to be one contributory factor among many.

Paradigm lost?

In conclusion, it has in the past been assumed, implicitly rather than explicitly, that type 1 diabetes is a rare hit-or-miss disease of childhood. Investigations based around this assumption will be directed towards a 'cause'. The focus has been on critical events in early life, particularly new environmental exposures such as mutated viruses, vaccinations or novel dietary constituents. Primary intervention to protect against such environmental trigger factors might appear to offer the possibility of permanent freedom from disease. The view outlined here, which draws upon the ideas and observations of many investigators—although not necessarily in ways with which they would agree—shifts the emphasis from disease initiation to disease progression [7, 20, 23, 24, 29, 30]. It assumes that we all start life with the potential to mount an immune attack on our islets, a potential that is routinely suppressed by our immune systems. This balance can however be disturbed at an early stage of development, allowing potentially dangerous patterns of immune recognition to become established. The process is largely stochastic, but is modulated by genetic susceptibility. The analogy might be with a lottery in which each child holds at least one ticket conferring a chance of diabetes, but high-risk children have hundreds of tickets. If this assumption is correct, the long-standing emphasis on disease initiation is misplaced, and we should focus instead upon the issue of disease progression. This interpretation does not exclude a role for factors such as viruses or diet in disease initiation, but no longer requires them to explain the rise in incidence. The emphasis on disease progression, potentially modulated by both immunological and metabolic factors, holds out the hope of effective intervention: for environmentally mediated historical changes within our population could potentially be reversed. Before this can happen, we need to understand why our grandparents were so unlikely to get diabetes in childhood.

'In a world where underlying assumptions are all agreed upon, they may well remain unconscious or unspoken: a single all-encompassing paradigm is likely to be invisible from within, and undetectable from outside' [31]. Despite the explosion of new information, concepts central to our thinking about type 1 diabetes have changed relatively little over the past 30 years [32]. Is this because these constitute an assemblage of shared assumptions rather than a set of testable hypotheses? A small shift in perspective, as suggested here, changes the landscape in interesting ways. Evidence in favour of a 'spring harvest' hypothesis has accumulated, and could form the basis of renewed debate about the nature of the disease itself.

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