

# Type 1 diabetes

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Over the past decade, knowledge of the pathogenesis and natural history of type 1 diabetes has grown substantially, particularly with regard to disease prediction and heterogeneity, pancreatic pathology, and epidemiology. Technological improvements in insulin pumps and continuous glucose monitors help patients with type 1 diabetes manage the challenge of lifelong insulin administration. Agents that show promise for averting debilitating disease-associated complications have also been identified. However, despite broad organisational, intellectual, and fiscal investments, no means for preventing or curing type 1 diabetes exists, and, globally, the quality of diabetes management remains uneven. This Seminar discusses current progress in epidemiology, pathology, diagnosis, and treatment of type 1 diabetes, and prospects for an improved future for individuals with this disease.

## Introduction

Type 1 diabetes is generally thought to be precipitated by an immune-associated, if not directly immune-mediated, destruction of insulin-producing pancreatic  $\beta$  cells.<sup>1,2</sup> Historically, type 1 diabetes was largely considered a disorder in children and adolescents, but this opinion has changed over the past decade, so that age at symptomatic onset is no longer a restricting factor.<sup>3</sup> Polydipsia, polyphagia, and polyuria (the classic trio of symptoms associated with disease onset) along with overt hyperglycaemia remain diagnostic hallmarks in children and adolescents, and to a lesser extent in adults. An immediate need for exogenous insulin replacement is also a hallmark of type 1 diabetes, for which lifetime treatment is needed. Key questions remain regarding the epidemiology of type 1 diabetes, effectiveness of current therapies, understanding how the disorder develops, and preventing or curing the disease.

## Epidemiology

Although type 1 diabetes can be diagnosed at any age, it is one of the most common chronic diseases of childhood.<sup>4</sup> Peaks in presentation occur between 5–7 years of age and at or near puberty.<sup>5</sup> Whereas most autoimmune disorders disproportionately affect women, type 1 diabetes is slightly more common in boys and men.<sup>6</sup> The incidence of type 1 diabetes varies with seasonal changes and birth month. More cases are diagnosed in autumn and winter,<sup>7</sup> and being born in the spring is associated with a higher chance of having type 1 diabetes.<sup>8</sup> Development of type 1 diabetes-associated autoimmunity (ie, formation of islet autoantibodies) in the months or years before onset of symptomatic type 1 diabetes also shows some seasonal synchronisation.<sup>9</sup> These concepts support a theoretical role for an environmental agent initiating or driving the pathogenic processes in type 1 diabetes.

Globally, the incidence and prevalence of type 1 diabetes vary substantially (figure 1).<sup>10</sup> Type 1 diabetes is most common in Finland (>60 cases per 100 000 people each year) and Sardinia (around 40 cases per 100 000 people each year).<sup>16</sup> By contrast, the disorder is uncommon in China, India, and Venezuela (around 0.1 cases per 100 000 people each year). The global incidence of type 1

diabetes represents an epidemiological conundrum; wide variations in disease incidence are noted between neighbouring areas in Europe and in North America. For example, incidence in Estonia is less than one-third of the incidence in Finland, although the two countries are separated by less than 120 km.<sup>17</sup> The incidence of type 1 diabetes has been increasing worldwide for several decades.<sup>18</sup> In Finland, Germany, and Norway, annual increases in incidence of 2.4%, 2.6%, and 3.3%, respectively, have been reported.<sup>16,19,20</sup> In many countries, the rise in incidence of type 1 diabetes has fluctuated, although Sweden has recently seen incidence rates plateau.<sup>12</sup> If incidence rates continue to increase on their existing path, global incidence could double over the next decade.<sup>16</sup> Increases in incidence have not occurred equally across all age groups; in Europe, the most substantial increases have been noted in children younger than 5 years of age.<sup>5,21</sup> The mechanisms underlying these enigmas in geographical incidence and increased incidence rates of type 1 diabetes are unknown, but have largely been attributed to environmental influences. Genetic changes or more children being born from mothers with type 1 diabetes cannot solely explain such rapid rates of increased incidence.<sup>22</sup> Finally, genetic predisposition seems to be less of a factor now than it was in the past as a prerequisite for developing type 1 diabetes.<sup>23,24</sup>

A plethora of environmental influences have been purported to affect the epidemiology of type 1 diabetes,<sup>25</sup> with infant and adolescent diets,<sup>26</sup> vitamin D and vitamin D pathway constituents,<sup>27–29</sup> and viruses receiving the most focus.<sup>30,31</sup> Interest is growing in models to describe the influence of environment on type 1 diabetes, including the hygiene hypothesis<sup>32</sup> and gut microbiome,<sup>33</sup> however, no specific agents with an unequivocal influence on pathogenesis have been identified.

## Diagnosis

Diagnosis of diabetes has historically included fasting blood glucose higher than 7 mmol/L (126 mg/dL), any blood glucose of 11.1 mmol/L (200 mg/dL) or higher with symptoms of hyperglycaemia, or an abnormal 2 h oral glucose-tolerance test.<sup>34</sup> In 2009, the American Diabetes Association modified their guidelines for diabetes diagnosis to include glycated haemoglobin (HbA<sub>1c</sub>); a test

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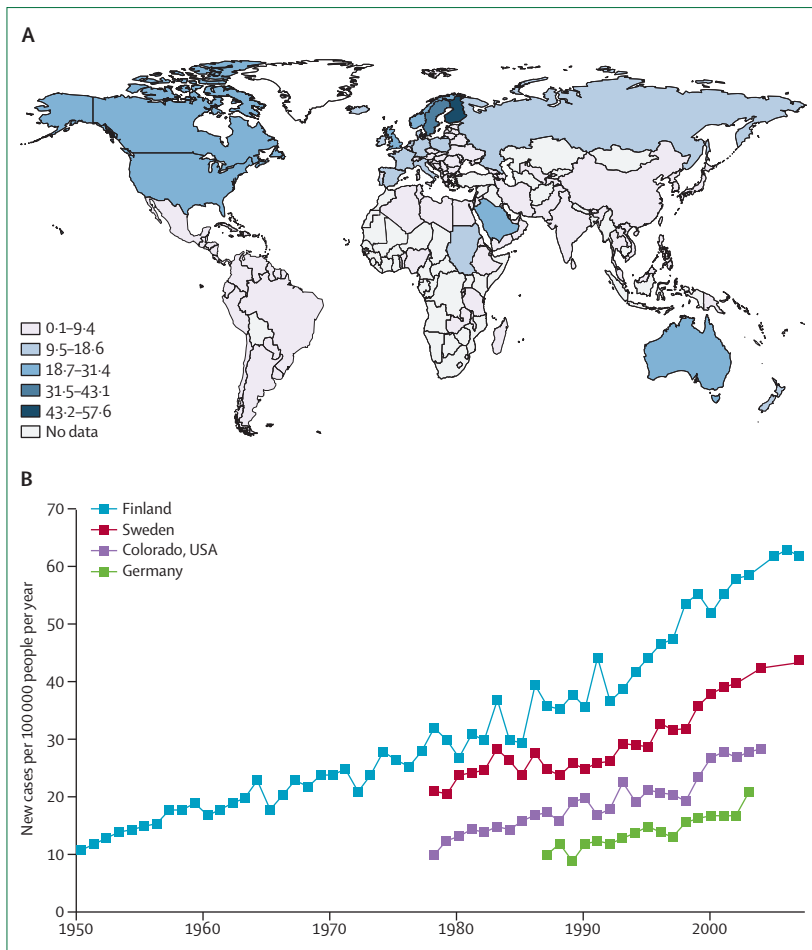
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**Figure 1:** Incidence of type 1 diabetes in children aged 0–14 years, by geographical region and over time (A) Estimated global incidence of type 1 diabetes, by region, in 2011.<sup>11</sup> (B) Time-based trends for the incidence of type 1 diabetes in children ages 0–14 years in areas with high or high-intermediate rates of disease.<sup>12–15</sup>

that averages blood glucose concentrations over 3 months) of 6.5% or higher.<sup>35</sup> Despite efforts to standardise diagnosis of type 1 diabetes, the causes and typology remain unclear. Particularly among adults, diagnosis of type 1 versus type 2 diabetes can be challenging. Around 5–15% of adults diagnosed with type 2 diabetes might actually have type 1 disease with islet autoantibodies present;<sup>36</sup> if this is the case, perhaps as many as 50% of actual type 1 diabetes cases are misdiagnosed as type 2, meaning that the number of cases of type 1 disease is vastly underestimated. Accurate diagnosis of this disorder is crucial for optimum care and avoiding complications, and correctly noting diabetic ketoacidosis at diagnosis of type 1 disease represents a key window for survival.<sup>37</sup>

Attempts to distinguish adult cases of type 1 diabetes from those with type 2 disease have resulted in the proposal of new disease classifications, including latent autoimmune disease of adults (LADA) and ketosis-prone diabetes.<sup>38,39</sup> The lack of firm diagnostic criteria for LADA,

including retrospective criteria and similarities between patients with type 1 diabetes and LADA, have stunted enthusiasm for adopting it as a novel category for diabetes.<sup>40</sup>

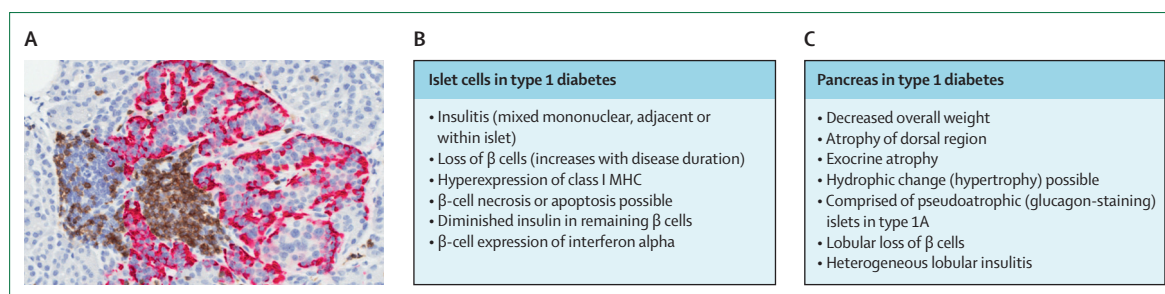
### Disease heterogeneity

Most cases of type 1 diabetes represent an immune, if not autoimmune-mediated disorder, meaning patients often show features of an immunological contribution to disease pathogenesis (eg, autoantibodies or genetic associations with genes controlling immune responses). However, not all patients with type 1 diabetes have these characteristics, leading to proposed classifications of type 1A (autoimmune) diabetes,<sup>41</sup> for the 70–90% of patients with type 1 disease that have immunological, self-reactive autoantibodies, and type 1B (idiopathic) diabetes, representing the remainder whose specific pathogenesis remains unclear.<sup>42</sup> A subset of individuals within this latter group have monogenic forms of diabetes, such as maturity onset diabetes of the young (MODY).<sup>43</sup> Despite knowledge gains that could allow for adopting this new set of terminologies for subgrouping cases of type 1 diabetes, the terms type 1A and type 1B diabetes are not commonly used; similarly, subtypes of type 2 diabetes in children are poorly characterised, particularly in minority populations in the USA.<sup>44</sup>

Other factors that complicate diagnosis of type 1 diabetes include the growing problem of obesity (both childhood and adult), difficulties in health-care provider recognition of disease, and increasingly diverse genetic admixtures due to migration and social changes.<sup>45–47</sup> For example, a third to half of Hispanic and African American children seem to have a form of type 1 diabetes without islet autoantibodies, and with pancreatic histology showing a lack of islets and complete loss of  $\beta$  cells—ie, pseudoatrophic islets.<sup>42</sup> A 2011 study of adult-onset type 1 diabetes suggested that autoimmune type 1 diabetes in children and adults differs by just a few age-dependent genetic effects;<sup>48</sup> however, overall, type 1 diabetes seems to represent a heterogeneous disease whose pathogenic processes, genetics, and phenotypic characteristics show marked variation.

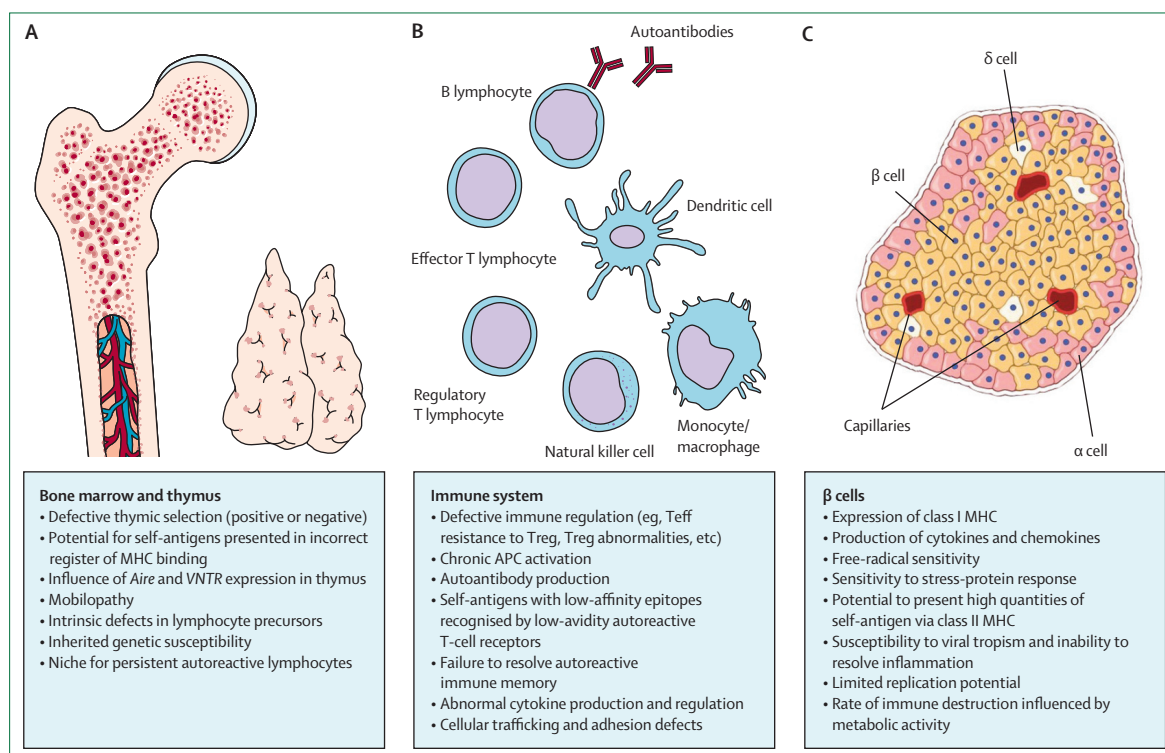
### Pathophysiology

Most research articles on the pathogenesis of type 1 diabetes begin by noting that the disorder results from an autoimmune destruction of insulin-secreting pancreatic  $\beta$  cells. The presence of a chronic inflammatory infiltrate that affects pancreatic islets at symptomatic onset of type 1 diabetes is the basis of this observation (figure 2).<sup>49</sup> Another dogma is that in patients with longstanding disease, the pancreas is devoid of insulin-producing cells and the remaining  $\beta$  cells are incapable of regeneration. Both of these concepts of pathogenesis of type 1 diabetes have been debated.<sup>50,51</sup> Recent data suggest that although most patients with longstanding type 1 diabetes have few  $\beta$  cells, if any, there is evidence for  $\beta$ -cell regeneration in infants and very young children (but not in adolescents or



**Figure 2: Pathological characteristics of the pancreas in type 1 diabetes**

(A) Islet infiltrate (ie, insulinitis) seen in a patient with recent-onset type 1 diabetes. Immunohistochemistry shows the intra-islet presence of CD3-positive cells (brown) and glucagon-producing alpha cells (pink). Image courtesy of M Campbell Thompson, University of Florida, Gainesville, FL, USA. (B) Histological features of islets and (C) gross pathological characteristics of the pancreas associated with the natural history of type 1 diabetes (ie, preonset, onset, postonset).



**Figure 3: Physiological contributions to the pathogenic processes that underlie type 1 diabetes**

A series of defects emanating from (A) the bone marrow and thymus, (B) immune system, and (C)  $\beta$  cells collectively lead to loss of insulin production by autoimmune mechanisms. These actions are continuous throughout the natural history of type 1 diabetes.<sup>54-56</sup> Teff=effector T cell. Treg=regulatory T cell. APC=anaphase-promoting complex.

adults).<sup>51,52</sup> Much of what we understand about the pathogenesis of type 1 diabetes derives from analysis of pancreatic specimens, serum, and peripheral-blood lymphocytes obtained from patients with the disorder.<sup>53,54</sup> Studies of these constituents suggest that a series of functional defects in the bone marrow and thymus, immune system, and  $\beta$  cells collectively contribute to the pathophysiology of type 1 diabetes (figure 3).

### Pancreatic pathology

Most studies of pancreatic pathology of type 1 diabetes involve retrospective, sample-based analysis of

pancreata obtained at autopsy from individuals who died at or near the time of diagnosis, revealing a range of islet cell and whole organ features (figure 2). To overcome limitations with investigations of autopsy tissue, and to extend studies of pancreatic pathology throughout the natural history of type 1 diabetes, efforts are being made in Belgium, Finland, and the USA (Network for Pancreatic Organ Donors with Diabetes [nPOD]<sup>57</sup>) to collect tissues from cadaveric donors with serological evidence of anti-islet autoimmunity (ie, type 1 diabetes-associated autoantibodies)—a subset of whom would presumably have developed type 1 diabetes

if they had survived. Additionally, the nPOD effort attempts to extend investigations to the entire pancreas, rather than be limited by use of a biopsy sample. Through these and other studies, analyses of pancreata from individuals with recent-onset type 1 diabetes suggest that around 70% of islets display complete insulin absence;<sup>51,52</sup> nearly 20% of insulin-containing islets, as opposed to only 1% of insulin-deficient islets, are inflamed (ie, insulinitis), and many pancreata have non-inflamed insulin-containing islets that seem to be normal.<sup>58,59</sup> In patients with type 1 diabetes with surviving  $\beta$  cells, insulinitic lesions are usually lobular, analogous to the lobular loss of melanocytes in vitiligo.<sup>60</sup> Although it is often stated that symptoms occur when 90–95% of  $\beta$  cells are lost, diagnosis of type 1 diabetes can occur when roughly two-thirds of the islets are devoid of insulin-producing cells.<sup>61,62</sup> Among individuals who have had type 1 diabetes for more than 5 years, most of the remaining islets are insulin deficient, containing a normal complement of other hormone-secreting cells (ie,  $\alpha$  cells that secrete glucagon,  $\delta$  cells that secrete somatostatin, and PP cells that secrete pancreatic polypeptide).<sup>62</sup> Thus, type 1 diabetes involves a selective loss of  $\beta$  cells. In terms of potential pathogenic mechanisms, CD8+ T cells are the most predominant population within the insulinitis lesion, followed by (in declining order) macrophages (CD68+), CD4+ T cells, B lymphocytes (CD20+), and plasma cells (CD138+).<sup>62</sup> Surprisingly, FOXP3+ cells (ie, regulatory T cells; a population of intense research interest<sup>2</sup>) and natural killer cells are rare in this lesion. Although much focus has been directed at inflammatory-cell composition, other pancreatic features in type 1 diabetes could have pathogenic significance (figure 3). One of the most underappreciated aspects of disease might be pancreatic size. Recent efforts suggest that at the time of diagnosis of type 1 diabetes, and in the period before disease onset (ie, autoantibodies are present), affected individuals have a smaller pancreas compared with age-matched, BMI-matched, and age-plus-BMI-matched individuals.<sup>63,64</sup> This feature, combined with the absence of insulinitis, suggests that multiple mechanisms lead to the loss of  $\beta$  cells in the pathogenesis of type 1 diabetes.

### Serological

A key distinguishing feature between type 1 and type 2 diabetes is the presence of autoantibodies against  $\beta$ -cell autoantigens. More than 90% of individuals with newly diagnosed type 1 diabetes have one or more of the following autoantibodies at disease onset:<sup>53</sup> those reactive to insulin (IAA), glutamic acid decarboxylase (GADA), insulinoma-associated autoantigen 2 (IA2A), and zinc transporter 8 (ZnT8A).<sup>65</sup> These autoantibodies can appear as early as 6 months of age, with a peak incidence before 2 years of age in genetically susceptible individuals;<sup>66</sup> thus, they are present months to years before symptomatic onset. In addition to having diagnostic value in

type 1 diabetes, autoantibodies can help identify people with an increased risk for developing the disease, through detection in first-degree relatives or in the general population. IAA concentration correlates with the rate of progression to overt type 1 diabetes in children followed from birth.<sup>67,68</sup> This finding, combined with an extensive series of independent investigations in humans and in rodent models of type 1 diabetes, support the growing notion that proinsulin is a key autoantigen in the disease;<sup>69</sup> a concept that might partly explain the selective  $\beta$ -cell loss in type 1 diabetes.

Lipid and metabolite profiles can also serve as markers for impending type 1 diabetes; these markers include decreased phosphatidylcholine at birth, and reduced triglycerides and antioxidant ether phospholipids followed by increased proinflammatory lysophosphatidylcholine several months before seroconversion to autoantibody positivity.<sup>70</sup> Another study found higher concentrations of odd-chain triglycerides and polyunsaturated fatty acid-containing phospholipids, and lower concentrations of methionine, in those who developed type 1 diabetes-associated autoantibodies.<sup>71</sup>

### Genetics

Type 1 diabetes is clearly a polygenic disorder, with nearly 40 loci (so far) known to affect disease susceptibility.<sup>72</sup> The HLA region on chromosome 6 (ie, the *IDDM1* locus) provides perhaps one-half of the genetic susceptibility that leads to risk of type 1 diabetes.<sup>73</sup> Of the many HLA types, HLA class II show the strongest association with type 1 diabetes, where haplotypes *DRB1\*0401-DQB1\*0302* and *DRB1\*0301-DQB1\*0201* confer the greatest susceptibility, and *DRB1\*1501* and *DQA1\*0102-DQB1\*0602* provide disease resistance.<sup>74</sup> Class I MHCs also seem to influence risk for type 1 diabetes, independent of class II molecules.<sup>73</sup> Of the remaining loci, only those for the insulin VNTR, *PTPN22*, *CTLA4*, and *IL2RA* are associated with odds ratios greater than 1.1.<sup>75</sup> Most of the loci associated with risk of type 1 diabetes are thought to involve immune responses,<sup>72</sup> supporting the notion that the genetic influences involve mechanisms that collectively contribute to aberrant immune responsiveness, including the development and maintenance of tolerance. This mechanism might help explain the differing rates of progression to type 1 diabetes in adults versus children, where only minor variations in genetic susceptibility have been noted.<sup>48</sup> Genetic susceptibility might also influence responses to environmental stimuli or physiological pathways (eg, vitamin D and interferon-induced helicase).<sup>29,76</sup>

### Natural history

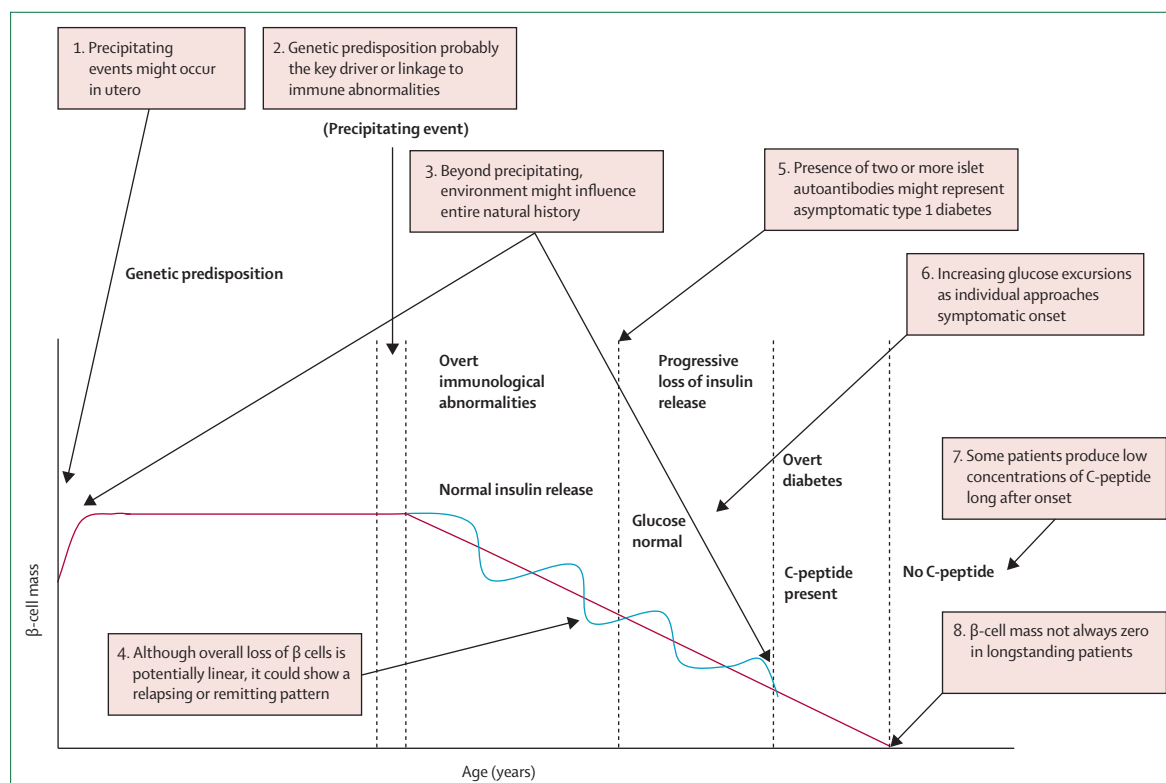
A model originally posed in 1986,<sup>77</sup> updated in our 2001 article,<sup>78</sup> and modified subsequently, poses that individuals are born with various degrees of genetic susceptibility for type 1 diabetes. Although this model has stood the test of time, some modifications should be

considered due to knowledge gains (figure 4). For example, environmental influences might occur as early as in utero and probably continue during the first months to years of life, thereby affecting the onset and continuance of  $\beta$ -cell autoimmunity. Physiological events, including immune-system development and normal turnover of  $\beta$  cells, might also contribute to these pathogenic processes.<sup>55</sup> Inherent immune dysregulation, probably facilitated by genetic susceptibility, results in early serological evidence of  $\beta$ -cell destruction—ie, altered aminoacids and autoantibodies associated with type 1 diabetes. In most individuals, changes in insulin secretion and glucose tolerance occur months to decades after multiple islet autoantibodies are detected.<sup>79</sup> Not all individuals with anti- $\beta$ -cell autoimmunity progress to overt disease (less than 5% who express a single type 1 diabetes-associated autoantibody progress<sup>41</sup>), for reasons unknown. Metabolic changes in the natural history of type 1 diabetes are marked by decreased early C-peptide response at least 2 years before onset,<sup>80</sup> increased glucose fluctuations as an individual approaches onset,<sup>81</sup> and an overall linear rise, with a last-minute surge, in plasma glucose in the months before onset.<sup>82</sup> Once a critical mass (not well defined) of  $\beta$  cells is destroyed, symptomatic onset occurs, and the need for exogenous insulin replacement begins. This symptomatic onset

happens after a silent phase that lasts for months to many years, that could, in genetically susceptible individuals with multiple autoantibodies, be considered asymptomatic type 1 diabetes. This classification seems appropriate in view of the ongoing disease processes and the near certainty that such individuals will eventually become symptomatic (insulin dependent). The loss of  $\beta$ -cell mass probably affects the performance of remaining  $\beta$  cells and other islet cell types, as shown by functional (and structural) studies. This disease feature will probably have implications for detecting and defining the stage of decline and the effect of therapeutic interventions.<sup>83</sup> After diagnosis, the ability to retain residual  $\beta$ -cell function (assessed by production of C-peptide) is heterogeneous, in terms of the time it takes to reach an undetectable stage and the number of patients who, despite decades with type 1 diabetes, retain the ability to produce C-peptide.<sup>84</sup> Thus, disease heterogeneity is an important aspect of type 1 diabetes, and suggests a role for genetics, age at disease onset, and intensity of disease management on the ability to retain  $\beta$ -cell function.

### Management of type 1 diabetes

The discovery of insulin in 1921–22 was clearly the most significant therapeutic event in the history of type 1 diabetes; however, exogenous insulin replacement



**Figure 4:** The natural history of type 1 diabetes—a 25-year-old concept revisited

A re-creation of the model of type 1 diabetes, originally proposed in 1986, is shown in black.<sup>77</sup> Additions and conjectures based on recent knowledge gains are shown in purple.



does not always provide the metabolic regulation necessary to avoid one or more disease associated-complications (eg, retinopathy, neuropathy, cardiovascular disease, and hypoglycaemia). As a result, diabetes management in modern countries often includes use of insulin analogues and mechanical technologies (eg, insulin pumps and continuous glucose monitors) for improved treatment of type 1 disease.<sup>85</sup> In the future, therapies that closer emulate the physiological role of the endocrine pancreas will, hopefully, improve lifestyles in addition to preventing complications. As a first step, global disparities in insulin access and diabetes management must be addressed.

#### Present care

After initial diagnosis and metabolic stabilisation, some patients with type 1 diabetes retain the ability to produce endogenous insulin. Although this endogenous secretion is typically low, maintenance is important since it is associated with less retinopathy and less-severe hypoglycaemia at later stages of the disease.<sup>86</sup> Therefore, preserving insulin secretion after disease onset is increasingly a therapeutic goal, and can involve intensive insulin therapy, mechanical technologies, or, as in several trials, immune intervention to disrupt  $\beta$ -cell destruction. C-peptide is secreted from  $\beta$  cells at a one-to-one ratio with insulin, and analysis of C-peptide concentration after disease onset shows that loss is more rapid in the first year after diagnosis than in the second year.<sup>83</sup> Furthermore, children and adolescents lose endogenous insulin production at a greater rate than do adults with type 1 diabetes.

Several methods exist for metabolic optimisation via insulin therapy. With multiple daily injections, a long-acting insulin analogue provides basal insulin and a rapid-acting insulin is administered before meals, based on grams of carbohydrate consumed (ie, basal-bolus therapy). Over the past decade, use of continuous subcutaneous insulin infusions (CSII; insulin pumps) has increased substantially.<sup>87</sup> A randomised controlled trial in adults with type 1 diabetes reported lower HbA<sub>1c</sub> concentrations with sensor-augmented pump therapy than with injection therapy, and a greater proportion of patients reaching the targeted levels of HbA<sub>1c</sub>.<sup>88</sup> A meta-analysis has also shown that insulin pumps lower HbA<sub>1c</sub> concentrations more than multiple daily injections in adults with type 1 diabetes, with similar rates of hypoglycaemia.<sup>89</sup> However, whether CSII is better, overall, than multiple daily injections for management of type 1 diabetes is debated, since outcomes reported in studies have varied substantially.<sup>90</sup>

In addition to improved insulin preparations and delivery systems, advancements to enhance glycaemic control and lessened hypoglycaemia include point-of-care HbA<sub>1c</sub> measurements, self-monitoring blood-glucose reports, and real-time continuous glucose monitors. Tamborlane and colleagues<sup>91</sup> reported that a

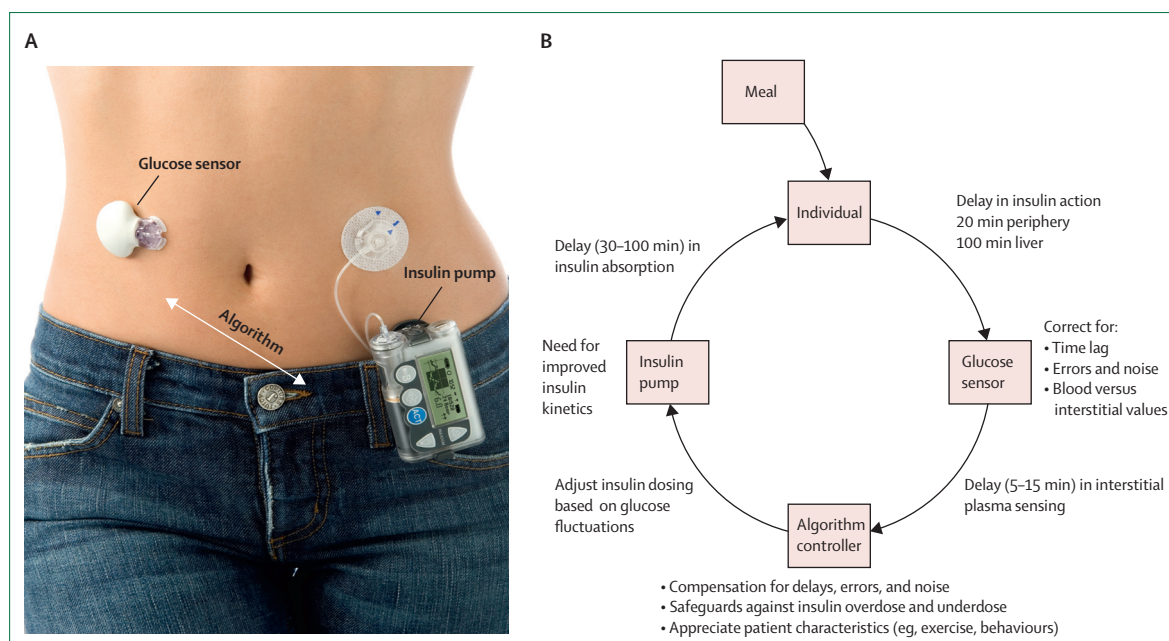
real-time continuous glucose monitoring system decreased the amount of time spent in hypoglycaemia (<4 mmol/L [70 mg/dL]) and lowered HbA<sub>1c</sub> when used by patients an average of 6 days a week. In this study, the degree of HbA<sub>1c</sub> reduction directly correlated with higher HbA<sub>1c</sub> concentrations before beginning continuous glucose monitoring. In a second study, continuous glucose monitoring lowered nocturnal hypoglycaemia in children (<18 years) with type 1 diabetes, compared with self-monitored blood glucose.<sup>92</sup> Therefore, continuous glucose monitoring is most appropriate for highly motivated patients with type 1 diabetes who are willing to wear the monitoring device, and those with continuous poor control during intensive insulin therapy.<sup>93</sup>

With insulin pumps and continuous glucose monitoring improving diabetes care, these two technologies are now being used together as sensor-augmented pump therapy. A trial comparing a sensor-augmented pump with multiple daily injection therapy showed significant improvement in HbA<sub>1c</sub> reduction with less hypoglycaemia in the sensor-augmented pump cohort.<sup>88,94</sup> Although current sensor-augmented pump therapy uses each device independently, integration of both systems is being investigated. A key element for such efforts involves low-glucose suspend systems that monitor blood glucose with a continuous glucose monitor and suspend insulin delivery when glucose falls below a preset threshold for up to 2 h, to prevent hypoglycaemic episodes.<sup>95</sup> Low-glucose suspend systems are currently available for clinical use in Europe, but remain in clinic trial testing in the USA.

#### Future care

Insulin pumps and continuous glucose monitors are making substantial progress in diabetes care, with additional improvements on the horizon. Efforts are underway to combine insulin pumps and continuous glucose monitors with a computer algorithm—ie, an integrated closed-loop system, or artificial pancreas (figure 5). The integrated closed-loop systems tested so far have reported favourable results,<sup>97</sup> when comparing the safety and efficacy of overnight closed-loop delivery of insulin with conventional insulin-pump therapy in adults with type 1 diabetes, closed-loop delivery improved overnight control of glycaemia and reduced the risk of nocturnal hypoglycaemia.<sup>98,99</sup> It is hoped that newer generations of continuous glucose monitors will have improved signal transmission and accuracy, and avoid the need for finger-stick glucose calibration.

New insulin analogues, incretins, and other hormones are being investigated for their ability to improve management of type 1 diabetes. Examples include insulin degludec (recently approved for use in the EU, although approval declined by the US Food and Drug Administration), an analogue that might improve basal insulin administration in patients with type 1 diabetes, since it provides effective glycaemic control and reduces



**Figure 5: Closed-loop system for type 1 diabetes therapy (artificial pancreas)**

(A) Prototype of a closed-loop system.<sup>96</sup> (B) Components of a closed-loop system. Three potential delays in the system include glucose sensing in interstitial fluid, insulin absorption (depends on use of rapid vs regular insulin), and insulin action in peripheral tissues and liver.

the risk of nocturnal hypoglycaemia.<sup>100</sup> GLP-1 might also prove beneficial, with studies noting that this incretin decreased peak postprandial glucose by 45% regardless of residual  $\beta$ -cell function.<sup>101</sup> The hormone pramlintide has been shown to reduce postprandial hyperglycaemia, bodyweight, insulin dosage, and HbA<sub>1c</sub> concentrations, and to reduce postprandial glucagon and glucose excursions and slow gastric emptying.<sup>102</sup> Leptin, the adipocyte hormone, might also benefit type 1 diabetes therapy via its ability to reverse a catabolic state through suppression of hyperglucagonaemia.<sup>103</sup> Amidst the optimism surrounding potential benefits with these new therapies, the need for long-term studies validating their safety in large populations remains.

### Burden of type 1 diabetes: complications, excess mortality, and insulin access

The physical, social, and economic costs of type 1 diabetes are difficult to calculate, and attempts to quantify these variables typically do not distinguish between type 1 and type 2 disease. However, two studies have provided cost estimates specifically for type 1 diabetes, proposing an annual figure of \$14.4–14.9 billion in the USA.<sup>104,105</sup> Regardless of the financial costs, achieving normoglycaemia is an important therapeutic goal for patients with type 1 diabetes, especially for avoiding complications.

### Complications associated with type 1 diabetes

Complications in type 1 (and type 2) diabetes are classified as macrovascular or microvascular. Cardiovascular

disease is becoming a more common macrovascular complication as individuals with type 1 diabetes live longer.<sup>106</sup> Individuals with type 1 diabetes have a ten-times higher risk for cardiovascular events (eg, myocardial infarction, stroke, angina, and the need for coronary-artery revascularisation) than age-matched non-diabetic populations.<sup>107</sup> The Pittsburgh Epidemiology of Diabetes Complications study<sup>108</sup> of type 1 diabetes reported cardiovascular events in adult patients younger than 40 years of age to be 1% per year, and three times higher in individuals older than 55 years. The Epidemiology of Diabetes Interventions and Complications (EDIC) study,<sup>109</sup> which followed participants with type 1 diabetes for long-term complications, found intensive diabetes treatment reduced the risk of cardiovascular events by 42% compared with conventional treatment. Patients with type 1 diabetes have less favourable outcomes than non-diabetic patients after an acute coronary event,<sup>110</sup> a finding that might be explained by a recent report that, after myocardial infarction, patients with type 1 diabetes express antibodies to cardiac proteins, whereas patients with type 2 diabetes do not.<sup>111</sup> The risk for microvascular complications, including retinopathy, nephropathy, and neuropathy, decreases with intensive insulin therapy. Over the past 5 years, several large clinical trials have advanced the prediction and prevention of microvascular complications (table 1).

### Access to insulin

Despite the progress made for treatment of type 1 diabetes, individuals in many parts of the world die

	Complications assessed	Main findings
Diabetes Control and Complications Trial (DCCT)/Pittsburgh Epidemiology of Diabetes Complications study (2009) <sup>112</sup>	Cardiovascular disease, nephropathy, retinopathy	The frequencies of serious complications in patients with type 1 diabetes, especially when treated intensively, are lower than those reported historically
Finnish Diabetic Nephropathy (FinnDiane) Study (2009) <sup>113</sup>	Cardiovascular disease, nephropathy	In patients with type 1 diabetes, variations in glycated haemoglobin concentration predicted the incidence of microalbuminuria and progression to renal disease, and incidence of cardiovascular disease
DCCT/ Epidemiology of Diabetes Interventions and Complications (EDIC) study (2011) <sup>114</sup>	Nephropathy	In patients with type 1 diabetes and persistent microalbuminuria, intensive glycaemic control, blood pressure control, and favourable lipid panels lead to fewer long-term renal complications
FinnDiane (2009) <sup>115</sup>	Nephropathy	An independent and graded association exists between the presence and severity of kidney disease and premature mortality in type 1 diabetes
Genetics of Diabetes in Kidney Collection (2009) <sup>116</sup>	Nephropathy	Identified genes associated with susceptibility to diabetic nephropathy, near the <i>FRMD3</i> and <i>CARS</i> loci
Swedish Renal Registry (2010) <sup>117</sup>	Nephropathy	Substantial differences in risk for nephropathy in male versus female patients with type 1 diabetes, with age at diagnosis an important factor (early diagnosis lowers risk)
DCCT/EDIC (2009) <sup>118</sup>	Autonomic neuropathy	Patients given intensive insulin therapy had less cardiac autonomic neuropathy than those who received conventional treatment
Acetyl-L-carnitine Clinical Trials (2009) <sup>119</sup>	Neuropathy	Raised triglycerides correlate with progression of diabetic neuropathy
DCCT/EDIC (2008) <sup>120</sup>	Retinopathy	Intensive insulin therapy (vs conventional therapy) reduces development and progression of diabetic retinopathy, with a treatment-related difference (metabolic memory) continuing for at least 10 years
Diabetic REtinopathy Candesartan Trials (DIRECT; 2008) <sup>121</sup>	Retinopathy	The angiotensin receptor blocker, candesartan, reduces retinopathy development but does not stop retinopathy progression

**Table 1: Large-scale studies on prediction and prevention of complications associated with type 1 diabetes**

because of lack of access to insulin.<sup>122</sup> For example, in Mozambique, the life expectancy for a newly diagnosed child with type 1 diabetes is 7 months.<sup>123</sup> Inequalities in the availability of technologies to reduce complications, improve quality of life, and improve diabetes management (eg, HbA<sub>1c</sub> testing and blood-glucose monitoring) also raise ethical concerns. Much public debate has centred on why the global community accepts this treatment disparity.<sup>124</sup> Fortunately, organisations such as the International Diabetes Federation, Life for a Child, Insulin for Life, and others are developing means to alleviate this disparity.

### Prevention and cure

Nearly three decades have passed since the first immune-based therapies, using ciclosporin, were attempted to reverse type 1 diabetes.<sup>125</sup> Many practical and intellectual advances have been made since then, including improved metabolic testing, better understanding of disease pathogenesis, and availability of immune markers.<sup>126</sup> Efforts to prevent or cure type 1 diabetes are now done via large collaborative networks (eg, NIH TrialNet, Immune Tolerance Network, and Islet Cell Transplantation Consortium), with rigorous mechanistic assays and uniform protocols. Finally, although controversial, therapeutic interventions have clearly benefited from studies in animal models of type 1 diabetes, particularly the NOD mouse.<sup>127</sup>

### Primary and secondary prevention

Since type 1 diabetes is now a predictable disease, several large trials are investigating methods to prevent or delay

the onset of disease. Primary prevention studies, in individuals with a genetic risk for type 1 diabetes but without islet autoantibodies, have largely focused on dietary modifications early in infancy. A study in Finland<sup>128</sup> identified 230 infants with a first-degree relative with type 1 diabetes, and randomly assigned infants to receive a hydrolysed infant formula or conventional formula whenever breast milk was not available during the first 6–8 months of life. Children who received the hydrolysed formula were less likely to develop two or more islet autoantibodies compared with those who received the conventional formula, with an unadjusted hazard ratio of 0.52.<sup>128</sup> Another trial removed bovine insulin from infant formula and reported less progression (compared with infants who received normal cow's milk formula) to the development of one islet autoantibody after 3 years of follow-up.<sup>129</sup>

Studies of secondary prevention, to delay onset of type 1 diabetes, are done in individuals with multiple islet autoantibodies but without overt hyperglycaemia. In one trial, individuals with at least two islet autoantibodies (one being an antibody against insulin) who had a first-degree relative with type 1 diabetes, received oral insulin.<sup>130</sup> Overall, administration of oral insulin did not delay progression to overt diabetes, but a post-hoc analysis suggested that individuals with high titre insulin autoantibodies benefited from treatment—it was estimated that diabetes onset was delayed as much as 5 years.<sup>131</sup> Other agents used for secondary prevention, nicotinamide and intranasal insulin, have not been shown to delay or prevent diabetes onset.<sup>132,133</sup>



## Reversal

Currently, there are no approved agents to stop the autoimmune destruction of  $\beta$  cells after diagnosis of type 1 diabetes. In the past 5 years, interest in reversal of type 1 diabetes has grown.<sup>134</sup> In addition to preserving production of C-peptide, a key goal is to induce immune tolerance against  $\beta$  cells and thereby halt autoimmune destruction. Most approaches involve provision of self-antigen (eg, vaccination with specific islet-cell proteins, such as insulin or GAD) or immune suppression (table 2). Disappointingly, after promising phase 1–2 trials in patients with recent-onset type 1 diabetes and detectable endogenous insulin production, phase 3 trials of anti-CD3 antibodies (otelixizumab and teplizumab), and the Diamyd vaccine (GAD-alum immunotherapy) did not meet primary endpoints.<sup>135–141</sup> Administration of DiaPep277, a synthetic immunomodulator, at 3-month intervals resulted in less of a decline in stimulated C-peptide concentrations at 1 year in adults with type 1 diabetes than in the cohort that received placebo.<sup>142,143</sup> Other phase 2 studies of immune modulators showed evidence of therapeutic efficacy in settings of recent-onset type 1 diabetes; however, even with continued use, most did not show durable effects. For example, the fusion protein CTLA4-Ig (abatacept) preserved stimulated C-peptide concentration for only 9 months despite continuous intravenous administration for 2 years.<sup>138</sup> These results imply that single-agent immunosuppression alone might be insufficient to completely control the autoimmune destruction of  $\beta$  cells, or that more specific and targeted therapies are needed. Combination therapies that target several pathogenic pathways and improve  $\beta$ -cell viability might be needed to preserve endogenous insulin production in patients with type 1 diabetes. A 2007 trial of autologous haematopoietic stem-cell transplantation combined with high-dose immunosuppression (ie, cyclosporin and thymoglobulin) reported increased C-peptide production and insulin independence in most patients who received treatment at disease onset.<sup>144</sup> However, the effects of this invasive treatment waned over time, with loss of insulin independence

in most patients after 5 years.<sup>145</sup> It is crucial to re-examine the design and metabolic and immunological outcomes of these phase 2–3 trials, and to consider disease heterogeneity, to better understand how to approach reversal of type 1 diabetes.<sup>146,147</sup> Additionally, testing agents that target inflammation (eg, anakinra [interleukin-1 receptor antagonist] and canakinumab [anti-interleukin-1 $\beta$  compound]), alone or in combination could prove beneficial.<sup>148</sup>

## Islet-cell transplantation

In 2000, a breakthrough protocol was developed for islet transplantation without the use of glucocorticoids for immune suppression,<sup>149</sup> the initially promising results deteriorated so that at 5 years, only 10% of patients remained independent of exogenous insulin.<sup>150</sup> Therefore, islet transplantation remains an experimental procedure, with ongoing research focusing on new methods using biomaterials (eg, encapsulation), immune modulation, site of delivery, improved vascularisation, and more.<sup>151</sup> Many of the limitations for islet transplantation hold true for another promising area, the use of stem cells as insulin-producing surrogates for  $\beta$  cells. It remains hopeful that an insulin-producing cell (stem cell, cadaveric islet, xenogeneic islet, etc), combined with an immunoprotective barrier (ie, encapsulation) will provide a therapeutically meaningful advance.

## Unanswered questions

This is a season of change with respect to understanding of the epidemiology, pathogenesis, treatment, and prospects for curing type 1 diabetes. In hindsight, many long-held goals once thought readily achievable have been difficult to realise, and concepts regarded as dogmas have proven to be flawed.

## Lessons learned

Despite the advances in type 1 diabetes research and therapy, some researchers and clinicians are disappointed by a perceived lack of progress. Large investments in terms of time, finances (foundation, government, and

	Study phase and year	Main findings
Insulin APL (NBI-6042)	Phase 2; 2009	No change in metabolic response (ie, C-peptide preservation) <sup>135</sup>
Anti-CD20 (rituximab)	Phase 2; 2011	Preservation of C-peptide concentrations at 1 year, but no difference from placebo at 2 years <sup>136</sup>
Anti-CD3 (teplizumab)	Phase 3; 2011	Although phase 2 studies showed preservation of C-peptide concentrations, phase 1 trials (Protégé study) <sup>137</sup> showed no change in metabolic responses and the study stopped early
CTLA4–immunoglobulin fusion protein (abatacept)	Phase 2; 2011	T-cell co-stimulatory modulation slowed reduction in $\beta$ -cell function over 2 years, although preservation of C-peptide was seen for 9.6 months <sup>138</sup>
Anti-CD3 (otelixizumab)	Phase 3; 2011	Although phase 2 studies showed preservation of C-peptide concentrations, a phase 3 trial showed no change in metabolic response <sup>139</sup>
GAD65 protein (Diamyd)	Phase 3; 2012	Phase 2 studies reported preserved C-peptide concentration, with no improvements in insulin needs. Two phase 3 trials did not meet endpoints <sup>140,141</sup>
HSP60 (DiaPep277)	Phase 3; 2012	Phase 2 trials suggested increased C-peptide concentrations; a phase 3 trial noted C-peptide preservation at 1 year, but only in adults (age 16–45 years) with type 1 diabetes <sup>142</sup>

**Table 2: Agents assessed as immunomodulatory therapy to reverse type 1 diabetes**

industry-based), and patient resources have been directed to several promising areas—ie, islet-cell transplantation, stem cells, genetics, primary and secondary disease prevention, and reversal of type 1 diabetes—with results that are often deemed to have limited benefit.<sup>134</sup>

Type 1 diabetes has proven to be much more resistant than initially expected to therapeutic interventions with conventional or experimental agents, whether the goal is disease prevention or reversal.<sup>152</sup> Inability to overcome the autoimmune nature of this disease, perhaps the result of robust immunological memory combined with failure to attenuate deleterious immune responses that are not subject to normal regulation, is a hurdle that needs to be addressed with intense research. Similarly, islet-cell transplantation depends on overcoming recurrent autoimmunity and averting alloimmunity.<sup>153</sup> Additional hurdles for islet-cell transplantation include a limited donor pool and the need for chronic immunosuppression (or a method to induce long-term immunological tolerance) to allow for functional engraftment. To achieve progress with islet-cell transplantation, investigators are focusing on xenotransplantation, encapsulation, novel sites for cell delivery (eg, eye), and development of surrogate insulin-producing cells.<sup>151</sup>

Investigations into the genetic basis of type 1 diabetes have been criticised for making little headway into understanding the pathogenesis of this disease. The polygenic nature of type 1 diabetes (more than 40 loci have been associated with disease susceptibility or resistance<sup>72</sup>) combined with environmental associations mean that disease pathogenesis can be unpredictable. An additional complication arises from the fact that although many genotypic associations with the disease exist, the specific phenotypes resulting from these genetic influences are largely unknown. Efforts are underway to assign specific phenotypes to genotypes, and to improve understanding of the genetic risk for type 1 diabetes by genotyping at multiple susceptibility loci.<sup>154</sup>

Difficulty understanding the genetic complexity of type 1 diabetes is compounded by a lack of knowledge regarding the immune response in this disorder. Despite decades of investigation, the mechanisms by which  $\beta$  cells are eliminated or selectively destroyed (apart from antigen-specific immune responses) remain unclear.<sup>55</sup> Over the past decade, investigators have devoted much effort to describing the putative role for adaptive, rather than innate immune responses, in terms of their pathogenic contributions to type 1 diabetes. Understanding the innate and adaptive immune response, and the role of  $\beta$  cells in the pathogenesis of type 1 diabetes, will be crucial for development of improved therapies. Fortunately, well organised trial networks (eg, NIH TrialNet and Immune Tolerance Network) and registries (eg, T1D Exchange) can test agents capable of providing therapeutic benefit, improve patient recruitment, and increase the precision of disease prediction.<sup>155</sup> Additional modifications that

could improve the applicability of type 1 diabetes research include changes in clinical trial design (eg, adaptive trial design),<sup>156</sup> identifying more practical therapies (in terms of finance and delivery of public health care), better defining disease heterogeneity,<sup>147</sup> utilising animal models of type 1 diabetes more effectively,<sup>127</sup> and applying the concept that type 1 diabetes begins long before symptomatic onset. Redefining type 1 diabetes as having a silent or asymptomatic state (eg, multiple autoantibodies, genetic risk, with varying degrees of dysglycaemia) could allow therapeutic interventions to be given earlier in the natural history of disease when they might be more effective. This concept is based on studies in animal models of type 1 diabetes, where earlier interventions seem to be more efficacious, and the belief that intervention before a critical threshold of remnant  $\beta$ -cell mass is lost would avoid several sequelae that are often present at symptomatic onset (eg, glucose toxicity, stress response, etc).

#### Where do we go from here?

Knowledge voids that have long existed for type 1 diabetes, unfortunately, remain today. The most pressing questions are: what environmental constituents unequivocally contribute to the formation of type 1 diabetes? In what way does genetic susceptibility contribute to disease development? Can a safe and effective closed-loop therapy system be developed? What drugs should be used in attempts to prevent or reverse type 1 diabetes? Are agents capable of instilling long-term immunological tolerance available? Can improved markers for predicting disease development be obtained? Can  $\beta$ -cell replication and neogenesis be safely induced in humans? Finally, why are pancreatic  $\beta$  cells specifically targeted for destruction, and do inherent processes contribute to their demise? These questions form a roadmap for the next generation of investigations, and if properly addressed, should result in substantial improvements in the lives of individuals burdened with type 1 diabetes.

#### Contributors

All authors planned the outline, contributed to figures and tables, and wrote and approved the manuscript. MAA and AWM did the literature search.

#### Conflicts of interest

MAA serves, or has served, as an adviser to Genzyme, Diamyd, GlaxoSmithKline, Takeda, Tolorex, Coronado Biosciences, Sanofi, Exsulim, Grifols, and Amylin. GSE served as an adviser to Sanofi. GSE and AWM received research support from Novartis.

#### Search strategy and selection criteria

We searched Medline from Jan 1, 2008, to Feb 1, 2013, with the terms "type 1 diabetes", with restrictions for studies in humans and articles published in English. Earlier articles were derived from our longstanding reference collections.

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