Type 1 Diabetes at a Crossroads!

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"Be at a crossroads": *to be at a stage in your life when you have to make a very important decision* (1). Type 1 diabetes at a crossroads? What does that really mean? It cannot mean that progress has not been made! Indeed, in the field of diabetes, reporting of new information is clearly outpacing our ability to incorporate new findings into clinical treatment options and recommendations. Over the recent past, important new information regarding the burden of diabetes, prevention, and screening and comprehensive discussions on new therapies have been reported (2–7). However, on closer inspection, the most impressive changes in treatment and preventive strategies have been focused on type 2 diabetes. What then are the major advances in type 1 diabetes? How close are we to realizing an intervention that can delay or prevent type 1 diabetes? Are we any closer to a cure today than we were 10 years ago? What progress has been made toward the "holy grail" of offering a fully functioning artificial pancreas (AP)? To address these questions, our editorial team has elected to feature these topics in a series of articles in this issue of *Diabetes Care*. Specifically, articles in this issue describe research related to the present status of treatment methods and clinical outcomes in type 1 diabetes in the U.S.; discuss current concepts on the pathogenesis, prediction, and prevention of the disease; review the successes and ongoing challenges of islet transplantation; and describe a pathway for the translation of advances in diabetes technology into an AP suitable for home use by large numbers of patients (8–15).

The limitations of current treatment of type 1 diabetes are addressed in the report by Miller et al. (8), which summarizes the most recent data collected on 16,601 individuals participating in the T1D Exchange clinic registry—patients who have been receiving care at leading adult and pediatric diabetes treatment centers in the U.S. While the overall mean HbA_{1c} level in the entire population of 2- to 93-year-olds was 8.4% (68.4 mmol/mol), the mean HbA_{1c} level in adolescents between 13 and 17 years of age was nearly 9.0% (74.9 mmol/mol), which is not very different from baseline HbA_{1c} levels in adolescents receiving conventional treatment in the Diabetes Control and Complications Trial (DCCT) in the 1980s. Moreover, it takes until age 30 years before HbA_{1c} finally reaches "adult levels" of 7.5–7.8% (58–62 mmol/mol). Unfortunately, severe hypoglycemia and diabetic ketoacidosis remain all too common complications of treatment in this large sample of patients. This report provides a sobering reminder that there remains considerable room for improving outcomes as "only a minority of children and adults with type 1 diabetes achieve HbA_{1c} targets" (8). This article also confirms the overall concern with the current state of treatment of type 1 diabetes and why we are featuring type 1 diabetes in this special issue.

As we look toward new ways to prevent and cure type 1 diabetes, an obvious starting point would be a review of how the understanding of the pathogenesis of the disease has evolved over the past few years. The article by Atkinson et al. (9) starts by describing the historical models of type 1 diabetes pathogenesis and how these models have guided prevention and reversal studies for decades. The authors then discuss emerging new concepts on the role of both the immune response and β-cells in the development of type 1 diabetes and how new knowledge relating to the pathogenesis and natural history will guide future efforts in prevention and reversal of the disease. The authors point out that "while progress has clearly been made toward understanding the initiating and sustaining events in the pathogenesis of type 1 diabetes . . . much more investigation and discovery are needed" (9).

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Continuing the theme of understanding the pathogenesis of type 1 diabetes, Ezio Bonifacio (10) provides an update on the use of biomarkers to predict the risk of the development of type 1 diabetes. In his elegant review, Bonifacio "proposes that there is now sufficient evidence to allow a broader use of islet autoantibodies as biomarkers to diagnose type 1 diabetes that is already at an asymptomatic stage, so that attempts to prevent clinical hyperglycemia become a feature of disease management" (10). He suggests that genetic and other biomarkers will be used to determine the likelihood that an infant will develop islet autoimmunity, and then metabolic assessments and biomarkers will be followed to determine the rate of progression to hyperglycemia.

In his Perspective article, Jay S. Skyler (11) describes the attempts over the past three decades to interdict the type 1 diabetes disease process to prevent type 1 diabetes and to preserve residual β-cell function in new-onset patients. Although it is very discouraging to note that there has been no prevention trial that has resulted in delay or prevention of type 1 diabetes, we are given some hope as he states that "there are many potential interventions that hold promise, particularly if they are used as components of combination therapy," but he also cautions that "to be successful, we must be patient, yet proceed with diligence" (11).

At this point in the special issue of *Diabetes Care*, we have only heard narratives reporting negative results in the goal of prevention . . . are you convinced we are at a crossroads yet?

The next questions addressed in this issue relate to advancing treatment options. For example, Bell et al. (12) comment on the limitations of the current approaches for mealtime insulin dosing in type 1 diabetes based primarily on carbohydrate counting and provide an analysis with a systematic review of this topic. They state that "studies indicated that high-fat/protein meals require more insulin than lower-fat/protein meals with identical carbohydrate content" (12). It is their opinion that these studies have important implications for translation and conclude that there is a need for new research that is focused on the development of new insulin-dosing algorithms based on meal composition rather than carbohydrate content alone (12).

The challenge in managing patients with problematic hypoglycemia is addressed by Choudhary et al. (13), who define problematic hypoglycemia as two or more episodes per year of severe hypoglycemia or as one episode that is associated with impaired awareness of hypoglycemia, extreme glycemic lability, or major fear and maladaptive behavior. They propose a tiered, four-stage approach to reducing the risk of hypoglycemia without jeopardizing overall metabolic control. Stage 1 consists of structured, hypoglycemia-specific education programs in patients using multiple daily injections and blood glucose monitoring. Stage 2 consists of either switching to insulin pump or adding continuous glucose monitoring if problems persist. Stage 3 involves the use of sensor-augmented pumps, preferably with automated threshold-suspend feature, where available, or very frequent contact with a specialized hypoglycemia service. For patients whose problematic hypoglycemia persists, islet or pancreas transplant should be considered (stage 4). The authors suggest that this "algorithm provides an evidence-informed approach to resolving problematic hypoglycemia; it should be used as a guide, with individual patient circumstances directing suitability and acceptability to ensure the prudent use of technology and scarce transplant resources" (13).

The issue continues with a very thoughtful narrative and update on islet transplantation by R. Paul Robertson (14). His Perspective provides a history of islet transplantation and contrasts allo- and autoislet transplantation with respect to procedures of islet procurement, islet isolation and transplantation, and the role and complications of immunosuppressive drugs. He also compares the posttransplant consequences on β-cell as well as α-cell function. It is his opinion that "the future of islet transplantation is very robust" and that as a scientific community "we are steadily making progress in the difficult task of β-cell replacement as a treatment for [type 1 diabetes]" (14).

In the final contribution in our special issue, Aaron Kowalski (15), who has led the JDRF support for this area of research, reviews the progress to date in the development of the AP. He reports that AP systems seek to replicate mechanically the islet physiology that is lost in diabetes. Although such systems cannot be expected to fully replicate the function of the islet, the required safety and feasibility of such systems have been demonstrated in controlled clinical research center settings and more recently in "real-world" environments. He also states that the "success of AP systems will be defined by successful integration into the diabetes health care system and by the ultimate metric: improved diabetes outcomes" (15). If that is the case, this area of development of type 1 diabetes takes a completely different turn from the sobering comments on prevention and reversal noted earlier. Consequently, our contention that we are at a crossroads still remains.

The editorial group at *Diabetes Care*, in recognizing the issues pertaining to type 1 diabetes, is once again proud to present a high-level collection of articles that provides the latest update from studies, opinions, and perspectives in the field. We started with a sobering view of the current state of treatment of type 1 diabetes from the T1D Exchange clinic registry that calls for new approaches to the prevention, treatment, and cure of the disease. If one were keeping score, we had optimistic views on management of type 1 diabetes in regard to evidence-based medicine and optimism in the areas of islet transplant and AP systems. The information to date on prevention and reversal, however, has been disappointing. Based on the above, is type 1 diabetes, figuratively, "at a crossroads"? We will leave it to the reader to decide.

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