

## Preface

**I**N 1919, ELIZABETH EVANS HUGHES, then an 11-year-old girl, was diagnosed with juvenile diabetes. At that time, the diagnosis was a death sentence, and few people lived for more than weeks or months after the diagnosis. The greatest toll was on children, who succumbed rapidly because the source of insulin, pancreatic  $\beta$  cells, had been destroyed. Ms. Hughes survived with a starvation diet, consuming no more than 500 kcal per day combined with severe restrictions of her activity and the constant presence of a nurse by her side who continually monitored her body's processes and every gram of food consumed. In referring to the prognosis at the time, Elliot Joslin noted that "we literally starved the child and adult with the faint hope that something new in treatment would appear...." In 1922, that "most improbable" scientific breakthrough happened—Frederick Banting and Charles Best discovered insulin and, with the help of James Collip, purified the protein. Through her family's contact (she was the daughter of the Governor of New York) and her mother's pleading, Elizabeth became one of the first recipients of insulin in the first clinical trial. At the time she received insulin, her weight had declined from 75 lb at diagnosis to 45 lb. With insulin injections, she rapidly regained weight and recovered her life. Ultimately, Elizabeth attended college and had children. She became an advocate and devoted her philanthropic work to support education and lived a joyful life, particularly enjoying reading—her sole pleasure after her diagnosis. She died at the age of 73. Banting and Best won the Nobel Prize in 1923, and Banting, Best, and Collip shared the patent for insulin, which they sold to the University of Toronto for one dollar.

For the next 100 years, the treatment of diabetes, subsequently termed insulin-dependent and eventually type 1 diabetes (T1D), consisted of diet and chronic insulin injections. Although T1D is treatable, the inability to effectively control glucose levels remains a challenge and long-term complications remain a serious concern, even today. In the 1970s, investigators identified features of immunity associated with diabetes such as immune cell infiltration into the islets of Langerhans in those who died with diabetes. As the clinical features of T1D were distinguished from the more common type 2 diabetes (T2D), T1D was recognized as an immune-mediated disease. Two transformational studies in the 1980s, one conducted in the United States led by George Eisenbarth, and the other in France led by Jean-Francois Bach, showed that treatment with the immunosuppressive drug cyclosporine reversed diabetes, documenting the key role of autoimmunity in the pathogenesis of the disease. These results accelerated investigations into the immune, genetic, and environmental causes of the disease, including a role for  $\beta$  cells in their own demise. Insights gained from both murine and human studies led to deeper characterization of T1D as a model of antigen-driven autoimmune diseases, and discoveries in basic immunology and other fields, such as cancer immunobiology, led to a deeper understanding of the immunologic dysregulation that underlies T1D.

This book is the second in the *Cold Spring Harbor Perspectives in Medicine* series devoted to T1D. The chapters describe discoveries that have advanced our theories of T1D pathogenesis, spanning immunologic, genetic, and environmental research contributions to understanding of both disease susceptibility and pathogenesis. The book also reviews details of the role  $\beta$  cells play in T1D, how they interact with the immune system, and how this contributes to the disease. Finally, multiple chapters bridge the gap between the fundamental research and clinical studies aimed at prevention and treatment.

Chapter 1 (Herold and Krischer) provides an overview of the pathogenesis of T1D. Immune (autoantibodies) and metabolic (dysglycemia) markers have led to the concept of disease stages, pre- and post-insulin dependence, which represent mileposts in its progression. These disease features and

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serum biomarkers are critical individual patient features that define the disease course (termed endotypes) and potentially responses to immune therapies. This chapter and Chapter 2 by Hyöty et al. describe how environmental insults may enhance disease via innate and adaptive immune mechanisms but, as importantly, may prevent disease progression (the “hygiene hypothesis”), potentially explaining the increasing rates of T1D in past decades particularly in westernized countries.

As described by Nepom in Chapter 3, T1D represents a failure of normal immune tolerance. The failures leading to disease in innate and adaptive immune pathways are discussed in Chapters 10 and 11 by Smith et al. and Bertrand et al., respectively. Relevant naturally occurring genetic mutations are discussed in Chapters 4 (Chamberlain et al.) and 13 (Kang and Youngblood) as well as induced breakdown of tolerance following immunotherapies to treat cancer (Quandt et al., Chapter 16). Our concepts of the pathogenesis, diagnosis, and biomarkers of immunotherapy successes in T1D have been advanced with the use of new technologies and tools as described in Chapter 15 by Long and Linsley. The authors discuss how biomarkers of immune responses, especially in the setting of immune perturbations with biologics, can help to identify targets for treatment and mechanisms that are central to disease.

Multiple chapters in the book focus on T cells, which are thought to be the effectors that cause  $\beta$ -cell killing. Unlike immune responses elicited by viral infections, transplanted organs or other conventional challenges, autoimmunity displays specific characteristics such as chronic exposure to antigens, tissue specificity, and slow progression. Features that distinguish T cells that respond to autoantigens include stem-cell-like properties, as described in chapters by Kang and Youngblood and Schietinger et al. (Chapter 12) and may provide clues to why they are difficult to eliminate. Moreover, it is not just peptides produced by  $\beta$  cells in healthy individuals, but neoantigens to which tolerance has not been induced may be involved. These are discussed in Chapter 14 by Delong and Nakayama, while autoantigen therapies are described in Chapter 19 by Peakman and Santamaria.

Further disease insights have come from the study of tissues from animal models (Serreze et al., Chapter 5) and humans (Kusmartseva et al., Chapter 9). In addition to increasing our understanding of T1D pathogenesis, these efforts have identified cross talk between the target tissue ( $\beta$  cells) and immune cells that may lead to activation of immune cells and  $\beta$ -cell death. Samassa et al. (Chapter 6) focus on the communication between these systems and how they influence each other. Bhushan and Thompson (Chapter 7) speak to the internal and external stresses that instigate the process on both sides, while Hansen et al. (Chapter 8) delve into the question of whether the  $\beta$  cells or the immune system becomes dysfunctional first.

These advances in our understanding of the pathobiology of T1D have driven progress in development of treatments to change the course of the disease, as reviewed by Tatovic and Dayan (Chapter 18). Nepom (Chapter 3) describes how the breakdown and repair of immune tolerance has been achieved with novel therapeutics that “rebalance” the immune system. The approaches include using regulatory T cells, as described by Muller et al. (Chapter 17), and antigen-specific immune therapies (DeLong and Nakayama, Chapter 14, and Peakman and Santamaria, Chapter 19) building on the discoveries of the targets of immune cells. This is an ideal therapeutic approach because of their specificity for T1D. Islet transplantation and restoring  $\beta$ -cell function, especially without the need for chronic immune suppression, represents the ultimate cure for T1D and is discussed by Kieffer et al. (Chapter 21).

Based on the work of many researchers and multiple national and international networks, such as TrialNet, DAISY, TEDDY, DIPP, and BABYDIAB in the Eisenbarth model of T1D progression, the disease initiates before any clinical presentation. This suggests that patients can benefit from treatments before they present with severe metabolic derangement. In 2015, 96 years after Edith Hughes’ diagnosis, another girl, a 10-year-old, whose sister had insulin-dependent T1D, was found to have multiple autoantibodies and impaired glucose tolerance that suggested a 75% risk of progressing to clinical T1D within 5 years. She also enrolled in a clinical trial, but this time the trial was with

teplizumab to test whether the diagnosis of T1D might be delayed or prevented. Over the next nearly 9 years, without diabetes, she went to school without the need for a special diet, glucose monitoring, or insulin injections, and she danced, skied, traveled, and sailed. She went to the prom with her peers. She never set foot in the school nurse's office. She was eventually diagnosed with T1D not by clinical presentation with acute metabolic deterioration but through biochemical findings from a glucose tolerance test and free of insulin treatment. The story of the development and FDA approval of teplizumab to treat individuals at high risk of developing T1D, has changed the course of T1D—it is the first approved drug since insulin. The long journey beginning in preclinical studies and the hurdles that were overcome in development before its final approval after 30 years are discussed by Chatenoud et al. (Chapter 20).

We are in a new era for treatment, prevention, and eradication of T1D. Therapies are now more specific and seek immune modulation rather than immune suppression, which makes treatment safer and more acceptable, particularly for children. Finally, we are on the path to replace  $\beta$  cells even in those in whom they have been destroyed.

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