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EDITED BY

Jeffrey A. Bluestone
University of California, San Francisco

Mark A. Atkinson
University of Florida

Peter Arvan
University of Michigan

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Front cover artwork: Image of a human islet stained for insulin using immunohistochemistry and a red chromogen. The islet shows a normal architecture while three single β cells in the lower part of the image show the diversity in β-cell distribution found in normal human pancreas. The pancreas was recovered from a 24-year-old female organ donor without diabetes through the JDRF Network for Pancreatic Organ Donors with Diabetes program. Image provided by Dr. Martha Campbell-Thompson, Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, FL.

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Preface

A YOUNG GIRL, 4 YEARS OLD, WAKES UP in the middle of the night in a cold sweat. Her bed is soaking wet and smells of urine. She cries out to her mom and dad for help. They rush to her bedside where they find her vomiting, delusional, and in severe pain. Her parents rush her to the hospital where she is found to have a blood sugar level of 1040 mg/dL (normal is 70–100) and suffering symptoms related to diabetic ketoacidosis. With this, yet another child is diagnosed with type 1 diabetes mellitus (T1DM), an autoimmune disease that manifests itself as uncontrolled high blood sugar (glucose) levels as a direct result of pancreatic β-cell loss and dysfunction.

β cells, part of a specialized cluster of cells within the pancreas known as the islets of Langerhans, produce insulin, the key metabolic regulator of blood glucose. Loss of these cells leads to uncontrollable diabetes and death of the patient if insulin replacement therapy is not administered daily (in fact, a multitime per day basis in today's treatment regimen). Less than 100 years ago, a Romanian physiologist, Nicolae Paulescu, discovered insulin. Yet it was Frederick Banting and Charles Best (a student of J.J.R. Macleod) who determined that the pancreas was the source of this vital hormone and that insulin could be extracted from the islets to treat patients with this devastating disease. Today, we see the benefits of decades of extraordinary progress in the treatment of this disease. This includes the development of multiple forms of insulin (i.e., insulin analogs) designed to vary in their onset and duration of action, improved blood glucose monitoring devices (from small and rapid handheld devices to those devised to provide continuous readings), and pumps that effectively administer insulin without the need for repeated daily injections. But the undeniable truth is that we continue to treat the symptoms of diabetes and, unfortunately, most individuals do not avoid many disease-associated complications. Indeed, long-term failure to achieve continual blood glucose control can result in neuropathy, kidney failure, loss of eyesight, the need for limb amputation, increased susceptibility to diabetic coma, and more. In fact, for reasons that are not fully understood, even those patients with exquisite blood glucose control can suffer from these devastating long-term complications. Perhaps most disappointing, T1DM has seen a profound increase in incidence each decade over the past 50 years, with the highest increase in incidence observed in children less than 5 years of age.

This Cold Spring Harbor Laboratory Press book seeks to update the reader to current thinking regarding the pathogenesis of T1DM—the interaction of the immune system and the β cell that leads to its demise. With this effort, we hope to provide a coherent and concise review of the state of the field and, with it, a path forward for researchers committed to a better understanding of the cause and complexities of T1DM as well as a path to novel treatments that can prevent and cure the disorder. As editors, we sat down to discuss the development of this project and immediately realized that we could not provide a comprehensive work dealing with all areas relevant to T1DM. For example, we would not be able to give the field of diabetes complications or clinical care the justice they deserve with the page limitations for this text. Likewise, we could not discuss all the recent advances in insulin formulations and insulin delivery devices nor the potential future of what has effectively been dubbed "the artificial pancreas." Beyond this, we could only provide limited discussion of the epidemiology of the disease and the role of health care infrastructure worldwide in dealing with this disorder. With this, we decided to focus on key causative and therapeutic areas that will likely drive the T1DM research agenda for the next decade and hopefully advance

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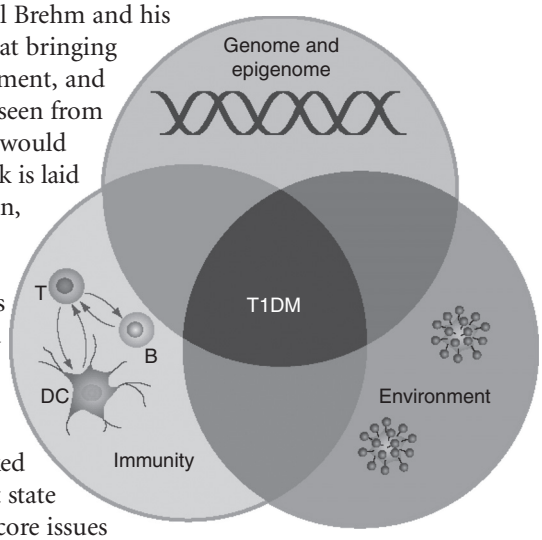
efforts toward a cure. To that end, we sought out those who represent international leaders in the T1DM research field. We also took advantage of a coalition of scientists that came together to discuss, cooperate, and conduct collaborative experiments in the areas of immunology and β-cell biology for our individual efforts and the greater good. This group, known as the Brehm coalition, was started by an enlightened philanthropist Bill Brehm and his wife Dee, and it was built on the proposition that bringing together scientists engaged in the etiology, treatment, and study of the basic underpinnings of the disease seen from the eyes of immunologists and β-cell biologists would lead to new collaborations and insights. This book is laid out in the same way. Beyond the Brehm coalition, we asked outstanding members of the T1DM community to provide chapters to fill gaps and expand the scope. We focused on the three pillars of diabetes research: genetics, environment, and immune pathogenesis of disease. We view this as three elements of a Venn diagram that come together to promote the development of this disorder (see the figure[1]). In the process, we asked the authors to balance summarizing the current state of the field and providing deep thinking about core issues solved or yet to be solved. Each author was requested to go the extra step and consider the implications of the work they summarize in terms of its impact on the future. In short, we wanted everyone to be challenged in a way that would stretch our thinking.



The result is a comprehensive book that deals with the various areas of diabetes emphasized above. The book starts with an introductory chapter by Atkinson on the pathogenesis and natural history of T1DM. In this chapter, the author introduces the disease using a historical approach, which highlights the many advances that have led to the current state of understanding of disease etiology and pathogenesis. He summarizes emerging evidence that supports the notion that the pathogenesis of T1DM is connected closely with both genome and environmental inputs based on epidemiological and scientific evidence. He ends the chapter with a clear description of the current understanding of the pathogenesis of the disease, highlighting both the role of the adaptive and innate immune responses in disease progression. This opening chapter is followed by a detailed dissection of peripheral tolerance, as well as the molecular and cellular brakes that control autoreactivity. Jeker, Bour-Jordan, and Bluestone highlight the role of both intrinsic and extrinsic control mechanisms and how they go awry in patients susceptible to autoimmune diseases in general and T1DM in particular. The next two chapters examine the target of T1DM, the insulin-producing β cells. In his chapter, Hebrok goes through a systematic presentation of the processes that control β-cell development and the ability to recapitulate this developmental progression using human embryonic stem (hES) cells. Understanding the developmental processes, including rounds of cell death, growth, and differentiation, can shed light on the initiation of the disease process. More importantly, the ability to recapitulate these developmental decisions using hES cells has clear therapeutic consequences. In the chapter written by Papa, we learn about the consequences of immune insult and other stress events on β-cell survival. He summarizes efforts to dissect the properties of β cells (both induced and intrinsic) that contribute to their own demise. The studies leave little if

[1]Adapted from Ermann J, Fathman CG. 2001. *Nat Immunol* **2:** 759–761.

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any doubt that β cells participate in their own destruction—not only by the specific autoantigenic molecules they express, but through changes that occur in the β cells leading to the suicide of the cells themselves.

The book then turns its attention to an in-depth analysis of the various pathways that promote the development and progression of the disease. Noble and Erlich focus on the detailed genetics of T1DM. It has been clear for many years that the major histocompatibility complex encoded class II molecules (HLA in humans) are the strongest genes associated with the disease. In this chapter, the basis and structural connection of the susceptible HLA loci are described in detail, with connection to human T1DM described including the complexities of positive and negative regulatory pathways in the HLA-linked disease processes. In addition, over the past 10 years, more than 20 additional molecules/loci have been implicated in disease susceptibility including insulin itself, as well as a series of immune modulatory genes. The authors of this chapter highlight these additional modulators of disease and provide an integrated genetic model of disease progression. The chapter by Pietropaolo, Towns, and Eisenbarth turns to the immune predictors of disease that follows directly from the aforementioned genetic predisposition. The role of the humoral response as a marker of both disease susceptibility and progression is vital to current efforts to more accurately predict disease onset. The impact of current autoantibody testing is not only confined to understanding the timing of disease development and its natural course, but also to the very nature of the autoantigens and their role in disease pathogenesis. Building on the biomarker theme, the chapter by Lebastchi and Herold focuses on the current uses of technology to define the immunologic and metabolic process that are used to monitor disease progression. In their chapter, the authors describe the current uses of immune probes such as soluble MHC-peptide complexes, termed tetramers, to identify autoimmune T cells and specialized assays, like enzyme-linked immunospot assays, to define the function of the aggressive and suppressive T cells. The second half of the chapter is devoted to the current state-of-the-art metabolic assays that are used to monitor disease progression. The need and utility of these assays is highlighted by their demonstrated use in a series of clinical intervention studies involving recently diagnosed T1DM patients, as well as a description of how these assays can be used to monitor therapeutic interventions.

Finally, in this portion of the book, there are three chapters focused on the nature of the autoantigens involved in T1DM. The disease itself is mediated by the destruction of β cells by T cells that recognize islet self-antigens as foreign. A better understanding of the processes by which the antigens are created and the basis for escape from thymic deletion are key to modifying the inescapable destruction of the insulin-producing cells during disease progression and ultimately, developing an effective vaccine to prevent the disease totally. In the first of the three chapters, by Arvan, Pietropaolo, Ostrov, and Rhodes, the authors focus on the cell biology of the islet and related tissues to better define the role of stress and secretory pathways in the generation of autoantigenic peptides. These metabolic decisions can create a unique set of peptides that are processed and presented differently than that which normally occurs in the thymus. Processes such as proteasomal digestion of misfolded products, exocytosis and endocytosis of cell surface products, or antigen release from dying β cells can all influence the nature and composition of the antigenic molecules. The chapter by Marrack and Kappler takes the processing issue one step further as they describe a new level of control of antigenic peptide presentation. As stated above, the key to immune recognition of autoantigens is the ability of T cells to recognize and respond to small peptides embedded in the groove of an MHC class I or class II molecule. This chapter summarizes recent insights into the structural basis for this MHC-peptide complex and the possibility that the protein processing pathways described above can actually alter the way the small polypeptides "sit" in the MHC groove, leading to unique epitopes recognized by rare T cells that escape thymic selection. The third chapter, by Roep and Peakman, focuses on the precise identification of key proteins in and around the β cell that can drive the autoimmune response. They summarize elegant studies that have been used to characterize the nature of the

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autoantigens, the basis of autoantigen presentation by cells of the immune system, as well as approaches that are being pursued to modify autoimmune responses through antigen-based immunotherapy—a potent therapeutic arena described in more depth in a later chapter in the book.

The next portion of the book turns to the environment and its role in the initiation and progression of the disease. The chapter by Bach and Chatenoud highlights the current hypotheses surrounding the role of the environment and incidence of T1D. They provide an in-depth discussion of the hygiene hypothesis that suggests that the "cleaner" environment experienced by individuals living in advanced first-world countries is responsible for the increased incidence of the disease. This hypothesis is based on the notion that immune homeostasis suffers from a lack of education by infectious parasites, bacteria, and other pathogens that are endemic to other less advanced countries. In a similar vein, Knip and Simell's chapter focuses on specific noncommunicable environmental changes such as formula milk for newborns and sunlight-related vitamin D levels as they relate to the increased incidence in highly developed countries. On the other side of the equation, the chapter by Coppieters, Boettler, and von Herrath notes infectious agents that might be directly responsible for disease etiology, including both specific and generalized viral infections. In this regard, in their chapter, Odegaard and Chawla underline the connectivity between the innate immune response that is influenced by infection and the environment and the development of diabetes, both type 1 and type 2. The authors highlight recent advances in our understanding of the tissue-specific immune responses—in this case, the macrophage subsets that influence the balance of protective and pathogenic immunity not just in the target organ, the pancreas itself, but in the peripheral tissues such as the fat and muscle that act in concert with the insulin produced by the β cells to modulate blood glucose levels.

The final chapters in the book focus on the future—the new approaches, both experimental and clinical, that are expected to lead to a cure for the disease. In this section, Brehm, Powers, Shultz, and Greiner contribute a chapter on the current and future use of new animal models to both mimic T1DM and provide ideal models for therapeutic intervention and biomarker discovery. The humanized mouse, which takes advantage of key advances in human cell engraftment, peptide recognition in the context of human HLA molecules, and the directed attack on human β cells, has revolutionized the field and is slowly becoming the model of choice to mimic human disease. The other chapters in the last portion of the book focus on the state of immunotherapies in humans with T1DM. Clemente-Casares, Tsai, Huang, and Santamaria describe current efforts to use autoantigens as therapeutics. Chatenoud, Warncke, and Ziegler highlight the tremendous progress in halting the autoimmune response in early stages of disease progression, including the period just after disease onset. The experimental and clinical efforts target all the key cellular and cytokine pathways with a goal of moving toward combination therapies to prolong disease remission beyond current temporary effects. Finally, the book ends with a chapter devoted to islet transplantation, pioneered by one of the authors, Dr. Shapiro. This chapter, by McCall and Shapiro, brings the book to a close by integrating many of the themes of the previous chapters. The authors demonstrate the continued success in bringing islet transplantation to the clinic but note the challenges spanning the best immune modulatory drugs, the insufficiency of donor supply, and the quality of cadaver-derived islets, as well as the role of the innate and adaptive immune response in mediating islet cell transplant rejection.

In summary, this book represents an attempt to bring together our current understanding of the various aspects of the genetics, environment, and immune pathogenesis of this disease. We hope that this effort sets the table for future investigations that will advance our understanding and treatment. From this platform, and with a deeper understanding of the science of type 1 diabetes, the editors look forward to increasing efforts to develop new approaches that can either prevent autoimmune diabetes, mitigate against the complexities of ongoing T1D management, or serve as a platform for β-cell replacement. In our view, the best chance for development of such therapies will involve

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cross-disciplinary studies that exploit expertise in each of areas the highlighted above. We encourage those interested to work across the platform, exploring the diversity and scope of ideas in order to sample not only where the field is, but where it needs to go.

Finally, the editors wish to thank Richard Sever and Barbara Acosta at Cold Spring Harbor Laboratory Press and the many contributors for this book. In addition, this work would not be possible without the talented students, technicians, and fellows in each of the labs; the funding from the government, philanthropic organizations and individuals, and academic institutions; and the many colleagues who challenge us each day to develop a cure for the children and adults who live every day with this terrible disease.

Jeffrey A. Bluestone
Mark A. Atkinson
Peter Arvan

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