Foreword

The tiny islets of Langerhans receive an extraordinary amount of attention from a variety of interested parties, many of whom will enthusiastically welcome publication of the second edition of the "Islets of Langerhans," ably edited by Md. Shahidul Islam, M.D., Ph.D., of the Karolinska Institute, Stockholm, Sweden. The amount of attention paid to islets is well deserved because the failure of their β cells to produce sufficient amounts of insulin results in diabetes, with its climbing prevalence worldwide and devastating complications. In type 1 diabetes the β cells are almost completely decimated by the vicious process of autoimmunity. With the far more common type 2 diabetes, the insulin resistance associated with obesity and our sedentary life style is linked to reduced β cell mass and function. The simplest view is that the β cells die because they are stressed by overwork, resulting in reduction of insulin secretion, which allows glucose levels to rise enough to cause further impairment of secretion through a process called glucotoxicity. Thus there is a loss of both β cell mass and function, resulting in the concept of decreased functional mass. Most people with insulin resistance never develop type 2 diabetes, which leads to the conclusion the β cell failure is the sine qua non for the development of the diabetic state.

Following from the above, the premise that β cell failure is the root cause of diabetes is conceptually very simple, which leads to the conclusion that the diabetic state should be reversed by administering insulin with injections, restoring β cell function with medication or by replenishment of the β cell deficit with transplantation or regeneration. Indeed, the all important proof-of-principle was achieved in the 1990s with the demonstration that both types 1 and 2 diabetes could be reversed with islet transplantation either as isolated islets placed in the liver or as whole organ pancreas transplants.

This second edition of "The Islets of Langerhans" is very timely, because in spite of the seeming simplicity of the basis of diabetes and progress with β cell replacement, we are still too far from our goal of providing these treatments for those in need. We need to understand islets on the most basic level so that preclinical therapeutic approaches can be explored and then taken to patients. The 49 chapters in "The Islets of Langerhans" provide up-to-date information on a carefully selected range of topics.

Important Unsolved Islet Puzzles

Knowing full well there are many opinions about which unsolved islet questions are most important, I will briefly mention a selection of issues that have captured my attention.

The islet as an organ The anatomy of islets is high organized with its cellular arrangements and islet-acinar portal blood flow. We know that β cell secretion has a major influence on glucagon secretion, but we have much to learn about the other interactions between beta, alpha and delta cells and how secretion from all of these influences downstream acinar cell development and maintenance. The role of the pancreatic polypeptide (PP) cells remains very much a mystery.

The mystery of glucose-stimulated insulin secretion (GSIS) For years we have had some understanding of the so-called K_{ATP} pathway of GSIS, yet we have little understanding of the quantitatively important K_{ATP}-independent pathway. This remains a major unsolved problem in β cell biology.

Finding new pharmacologic targets for insulin secretion Many of the chapters focus on the cell biology of insulin secretion, and there is much to be learned about these very basic facets, such is glucose and fat metabolism, ion and other transporters, mitochondrial function, calcium handling, phosphorylation reactions, insulin biosynthesis and more. A key question is how much more insulin secretion can we get out of a β cell? Simply put, if the cell is depolarized and fully stimulated by cyclic AMP, what approaches can be used to generate more insulin secretion?

Dedifferentiation of β cells and islet cell plasticity The phenotype of β cells in the diabetic state is deranged and accompanied by dysfunctional insulin secretion, with evidence pointing to glucotoxicity as the major driving force responsible for these changes. Restoration of normal glucose levels reverse these changes, but questions remain as to whether these β cells dedifferentiate toward a pluripotent progenitor state or some other distinct phenotype. The field is now swirling with the concept of islet cell plasticity, such as the potential alpha and delta cells being converted to β cells. There is also a big question about the alpha cell hyperplasia seen when glucagon action is inhibited: what is the signal of alpha cell growth?

The need for more β cells The β cell deficiency of diabetes could be restored by regeneration of new β cells in the pancreas or by transplanting β cells from some other source. As described in several chapters, this is one of the main priorities in diabetes research. Adult human β cells replicate very slowly but there has been great progress in understanding cell cycle mechanisms, which could somehow be exploited. Exciting progress has also be made with making mature β cells from human embryonic stem cells and from induced pluripotent stem cells. There have also been advances in exploiting the potential of exocrine multipotent progenitor cells and in bioengineering. Porcine cells also remain on the list.

Why do β cells die and how can this be prevented? We know that β cells in type 1 diabetes are killed by the immune system, and have watched impressive advances in defining the interactions among effector T cells, T regulatory cells, B cells, and the innate immune system. The process is very aggressive and there is a great need to control it with minimal or no immunosuppression. The Holy Grail is

restoration of tolerance. An old approach receiving renewed attention is encapsulation of islets to protect them from immune killing. The new biomaterials and approaches are exciting but we cannot yet be confident about its eventual value. In the context of type 2 diabetes much has been written about how β cells die, with mechanisms receiving the most attention being oxidative stress, endoplasmic reticulum stress, toxicity from IAPP oligomers, and the general concept of "overwork." The reality is that the death rate is very low and we have little idea about which mechanisms are the most important.

Of course there are many other important questions, but this sampling fits well with the contents of this valuable new edition of "The islets of Langerhans." Its chapters contain important information about these key questions, which make it likely that hours spent reading this book should help our field connect the critical dots that will result in new treatments for people with diabetes.

Gordon C. Weir, M.D.
Co-Head Section on Islet Cell & Regenerative Biology
Diabetes Health and Wellness Foundation Chair
Joslin Diabetes Center
Professor of Medicine
Harvard Medical School