Quantifying β-Cells in Health and Disease: The Past, the Present, and the Need

Through the studies of a number of pathologists, the past has taught us a great deal about islet pathology. A reduction in the quantity of β-cells in hyperglycemic individuals was described over 110 years ago by Eugene Opie (1) in an elegant report that included hand-drawn color micrographs. These illustrations clearly bring attention to the fact that the islet has lost numerous cells and that it also contains hyaline deposits, which we now recognize may be part of the destructive process. The past also included quantification of the number of endocrine cells by MacLean and Ogilvie (2) who demonstrated that β-cell mass is decreased in patients with phenotypic type 2 diabetes, but that the mass of α-cells is not diminished. And then, over 50 years ago, Bell (3) published a report of his studies of hyalinosis in islets that were based on the examination of pancreas sections from 3,959 individuals who were not known to have diabetes and 1,661 with diabetes. He observed hyaline to be more frequent in individuals with diabetes and that the number of affected individuals increased with age. While diabetes was certainly not the epidemic we now face, Bell stated in his commentary that "Hyaline islets are an expression of unrecognized or potential diabetes"—a clear recognition of the link of these deposits to diabetes and the problem of undiagnosed diabetes.

The present includes the study by Saisho et al. (4), which appears in this issue of *Diabetes Care*. This article builds on the past and the present. The authors describe their findings in pancreas samples obtained at the autopsies of 167 subjects with no known history of diabetes, who were lean or obese and ranged from 20 to 102 years of age. The authors report that obesity is associated with an increase in the number of β-cells and that with aging the number of β-cells appears to be well preserved, but the exocrine pancreas atrophies. Interestingly, they did not observe increases in either β-cell replication or apoptosis. These measures of β-cell turnover are made at a single point in time, and thus dynamic changes can easily be missed or may have occurred earlier in life. Such are the limitations of studies of the human pancreas. However, the use of human samples should not be ignored as they clearly inform and are essential since changes in animal models of diabetes, and particularly rodents, do not always duplicate those in human health or disease.

The obstacles faced in studying samples of human pancreas from a specimen bank are further highlighted in the study by Saisho et al. The authors used imaging technology in live humans to gain estimates of pancreas volume and have used these population-based volume data in conjunction with microscopy-based measurements on a small piece of pancreas to calculate changes in β-cell mass. While this is an interesting approach, it does not substitute fully for the determination of β-cell mass when morphological assessments—including endocrine cell quantification—are made on the same pancreas that has been dissected and weighed at the time of an autopsy. When the indirect and direct findings are similar, it is comforting and informative. However, when they are not, reality may be a lot more difficult to discern. This discrepancy is also highlighted in the article by Saisho et al., where the findings of no change in islet endocrine composition with aging contrast with the recent study by Rahier et al. (5), which reported aging to be associated with a small decline in β-cell mass.

What else have human studies in the present era taught us? First, the studies by Saisho et al. and others previously reported that obesity is associated with an increase in β-cells (5–7). Second, programmed cell death, known as apoptosis, is increased in type 2 diabetes and prediabetes and is associated with a decrease in β-cells (5,6,8,9). Third, the hyalinosis our predecessors described so well is amyloid, localized to the islet and the result of the aggregation of one of the β-cell's own secretory products, islet amyloid polypeptide (10). Fourth, the increase in β-cell apoptosis observed in diabetes is linked, at least in part, to increased islet amyloid deposition (9). And finally, the amyloid observed so classically in type 2 diabetes is also a nonimmune cause of the loss of β-cells following islet transplantation (11).

Present day cellular biology has provided us with insight into the mechanisms that may explain the loss of β-cell mass observed in type 2 diabetes. This knowledge has again relied in large part on work using animal tissues with some understanding derived from cultured human islets and autopsy samples. From these data it appears that glucose, fatty acids, and amyloid induce toxic effects on the β-cells that are not all mediated by the same mechanisms, but include the development of oxidative stress (12,13) and a more recently described process termed endoplasmic reticulum stress (14–16). The result of increased activity in these pathways is apoptosis, a form of programmed cell death, which has been demonstrated in human pancreas samples. It has also now been shown in human islets that exposure for a prolonged period to high glucose or to islet amyloid polypeptide induces inflammation (17,18). The result of this process is the production of the cytokine interleukin-1β, a molecule we have more traditionally considered to be a factor in β-cell loss in type 1 diabetes (19,20). Interesting avenues of exploration in the future will be to see whether the two forms of diabetes have more than cell loss and cytokine production as common features.

What then of the need? Clearly there are many—too many to detail here. However, to develop approaches that can slow or prevent the loss of β-cell mass that characterizes type 2 diabetes, we need a deeper understanding of its pathogenesis. We also need to answer the intriguing question of whether there is a genetic basis for this. Such is more than likely, given that many of the genes that have been identified are linked to the β-cell, and a number of them are related to molecules we may associate with cell growth rather than primarily function (21). However, to link genotype to a mass phenotype is going to take a Herculean effort in the number of samples on which we make estimates

of endocrine cell type. The morphological assessments could be through sample banks, but for many reasons the genotypic ones may be more difficult on archived samples. Thus, one may have to look forward to the development of novel technology that will allow us to add measurements of endocrine cell numbers in living individuals to our armamentarium. These will need to be sophisticated and sensitive, allowing us to discern decreases in cell numbers in individuals where the loss may be as little as 10%. As an alternative, and possibly as an early marker of disease onset or risk, markers of underlying damage such as "hyalinosis" (amyloid) could be targeted for imaging. Imaging methodology could also allow us to recognize whether targeted interventions can increase β-cell regeneration and restore β-cell numbers. Regardless of the magnitude of the challenge, human nature is such that groups have not shirked at the challenge, and progress has been reported (22). Thus, it is not unreasonable to expect the future will meet the need by continuing to build on the solid foundation laid by many in the past and the present.

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