Editorial

The Islet in Type 2 Diabetes: Back to Center Stage

Erol Cerasi, Christian Boitard, Suad Efendic, Ele Ferrannini, Jean-Claude Henquin, and Donald F. Steiner

This supplement heralds a new series of yearly workshops whose outcome will be published as a collection of review and research articles dedicated to a single theme: insulin secretion and β-cell biology, with emphasis on type 2 diabetes. The series is directed by the authors of this editorial and has been made possible by an unrestricted educational grant from Les Laboratoires Servier, Paris.

Why insulin secretion? Twenty-five years ago such a question would hardly have been raised. Work in several laboratories in the 1960s and 1970s had established beyond reasonable doubt that patients with type 2 diabetes or impaired glucose tolerance presented deranged insulin release kinetics and reduced insulin response to nutrients. The challenge to this view originated from the extraordinary developments over the ensuing two decades in the field of insulin receptor and glucose transporter biology and their translation into clinical investigation. Thus, insulin resistance became the *Leitmotiv* and dominated thinking, research, and treatment in type 2 diabetes. Diminished insulin efficacy had already been implicated as an etiological factor in non–insulin-dependent diabetes in the 1930s (1), and the presence of obesity in the vast majority of patients made it reasonable to assume that some degree of insulin resistance must exist in this disorder. Regretfully, however, the extensive publications of the 1980s and 1990s led to the almost universal acceptance that insulin resistance is the decisive defect in type 2 diabetes, that β-cells fare quite well (to the extent of inducing hyperinsulinemia) until late in the evolution of the disease, and that treatment must therefore be based on improving insulin sensitivity while giving low priority to agents that augment insulin delivery. Voices to the contrary have been raised both in the distant (2) and less distant (3,4) past and in the present (5,6); their impact has been limited, however, and insulin resistance still dominates the diabetes literature (e.g., the recent Perspective series in the *Journal of Clinical Investigation*: "On Diabetes: Insulin Resistance" [7–15]). The price paid has been diminished interest, hence research, in the islet field among basic scientists and in insulin secretion among clinical investigators, especially within the context of type 2 diabetes.

Recently, more balanced views have started to appear, as it has been realized that the biology of type 2 diabetes is not simple, that there exist few type 2 diabetic patients with pure β-cell defects or exclusively insulin resistance, and that in fact these two factors are interlinked (11,16,17). Nevertheless, it seems clear that without deranged insulin secretion, hyperglycemia cannot develop; thus, the β-cell *is* at the core of the problem, and much more research is needed on the normal and diseased islet if we wish to understand fully the pathophysiology of type 2 diabetes and identify more efficient therapeutic approaches. With this background in mind, the Servier-IGIS (International Group on Insulin Secretion) symposia have been designed to present the state-of-the-art on well-delineated topics pertinent to the β-cell in type 2 diabetes, with the hope that they may stimulate further basic and clinical investigation in this area.

The first Servier-IGIS Symposium, whose proceedings are presented here, has been dedicated to the question of β-cell survival in type 2 diabetes. This is a hot but controversial topic. Whereas data from several animal models of type 2 diabetes indicate that β-cell mass is reduced, this is not valid for all models, sometimes not even for different colonies of the same model. In humans, the situation is even more controversial because objective findings are so scarce. Furthermore, decreased or absent insulin secretion is often taken to indicate decreased β-cell mass. Even when there is access to the pancreas for quantitative morphology, the severe degranulation of β-cells observed in many animal models of type 2 diabetes renders the identification of a cell as a β-cell difficult, hence the element of uncertainty in determinations of β-cell mass. Nevertheless, there seems to be some degree of consensus in the diabetes community that, at least in its advanced stages, type 2 diabetes does present reduced β-cell mass. The question remains, however, as to how well-founded this assumption is.

In section 1 of this supplement, "β-Cell Differentiation and Growth," the reader will find the fundamentals of how β-cells develop and augment their mass. During the past decade, impressive progress has been made in the clarification of the molecular events that determine the fate of pluripotent cells in the embryo and direct them toward specific functions. These advances in developmental biology have helped us understand wherefrom emerge the cells that eventually form

From the Department of Endocrinology & Metabolism (E.C.), Hebrew University Hadassah Medical Center, Jerusalem, Israel; the Institut National de la Santé et de la Recherche Médicale U342 (C.B.), St. Vincent de Paul Hospital, Paris, France; the Department of Molecular Medicine (S.E.), Division of Endocrinology & Diabetes, Karolinska Hospital, Stockholm, Sweden; the Metabolism Unit (E.F.), CNR Institute of Clinical Physiology, University of Pisa, Pisa, Italy; the Department of Physiology, Endocrinology-Metabolism (J.-C.H.), Université Catholique de Louvain, Brussels, Belgium; and the Howard Hughes Medical Institute (D.F.S.), University of Chicago, Chicago, Illinois.

Address correspondence to E. Cerasi, Department of Endocrinology & Metabolism, Hadassah University Hospital, 91120 Jerusalem, Israel. E-mail: erol.cerasi@huji.ac.il.

The symposium and the publication of this article were made possible by an unrestricted educational grant from Les Laboratoires Servier.

the pancreas and the islet cells, emphasizing the dominating role that certain transcription factors play in these events. Nature again shows her sense of economy: many of the factors that direct the development of the embryonic islet are used again when new β-cells need to be generated in the adult organism. Indeed, we have learned in recent years that many tissues formerly thought to be finally differentiated and hence unreplaceable in the adult are plastic and renewable. The β-cell is no exception, as described in this section, which also emphasizes the importance of several hormones, growth factors, and substrates in this plasticity. The reader will also gain insight into the important (and often problematic) methodologies used to monitor β-cell mass and the factors that govern it.

Death is part of life, and tissue renewal requires cell death. Much of the information regarding the death of β-cells stems from studies in type 1 diabetes, a disease of β-cell death *par excellence*. Programmed cell death, apoptosis, seems to be the main mode of β-cell demise, though necrosis also occurs frequently. Section 2, "β-Cell Apoptosis," draws heavily on what has been learned over the past years from studying the mechanisms of islet destruction in type 1 diabetes, mainly in experimental systems and model animals. The situation in type 1 diabetes is complicated, since β-cell death mechanisms vary along the progression of the disease. Whereas initially a physiological β-cell apoptotic rate may be sufficient to present autoantigens and activate autoreactive T-cells, the massive β-cell death that occurs later in the disease results from direct lysis by cytotoxic T-cells or indirect lysis through the combined action of cytokines produced within the islet infiltrate. Obviously cytotoxic T-cells are not implicated in type 2 diabetes; in contrast, much can be learned from the mechanisms of cytokine action on β-cells. Moreover, for the investigator and clinician concerned with type 2 diabetes, a fascinating message emerges from section 2: Several physiological regulators of β-cell function, under given conditions, may ignite the apoptotic process. Thus, changes in ATP-dependent K^+ channel properties (a key player in the first steps of insulin secretion) may augment the β-cell death rate; also, several studies indicate that prolonged elevation of cytosolic Ca^{2+} (again, a prime physiological regulator of insulin release) causes apoptosis. This leads many researchers to the conclusion that despite wide differences in etiology, β-cell death in type 1 and type 2 diabetes may share common mechanisms and hence may be amenable to analogous therapeutic interventions aimed at preventing loss of β-cell mass. A further common trait may be the active participation of the β-cell in the decision to die or to survive. Indeed, findings in several laboratories suggest that whether a β-cell responds with apoptosis or survives the insult depends on independent factors, such as the metabolic state and perhaps the genetic background of a given β-cell population. Although this view is gaining increasing support in the field of type 1 diabetes, perusal of sections 3 and 4 of this supplement enhances the belief that the situation may be similar, if not identical, in type 2 diabetes, at least as far as animal models of the disease are concerned.

Section 3 deals with "β-Cell Function and Turnover: Genetic and Metabolic Factors." The metabolic part of the story is older and therefore more established: both experimental work and clinical observations have repeatedly shown that an islet subjected to chronic stimulation with glucose, for example, ends by showing some degree of failure. This is in harmony with the view presented in section 2 regarding the role of physiological regulators in β-cell death. Several papers in section 3, using different experimental models and approaches, arrived at the conclusion that the nature of the stimulus that drives the β-cell to fail (e.g., glucose) is not the determining factor; it is the act of being chronically stimulated that is important. Such is not, however, the thinking in the "lipotoxicity" hypothesis, in which specific lipid-related molecular events are postulated to modify β-cell behavior and lead to apoptosis. One problem with this hypothesis is that it is convincingly demonstrated only in models of extreme lipid overload, a situation not usual in the islets of many commonly used type 2 diabetes models. The hypothesis of "glucotoxicity" has gained wider support; one wonders, however, whether this simply reflects the age-old habit of equating everything bad in diabetes with hyperglycemia. What about genetic factors? In section 2 it was shown that the response of a β-cell to cytokine attack is variable on genetic grounds. As to type 2 diabetes, species differences in the sensitivity of islets to the deleterious effect of glucose, for example, are well established. Articles in section 3 relate findings from rat and gerbil populations bred to develop spontaneous or diet-induced diabetes. β-Cell mass reduction may be an important factor; e.g., in the gerbil model (*Psammomys obesus*) or in GK rats of the Paris colony (but not in the Stockholm GK colony—hence the impact of environment and/or subtle genetic derivations). Whereas β-cell mass reduction in GK rats, when present, seems to occur already in fetal life, in *P. obesus* it is clearly secondary to the diet-induced hyperglycemia; thus, genetic factors may be of importance in determining the sensitivity to metabolic insult, rather than being directly causative of β-cell death. Perhaps the clearest demonstration of genetic impact on β-cell function comes from studies in patients with maturity-onset diabetes of the young; indeed, this section presents an elegant analysis of the clinical correlates of mutations in the various transcription factors that play such a prominent role in β-cell development (read section 1 again!). The emerging message is that these mutations always compromise β-cell function, causing variable alterations of insulin secretion depending on the mutated transcription factor. Interestingly, the diabetes that ensues often lacks significant peripheral insulin resistance, and in the case of hepatocyte nuclear factor-1α mutations, hyperglycemia develops in the face of *increased* sensitivity to insulin action.

Section 4, "β-Cell Mass and Function in Type 2 Diabetes," centers on two fundamental questions: how β-cells adapt their insulin production rate and their mass to meet increased demand, and whether in human type 2 diabetes the β-cell death rate is augmented and leads to β-cell mass loss. The first question seems simple to answer, but has proven impossible to satisfy with the minimal criteria of scientific rigor. The issue is: What is the insulin production rate of a *normal* β-cell under *prolonged* hyperglycemic and insulin-resistant conditions? This control experiment being impossible to generate, we do not know what to expect from an islet in a type 2 diabetic organism that would enable the supposition that β-cell function has been modified. A striking example is the insulin receptor–deficient transgenic mouse. These die early with severe diabetes; nevertheless, initially their β-cell mass and pancreatic insulin content are normal. Does this indicate that the claimed neces-

sity of insulin and insulin receptor substrate protein action in β-cells for normal function (17 and this section) is wrong or that these pups should have demonstrated markedly augmented β-cell function as an adaptation to severe insulin resistance, which did not occur in the absence of autocrine insulin effect? As to the second question, this supplement reserves a surprise. Two European groups, reporting on the postmortem appearance of the pancreas in type 2 diabetic patients, found either no or only modest reduction in β-cells and minimal destruction of islets, even in patients with longstanding diabetes. Furthermore, in detailed studies, the Brussels group presents evidence of normal β-cell insulin expression and processing even in islets with substantial amyloid deposition. A striking finding was the overall modest difference in amyloid deposition between diabetic and age-matched control subjects and the degree of heterogeneity not only between patients (with no correlation to duration or level of disease control) but also between islets of a same pancreas.

What can be concluded from the reports presented in this supplement? That type 2 diabetes is a heterogeneous disease is an accepted fact, but it is also an easy way out of the dilemma. Obviously, the caveat regarding insulin secretion in the former paragraph also applies to the morphology of the islets in type 2 diabetes: Would it not be reasonable to expect grossly enlarged islets full of β-cells if the pancreas were normal in the hyperglycemic and insulin-resistant patient? Nevertheless, we cannot but accept the fact that gross depletion of β-cell mass is not a sine qua non feature of human type 2 diabetes: a further caveat regarding the use of animal models and the extrapolations to human diabetes that may be permissible; at best, the available animal models represent specific subtypes of the human disease. The conclusion that imposes itself, nevertheless, is that even if there may exist inadequacy in the ability of the β-cell mass to adapt to increased insulin demand, this can hardly be the main pathogenic factor in type 2 diabetes. Neither does amyloid deposition seem to be of a magnitude to explain the grossly reduced insulin production in the longstanding diabetic patient. Thus, we are left with the inability of the β-cell to secrete adequate amounts of insulin, which has constantly been demonstrated in type 2 diabetic patients from the early stage of impaired glucose tolerance on through the course of the disease. Major effort is therefore needed to clarify the mechanisms of insulin secretion in normal and pathological conditions.

ACKNOWLEDGMENTS

The authors, members of IGIS (International Group on Insulin Secretion), are grateful to Dr. Jean-Philippe Seta, CEO of Servier, for his long-term commitment to this project. Our sincere thanks go to Dr. Didier Halimi and Ms. Rowena McKeown (Paris) for their continuous logistic and other support. We also thank Dr. Gordon C. Weir, Editor-in-Chief of *Diabetes*, for his role in the preparation of this supplement.

REFERENCES

1. Himsworth HP: Diabetes mellitus: its differentiation into insulin sensitive and insulin insensitive types. *Lancet* i:1117–1121, 1936
2. Cerasi E, Luft R: Plasma insulin response to sustained hyperglycaemia induced by glucose infusion in human subjects. *Lancet* ii:1359–1361, 1963
3. Efendic S, Luft R, Wajngot A: Aspects of the pathogenesis of type 2 diabetes. *Endocr Rev* 5:395–410, 1984
4. Nesher R, Della Casa L, Litvin Y, Sinai J, Del Rio G, Pevsner B, Wax Y, Cerasi E: Insulin deficiency and insulin resistance in type 2 (non-insulin-dependent) diabetes: quantitative contributions of pancreatic and peripheral responses to glucose homeostasis. *Eur J Clin Invest* 17:266–274, 1987
5. Ilkova H, Glaser B, Tunçkale A, Bagriaçik N, Cerasi E: Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care* 20:1353–1356, 1997
6. Gerich JE: Insulin resistance is not necessarily an essential component of type 2 diabetes. *J Clin Endocrinol Metab* 85:2113–2115, 2000
7. Saltiel AR: The molecular and physiological basis of insulin resistance: emerging implications for metabolic and cardiovascular disease. *J Clin Invest* 106:163–164, 2000
8. Pessin JE, Saltiel AR: Signalling pathways in insulin action: molecular targets of insulin resistance. *J Clin Invest* 106:165–169, 2000
9. Shulman GI: Cellular mechanisms of insulin resistance. *J Clin Invest* 106:171–176, 2000
10. Stern MP: Strategies and prospects for finding insulin resistance genes. *J Clin Invest* 106:323–327, 2000
11. Cavaghan MK, Ehrman DA, Polonsky KS: Interactions between insulin resistance and insulin secretion in the development of glucose intolerance. *J Clin Invest* 106:329–333, 2000
12. Ginsberg HN: Insulin resistance and cardiovascular disease. *J Clin Invest* 106: 453–458, 2000
13. Kadowaki T: Insights into insulin resistance and type 2 diabetes from knockout mouse models. *J Clin Invest* 106:459–465, 2000
14. Olefsky JM: Treatment of insulin resistance with peroxisome proliferator-activated receptor γ agonists. *J Clin Invest* 106:467–472, 2000
15. Kahn BB, Flier JS: Obesity and insulin resistance. *J Clin Invest* 106:473–481, 2000
16. Cerasi E: Insulin deficiency and insulin resistance in the pathogenesis of type 2 diabetes: is a divorce possible? *Diabetologia* 38:992–997, 1995
17. Kulkarni RN, Bruning JC, Winnay JN, Postic C, Magnuson MA, Kahn CR: Tissue-specific knockout of the insulin receptor in pancreatic beta cells creates an insulin secretory defect similar to that in type 2 diabetes. *Cell* 96:329–339, 1999