The Juvenile Diabetes Research Foundation at Forty: Updates of Research in Type 1 Diabetes

Concepcion R. Nierras,[1] Mark A. Atkinson,[2] and Robert A. Goldstein[1]

Forty years ago, a small group of families founded an organization that has become known as the Juvenile Diabetes Research Foundation (JDRF), a group dedicated to finding a cure for type 1 diabetes and its complications through the support of research. JDRF implemented what at the time represented a distinctive paradigm: the involvement of lay volunteers in decisions regarding research funding, in developing and implementing policies pertaining to research directions, and in providing public advocacy for people with type 1 diabetes. This organizational format was generationally bold and provided a clear signal that JDRF's volunteers desired to partner with the scientific community and with all who shared their common agenda of helping individuals with type 1 diabetes. Over the years, JDRF has partnered with a diverse array of organizations with shared purpose, including the National Institutes of Health (NIH), various international funding organizations (e.g., European Association for the Study of Diabetes, Wellcome Trust, Australia National Health and Medical Research Council, Canadian Institutes for Health Research, Singapore A*STAR), and other foundations, most notably, the American Diabetes Association (ADA).

In 2010, the 40th anniversary of JDRF's founding, it seems propitious to provide an update relaying the progress this "community of the caring" has achieved in helping those with type 1 diabetes, and to call for a renewed purpose-driven dialogue among the many partners seeking to find a cure for this disease. To this end, JDRF is pleased to partner with *Diabetes* on a series of "Perspectives in Diabetes" articles that will inform and update readers on the current state of research progress in type 1 diabetes and its complications as well as provide guidance for the direction of future research efforts on this disease. The series of articles opened with the contribution on islet cell transplantation (1), and includes the discussion of the genetics of type 1 diabetes (2) in this issue. Other articles in the series will tackle such topics as the pancreatic pathology, immunotherapies for type 1 diabetes, clinical trials in type 1 diabetes, advances in the prevention and treatment of diabetic retinopathy, and β-cell development.

Looking back on research advances as well as on the implementation of improved therapeutics over the past few decades can, depending on the eye of the beholder, be viewed as one where the glass is currently either half full or half empty. In the 1970s, there was a growing appreciation that the etiologies of type 1 and type 2 diabetes were fundamentally different; that type 1 diabetes was characterized by a distinctive association with the human leukocyte antigens of the major histocompatibility complex as well as the presence of islet cell autoantibodies (3,4). Studies by Gepts (5) and others noted that patients with diabetes of juvenile onset were often characterized by the presence of a lymphocytic infiltrate in the pancreatic islets. With these results, type 1 diabetes widely became considered an autoimmune disease resulting from an immune-mediated destruction of pancreatic β-cells in genetically predisposed individuals (6). Today we know that the pathogenic processes underlying the disease may take a long time (i.e., months to years) for most individuals, and the autoimmune attack results in the "silent" β-cell loss until the point of symptomatic onset. Many of the cells of the immune system that are involved in β-cell destruction have been identified. We believe that when 50–90% of the β-cells have been destroyed (a facet that appears to vary depending on age, weight, genetics, and other factors), the resulting hyperglycemia is diagnosed as diabetes. Chronic hyperglycemia and dysregulated blood glucose levels lead to the complications of diabetes—microvascular and macrovascular end-organ damage. Even in this high-level view, investigators now recognize opportunities to intervene at a variety of stages in the disease process based on knowledge regarding the natural history of type 1 diabetes (Fig. 1).

Thanks to the contributions of many scientists, there have been distinctive successes in type 1 diabetes research. The Diabetes Complications and Control Trial (DCCT) definitively showed that tight control of blood glucose levels prevents the complications of type 1 diabetes (7). The Epidemiology of Diabetes Complications (EDIC) study, the continuation of the DCCT, continues to provide significant results regarding metabolic memory and its benefit in preventing complications (8). Islet transplantation has successfully reversed type 1 diabetes in select (albeit small) groups of patients, even if only transiently (9). The community has implemented and learned from a series of type 1 diabetes prevention trials; we now have a much more informed basis for future efforts (10,11). And recent trials (e.g., anti-CD3, Rituximab, and Diamyd) to preserve β-cell function in new-onset type 1 diabetic patients have shown promising results (12–15). This commentary will not recapitulate or discuss these studies; the various "Perspectives in Diabetes" articles will thoroughly present these details. The bottom line message of this series—beyond sharing both words of thanks and congratulations—is that, today, people diagnosed with type 1 diabetes are living better and longer (16).

From the [1]Juvenile Diabetes Research Foundation, New York, New York; and the [2]Departments of Pathology and Pediatrics, University of Florida College of Medicine, Gainesville, Forida.
Corresponding author: Robert A. Goldstein, gold@jdrf.org.
DOI: 10.2337/db10-0622

See accompanying article, p. 1561.

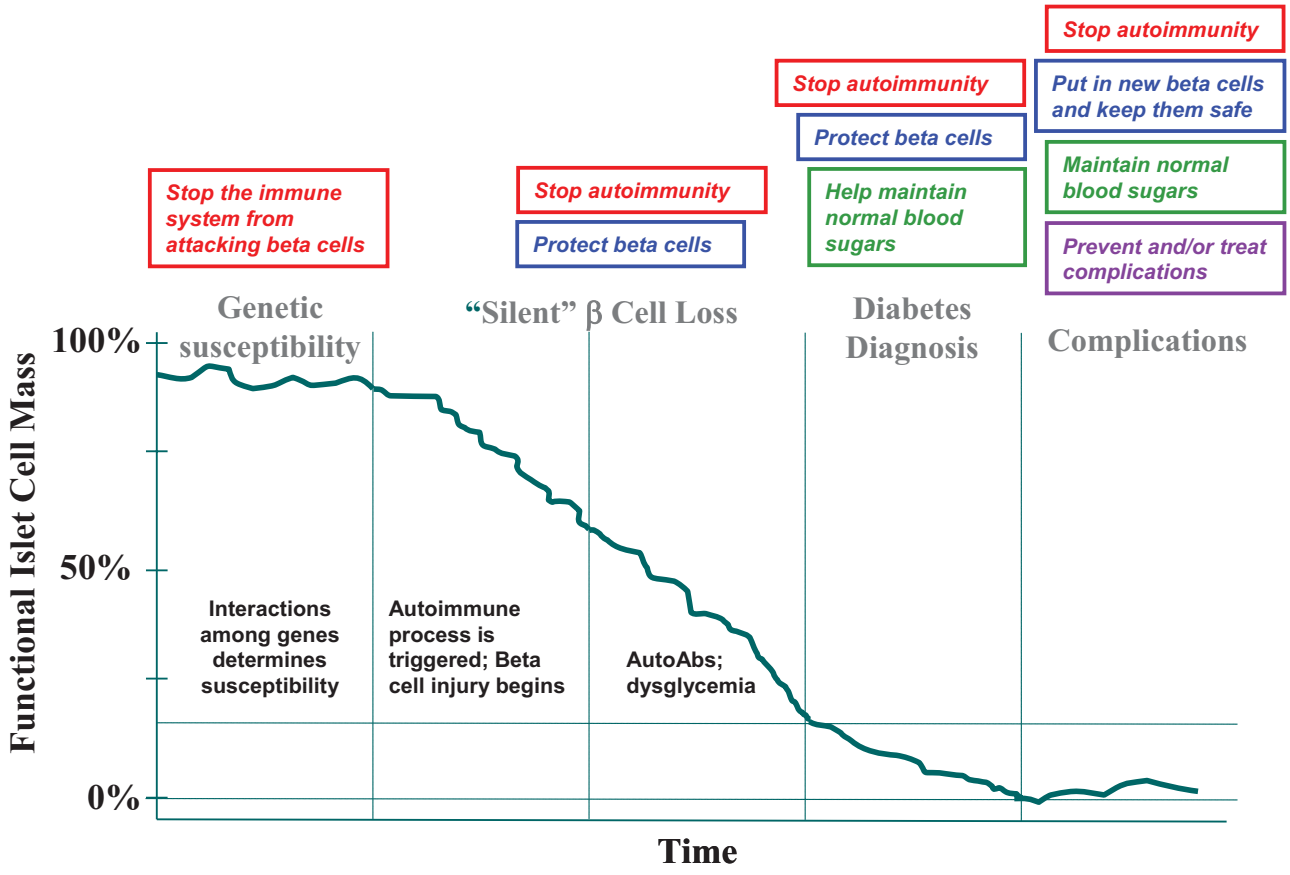

FIG. 1. The diagram outlines the natural history of type 1 diabetes and its complications (adapted from ref. 6). Therapeutic goals are mapped for each stage of disease. AutoAbs, to come from author.

What have we learned in our 40 years of effort? JDRF recently conducted an informal poll of scientists and asked them to nominate the research highlights of the last 40 years. There were many, many suggestions, but the lessons learned may be summarized as:

1) Type 1 diabetes is different from other forms of diabetes because of autoimmunity. We need to halt the autoimmune response at every stage of disease.
2) The β-cell is the focus of all forms of diabetes. In type 1 diabetes, we will need to replace lost β-cells or regrow new ones.
3) Controlling blood glucose is the key to preventing complications.
4) There are common pathways that lead to multiple complications.

Even as these statements highlight research progress, they also call attention to current challenges, areas of active investigation, and surprising discoveries to come.

We still have much to learn about the pathways that lead to type 1 diabetes. We also must identify the environmental triggers that precipitate and/or propagate the autoimmune process. We are only just beginning to appreciate the extent of heterogeneity of human disease with intriguing but still early results from the Network for Pancreatic Organ Donors with Diabetes (nPOD) effort (17). We need to understand the immune pathways that lead to disease, to identify better biomarkers, and to develop immune therapies. We must more fully characterize the metabolic potential in both new-onset and established type 1 diabetes. We need to fully elucidate the details of β-cell development. Many active efforts to improve islet transplantation remain and must be explored. We must investigate in detail the effects of chronic hyperglycemia at both a system-wide and an organ-specific level. These research activities will, collectively, produce the opportunities required to prevent, treat, and cure type 1 diabetes.

One vital lesson learned from the last 40 years is that the combined efforts of a great many people will be required to achieve the goal of a cure for all people with type 1 diabetes. Put another way: partnering creates opportunities. There is a partnership between the research community and the volunteers who participate in clinical research, serve as advocates, and raise money. Partnerships with NIH have supported research consortia, fostered innovative new programs, and made significant research resources available to investigators interested in studying type 1 diabetes (18). Partnerships among funding organizations, foundations, and enterprises have increased opportunities for research in type 1 diabetes. We will continue to explore different ways to engage research scientists, drug developers, regulatory agencies, and other funders to the purpose of helping individuals with type 1 diabetes.

The opportunities to impact this disease have never been greater. Working together, we will achieve our goal of a cure.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

C.R.N. wrote and edited the manuscript. M.A.A. organized the project, contributed to the discussion, and reviewed and edited the manuscript. R.A.G. contributed to discussion and reviewed and edited the manuscript.

The authors wish to thank the contributing authors to the "Perspectives in Diabetes" series; Teo Staeva, Jessica Dunne, Olivia Lou, Adrianne Wong, and Albert Hwa, JDRF, for their comments on this manuscript; and all those who have shared in the journey to find a cure for type 1 diabetes.

REFERENCES

1. Pociot F, Akolkar B, Concannon P, Erlich HA, Julier C, Morahan G, Nierras CR, Todd JA, Rich SS, Nerup J. Genetics of type 1 diabetes: what's next? Diabetes 2010;59:1561–1571
2. Robertson PR. Islet transplantation a decade later: strategies for filling a half full glass. Diabetes 2010;59:1285–1291
3. Nerup J, Platz P, Andersen OO, Christy M, Lyngsoe J, Poulsen JE, Ryder LP, Nielsen LS, Thomsen M, Svejgaard A. HL-A antigens and diabetes mellitus. Lancet 1974;2:864–866
4. Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet 1974;2:1279–1283
5. Gepts W. Pathologic anatomy of the pancreas in juvenile diabetes mellitus. Diabetes 1965;14:619–633
6. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet 2001;358:221–229
7. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
8. Molitch ME, Steffes M, Sun W, Rutledge B, Cleary P, de Boer IH, Zinman B, Lachin J; for the Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Diabetes Care 2010;33:1536–1543
9. Halban PA, German MS, Kahn SE, Weir GC. Current status of islet cell replacement and regeneration therapy. J Clin Endocrinol Metab 2010;95:1034–1043
10. Ziegler AG, Nepom GT. Prediction and pathogenesis in type 1 diabetes. Immunity 2010;32:468–478
11. Skyler JS, Type 1 Diabetes TrialNet Study Group. Update on worldwide efforts to prevent type 1 diabetes. Ann N Y Acad Sci 2008;1150:190–196
12. Chatenoud L. Immune therapy for type 1 diabetes mellitus: what is unique about anti-CD3 antibodies? Nat Rev Endocrinol 2010;6:149–157
13. Herold KC, Gitelman S, Greenbaum C, Puck J, Hagopian W, Gottlieb P, Sayre P, Bianchine P, Wong E, Seyfert-Margolis V, Bourcier K, Bluestone JA, Immune Tolerance Network ITN007AI Study Group. Treatment of patients with new onset type 1 diabetes with a single course of anti-CD3 mAb Teplizumab preserves insulin production for up to 5 years. Clin Immunol 2009;132:166–173
14. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, Gottlieb PA, Marks JB, McGee PF, Moran AM, Raskin P, Rodriguez H, Schatz DA, Wherrett D, Wilson DM, Lachin JM, Skyler JS, Type 1 Diabetes TrialNet Anti-CD20 Study Group. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med 2009;361:2143–2152
15. Ludvigsson J, Faresjö M, Hjorth M, Axelsson S, Chéramy M, Pihl M, Vaarala O, Forsander G, Ivarsson S, Johansson C, Lindh A, Nilsson NO, Aman J, Ortqvist E, Zerhouni P, Casas R. GAD treatment and insulin secretion in recent-onset type 1 diabetes. N Engl J Med 2008;59:1909–1920
16. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diabetes 2006;55:1463–1469
17. Juvenile Diabetes Research Foundation International. Network for Pancreatic Organ Donors with Diabetes (nPOD) [Internet], 2009. Available from http://jdrfnpod.org/. Accesssed May 25, 2010
18. U.S. Department of Health and Human Services. National Institute of Diabetes and Digestive and Kidney Diseases: Type 1 Diabetes (T1D) Special Statutory Funding Program–Opportunities for Type 1 Diabetes Investigators [Internet], 2006. Available from http://t1diabetes.nih.gov/funding.shtml. Accessed May 25, 2010