Dreams for Type 1 Diabetes: Shutting Off Autoimmunity and Stimulating \( \beta \)-Cell Regeneration

Gordon C. Weir and Susan Bonner-Weir

Section on Islet Cell Biology and Regenerative Medicine, Research Division, Joslin Diabetes Center, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts 02215

Although not the first study to show that inhibitors of dipeptidyl peptidase IV (DPP-IV) can reverse newly diagnosed diabetes in nonobese diabetic (NOD) mice (1), a study by Tian et al. (2) in this issue of *Endocrinology* confirms this finding with a different DPP-IV inhibitor (NVP-DPP728) and provides explanations for the reversal by finding reduced islet inflammation, increases in CD4+CD25+FoxP3+ regulatory T cells, and \( \beta \)-cell regeneration. Impressively, 6 wk of treatment with this agent reversed diabetes in 73% of the mice. DPP-IV inhibitors are used clinically to treat diabetes because they slow the breakdown of the incretin hormone glucagon-like peptide 1 (GLP-1), which can stimulate insulin secretion, inhibit \( \beta \)-cell apoptosis, and promote \( \beta \)-cell replication (3).

However, these inhibitors have long been known to have effects on the immune system, which presumably contributed to the marked reduction in islet inflammation. In particular, lymphocytes have a membrane-associated protein with DPP-IV activity, CD26, which has been shown to have important effects upon T-cell development, migration, and cytokine production (4). It has been previously shown that inhibition of DPP-IV can slow the progression of experimental allergic encephalitis and increase the production of TGF-\( \beta \), which is known to suppress autoimmunity (5).

In the present study, the reversal of diabetes was accompanied by a reduction of insulitis, an increase in CD4+CD25+FoxP3+ regulatory T cells, and an increase in circulating TGF-\( \beta \). Interestingly, the regulatory T cells were particularly plentiful in the thymus and pancreatic lymph nodes.

It is possible that the therapeutic benefit of the present study is not completely due to the effects of DPP-IV inhibition on the immune system but in part a result of increased circulating levels of GLP-1. Inhibition of CD26 is an attractive mechanism, but the actual contribution from this specific mechanism remains to be defined. It is even possible that GLP-1 can somehow ameliorate immune killing of \( \beta \)-cells independently of DPP-IV. We certainly have much more to learn about the effects of GLP-1 on the immune system (3). It is noteworthy that the combination of GLP-1 and gastrin has been shown to reverse diabetes in NOD mice, and this reversal was even seen in some mice with just GLP-1 treatment alone (6). The effect of GLP-1 on the target of the immune attack, the \( \beta \)-cell, may be very important. GLP-1 is known to have an antiapoptotic effect upon \( \beta \)-cells, probably by bolstering the insulin receptor substrate 2 signaling pathway (7, 8). Therefore, it is possible that a reduction of \( \beta \)-cell death and less release of antigen could somehow influence the balance of T-cell regulation and slow the rate of immune destruction. Clearly, more work is needed to sort out the relative contributions of DPP-IV inhibition and GLP-1 agonism.

Another addition to the equation is gastrin, the circulating levels of which can be increased with either injections of the peptide or the use of proton pump inhibitors. We know that gastrin given in combination with either epidermal growth factor or GLP-1 agonism can stimulate \( \beta \)-cell regeneration (6, 9). Now we must ask how gastrin might contribute to reduced autoimmune destruction.

The demonstration of \( \beta \)-cell regeneration, accompanied by increased \( \beta \)-cell replication, is similar to what has been found with some other but not all interventions that reverse diabetes in NOD mice. It seems likely that increases in \( \beta \)-cell mass result from replication of residual \( \beta \)-cells, although there is a provocative recent report sug-

Abbreviations: DPP-IV, Dipeptidyl peptidase IV; GLP-1, glucagon-like peptide 1; NOD, nonobese diabetic.
gesting that, during regeneration, new β-cells can be formed from transdifferentiation of islet α-cells (10). The α-1 antitrypsin treatment, which can also reverse diabetes in NOD mice and restored self-tolerance, is associated with impressive β-cell regeneration (11). There are other treatments that reverse diabetes in NOD mice, but for unclear reasons do not seem to have β-cell regeneration. These include treatment with anti-CD3 (12) and treatment with a combination of rapamycin, an IL-2 agonist, and an IL-15 antagonist (13). It may be that improvement in glycemia is in part also due to improved insulin action by reduction of inflammation and by improved insulin secretion due to lessening of glucotoxicity (14). When regeneration does occur, it is important but limited. In the present study, the insulin content of the pancreas was restored from about 5% to 35% of normal, but this could represent regranulation of β-cells rather than a comparable increase in β-cell mass. In the α-1 antitrypsin AAT study, β-cell mass was increased from 12% to 45% of normal. We know from anti-CD3 studies in NOD mice that diabetes can only be restored if treatment is instituted within a few days after the onset of hyperglycemia (15, 16). It appears that a critical number of β-cells must be present to allow significant regeneration and/or restoration of insulin secretion. The most important factor stimulating β-cell replication is probably hyperglycemia, although it seems that this process can be enhanced by therapeutic intervention with agents such as GLP-1 receptor agonists (17). No evidence in NOD mice has emerged pointing to a contribution from neogenesis, but because GLP-1 agonism can stimulate neogenesis in rodents (18), the possibility remains open.

A major hope for type 1 diabetes is that reversal of autoimmunity in humans during progression toward diabetes might be accompanied by β-cell regeneration. A number of interventions have been shown to delay progression of β-cell destruction in individuals with newly diagnosed diabetes (19–21). While some impressive remissions have occurred (21), there is little evidence that the improvements were due to increases in β-cell mass. The lack of methods to measure β-cell mass must make us cautious in drawing such a conclusion, but the improvement in insulin secretion is rapid, which fits well with reversal of glucotoxicity. A more gradual improvement in glycemia with a fall in insulin requirements might have been more suggestive of β-cell regeneration. Nonetheless, the possibility that regeneration might be enhanced through stimulation of neogenesis and/or β-cell replication remains a tantalizing possibility (22). We now know that the progression of type 1 diabetes can be slowed through inhibition of the adaptive immune system and inflammation. In addition to these approaches, we must now sort out the potential benefits of various combinations of DPP-IV inhibitors, GLP-1 agonism, and gastrin.

Acknowledgments
Address all correspondence and requests for reprints to: Gordon C. Weir, M.D., Section on Islet Cell Biology and Regenerative Medicine, Joslin Diabetes Center, One Joslin Place, Boston, Massachusetts 02215. E-mail: gordon.weir@joslin.harvard.edu.

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