for weight management. Weight gain after discontinuation of semaglutide and tirzepatide has been reported.[5,6] I am eager to read the results of Part 2 of the current trial, when available, exploring nadir weight and strategies for weight maintenance. I imagine that patients would be receptive to a monthly injection as a long-term strategy for weight maintenance. Many are already experimenting with less frequent administration of available agents despite a lack of proven evidence.

My enthusiasm for progress in this field is tempered by factors outside of medicine — factors that my medical degree make me ill equipped to manage. Yet, they represent the most common barrier to access and long-term adherence to these medications: costs and coverage. Diabetes and obesity are common threats to our health and longevity but are not viewed equally. Consider that different preparations of the same medication are marketed separately for diabetes and obesity. When these drugs are prescribed for obesity, obstacles arise. How will this agent be priced? Will insurance companies cover it? Will prior authorization be required? Will there be a monetary cap? Will available coupons make them affordable for my patient?

The development of incretin-based therapies is a triumph in the management of diabetes and obesity. For patients with obesity, this triumph is hampered by factors outside a physician's medical decision making. Complex factors beyond the scope of this editorial must be conquered if we are to realize the potential that these medications offer to the millions of persons with obesity and its complications.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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SCIENCE BEHIND THE STUDY

Replacement of Beta Cells for Type 1 Diabetes

Kevan C. Herold, M.D.,[1,2] and Jordan S. Pober, M.D., Ph.D.[1,2]

For more than 100 years, replacing insulin by injection has been the only treatment for clinical stage 3 (symptomatic) type 1 diabetes (see Key Concepts). Advanced techniques for insulin delivery still lack the precision, rapid kinetics, and flexibility that endogenous insulin-producing beta cells can achieve. Despite initial successes with the transplantation of cadaver-derived islets,[1] the requirement for multiple donors and failure to maintain insulin independence prompted further research to identify alternative sources of beta cells and new antirejection strategies.[2] In this issue of the *Journal*, Reichman et al.[3] and Carlsson et al.[4] report advances on each front.

KEY CONCEPTS

Immunosuppression

The inhibition of unwanted immune responses. In the context of allotransplantation, it is used to suppress immune responses that would otherwise result in the rejection of a foreign (or histoincompatible) organ or cellular graft. Immunosuppressive drugs are also used to treat autoimmune and inflammatory diseases. These drugs eliminate or block the activity of immune cells and soluble mediators secreted by immune cells (e.g., cytokines and antibodies) that recruit other immune cells. Immunosuppression can also occur as an unwanted side effect of drugs used in chemotherapy and as a consequence of an underlying pathologic process (e.g., cancer).

Induced pluripotent stem cell

A type of pluripotent stem cell derived from a nonpluripotent cell, typically an adult somatic cell such as a fibroblast, by transfection and the forced expression of stem-cell–associated genes.

Major histocompatibility complex (MHC)

A complex of linked genes encoding cell-surface proteins that display peptides produced by cleavage of intracellular proteins (in the case of class I MHC) or extracellular proteins that are processed (in the case of class II MHC). These molecules help T cells recognize foreign or mutated proteins. The human form of MHC is referred to as HLA.

Natural killer (NK) cell

A type of cytotoxic lymphocyte critical to the function of the innate immune system.

Type 1 diabetes

A chronic autoimmune disease caused by the immune-mediated destruction of insulin-producing pancreatic beta cells. It is one of the most common chronic diseases of childhood but can manifest at any age. Once beta cells are destroyed, they do not recover, and lifelong insulin replacement is required. Approaches involving the transplantation of insulin-producing beta cells are under clinical investigation.

An illustrated glossary is available at NEJM.org

MAKING BETA CELLS FROM STEM CELLS

Reichman et al. report results from patients with type 1 diabetes who received zimislecel, clusters of islet cells differentiated from a line of human embryonic stem cells[5] (Fig. 1). They administered the clusters of differentiated islet cells by infusion into the portal vein, coupled with glucocorticoid-free immunosuppression. The transplant achieved the primary objective of eliminating severe hypoglycemia; it improved glucose control (i.e., lowered the glycated hemoglobin level) and, in 10 of the 12 participants, eliminated the need for exogenous insulin. Cadaver-derived islets that are introduced in this manner are likely to lodge within the hepatic sinusoids and depend on diffusion for nutrients. In the normal pancreas, the islet microvasculature furnishes nutrients to cells throughout the islet, and the vascular basement membrane, vascular cells, and pericytes are implicated in beta-cell function, proliferation, and responses to inflammation. The absence of microvessels in the islet clusters may partly shield the transplanted beta cells from host immune responses; sustained immunosuppression is required to prevent rejection, increasing the risk of infection (infection caused the death of one patient in the study) and cancer. Whether the transplanted clusters will survive over the long term remains to be seen, and the regimen that was used does not obviously prevent progressive chronic rejection, which involves immune mechanisms distinct from those that mediate acute rejection.[7]

BELOW THE RADAR OF ADAPTIVE IMMUNITY?

Carlsson et al. describe a "three-hit" approach to evade acute rejection. Through genetic engineering, they created "hypoimmune islets" and tested them in a single patient. Intact islets were isolated from a pancreas donor with blood type O, dispersed into single cells, and genetically disrupted (with the use of nuclease Cas12b [clustered regularly interspaced short palindromic repeats {CRISPR}–CRISPR-associated protein 12b] and guide RNAs[8]) to eliminate the expression of class I and II major histocompatibility complex (MHC) molecules (Fig. 1). In the single participant, there was sustained production of insulin by the graft without the need for immune suppressants. MHC molecules are the most polymorphic

proteins encoded by the human genome, and two unrelated persons are unlikely to share all six alleles encoding the three class I loci and the three class II loci. Physiologically, these proteins serve as scaffolds that display antigens (peptides derived from other proteins) to T cells. In the context of a transplant, they are the major targets of rejection by the recipient's immune response.[9]

MUTING MHCI

CD8+ killer T cells may directly recognize nonself class I MHC molecules (HLA-A, -B, and -C) on graft islet cells, triggering beta-cell loss. β_2-microglobulin is an invariant component of class I MHC molecules; disrupting the gene that encodes it (*B2M*) prevents all class I molecules from being expressed. Carlsson et al. therefore sought to inactivate *B2M* through disrupting this gene.

MUTING MHCII

In organ transplantation, matching MHC alleles between donor and recipient weakens the allogeneic immune response, but even "fully matched" graft beta cells may be vulnerable to autoimmune destruction. This vulnerabity occurs because CD4+ effector T cells contribute to rejection by activating CD8+ T cells, antibody-producing B cells, and innate immune cells. To do so, CD4+ T cells must recognize antigens presented by class II MHC molecules on the surface of specialized antigen-presenting cells. In the context of a transplant, CD4+ T cells may cross-react to class II MHC on the cells of the graft (direct recognition) or shed intact graft class II MHC displayed on host dendritic cells (semi-direct recognition) or even peptides from degraded graft cells that can bind to self class II MHC on host dendritic cells and trigger CD4+ T-cell activation (indirect recognition). Carlsson et al. therefore set about inactivating all three class II MHC proteins (HLA-DR, -DP, and -DQ) by disrupting a single gene, *CIITA*, which encodes a protein essential for the synthesis of MHC class II proteins.

Finally, in addition to acute T-cell–mediated rejection, allogeneic cells are also subject to antibody-mediated rejection by preexisting or de novo (post-transplantation) antidonor antibodies. Because these antibodies primarily target nonself MHC molecules on donor cells, eliminating expression of class I and II MHC molecules should be protective.[10]

WHAT ABOUT INNATE IMMUNITY?

Innate immune cells may also attack foreign cells and contribute to rejection in the absence of T-cell–mediated or antibody-mediated activation. Macrophages may recognize and attack foreign cells with the use of leukocyte-like immunoglobulin receptor. Natural killer (NK) cells may attack foreign cells when their inhibitory killer immunoglobulin-like receptors sense the absence of self HLA-C or -B (i.e., missing self). To limit this, Carlsson et al. transfected the disbursed islet cells with a lentiviral vector containing *CD47*, which encodes a protein that induces an inhibitory ("don't eat me") signal to myeloid cells (Fig. 1).[11] The transfected cells rebuffed both blood monocytes and NK cells of the transplant recipient in studies in vitro.

The modified islets were introduced by intramuscular injection rather than portal-vein infusion and continued to function with no immunosuppression for the 12-week duration of the study. Although many of the islet cells showed only partial modifications or no modification (i.e., had a subset or even none of the intended genetic changes), the treatment was sufficient to limit host antigraft immune responses as assessed by post-transplant assays of cytotoxicity mediated by T cells, antibodies, and innate immune cells. Still, 12 weeks is short, and the extent of perfusion of the islets after intramuscular injection is unknown.

WHAT'S NEXT?

These studies are encouraging but preliminary. Additional and careful follow-up is essential to establish long-term efficacy and safety. The potential clinical benefits are substantial. Reichman et al. found that severe hypoglycemia was prevented in participants who received the full dose of zimislecel, a potentially limitless source of islets. The experience with hypoimmune islets was with a single participant who received less than 10% of the number needed for insulin independence; here, the methods of islet isolation and preparation are limiting. The genetic engineering used by Carlsson et al. could be applied to stem cells to obviate the need for immune

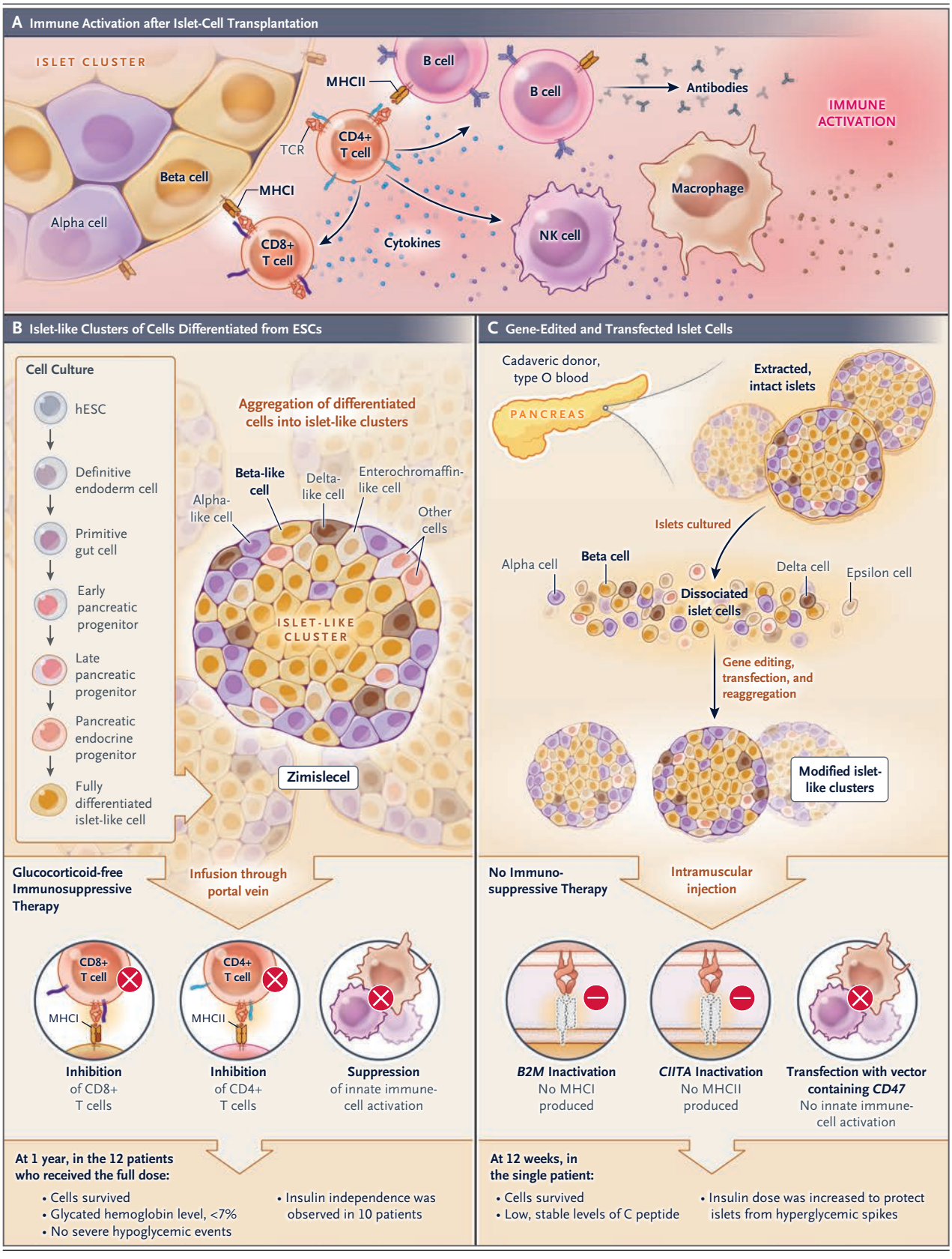

Figure 1 (facing page). Overcoming Barriers to Replacement of Beta Cells.

Immune recognition of transplanted cells involves the coordinated activity of adaptive and innate immune cells (Panel A). CD8+ T cells can recognize class I major histocompatibility complex (MHC) molecules and kill the graft, but there is also presentation of antigens that are derived from the graft and of class II MHC molecules to CD4+ T cells, with release of cytokines, activation of B cells that can produce antibodies against MHC molecules on the graft, and innate immune cells. Reichman et al.[3] describe the derivation of differentiated isletlike clusters from a line of human embryonic stem cells (hESC) line, involving culture with specific agents and associations with specific gene-expression signatures as they pass through six stages (Panel B).[6] They then infused the clustered islet cells into the portal vein of patients with type 1 diabetes. To prevent rejection of the transplanted clusters through the recognition of the cells by the recipients' immune systems, the study participants were given immunosuppressive therapy before receiving the cells and as a maintenance therapy after infusion. Carlsson et al.[4] harvested islets of Langerhans from the pancreas from an organ donor, dissociated the cells, and then altered them to render them resistant to rejection by the recipient's immune system (Panel C). More specifically, they shut down the expression of class I and II MHC genes through the inactivation of the genes *B2M* and *CIITA* and then transfected the edited cells with a gene encoding *CD47*, which inhibits innate immune cells. These "hypoimmune islets" produced insulin for 12 weeks in the absence of immunosuppression in one patient after implantation in the forearm muscle. ESC denotes embryonic stem cell, NK natural killer, and TCR T-cell receptor.

suppression.[12] An alternative strategy to prevent transplant allorejection would be to use islet organoids obtained from induced pluripotent stem cells derived from the patient.[13]

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Antiquated Tools to Fight an Ancient Foe

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Syphilis is one of the oldest known diseases. Approximately 209,000 cases were reported in the United States in 2023 — the highest number of reported cases since 1950 — including nearly 4000 congenital syphilis cases, which resulted in 279 stillbirths or infant deaths.[2] Our ability to prevent and control this infection has been limited by relatively few advances in the diagnosis and treatment of syphilis in the past 75 years. Diagnosis continues to rely on serologic markers of infection, which do not differentiate between treated and untreated infection and are difficult even for a syphilologist to interpret. Treatment has relied on a single drug (penicillin G) since