Islet transplantation is a treatment for diabetes that has the potential to normalize glucose levels and prevent the development of complications. In spite of the simplicity of the concept and the urgent need to provide such a treatment to patients, there has been a frustrating lack of progress. This perspective delves into the scientific and political impediments to success. The scientific barriers are the need to find a satisfactory source of insulin-producing tissue and the requirement to prevent this tissue from being destroyed by immune rejection and autoimmunity. The problems and potential of allografts, xenografts, and the development of cell lines are discussed. Multiple approaches to the prevention of immune destruction are considered, including immunobarrier devices, immunosuppression, development of tolerance, and genetic manipulation. The political barriers discussed include the problems of high expectations, the controversy surrounding targeted research, the balance between basic and applied research, the roles of industry and academia, the concerns about xenotransplantation, and the difficulties in developing a planned approach to the problem. *Diabetes* 46:1247-1256, 1997

Islet transplantation may be the most emotionally charged area in diabetes research because its availability would provide the equivalent of a cure, bringing not only freedom from the burdens of injections, glucose testing, and dietary restriction, but even more importantly, protection from the dreaded complications of diabetes. In the early 1970s, islet transplantation was found to cure diabetes in rats and mice (1,2). Because of the ease of this success, there were widely publicized predictions that a cure for diabetes was only a few years away; yet more than 25 years later, we can only provide successful islet transplants for a small handful of patients. The failure to meet these early expectations has become especially frustrating because even our most modern methods of treatment cannot provide good enough glycemic control to prevent most patients from developing complications. Many impatient observers and participants do not understand why islet transplantation is taking such a long time. The simple answer is that it is a hard problem. The purpose of this perspective is to discuss the scientific and political barriers responsible for this frustrating delay, with the hope of stimulating new thinking about how to accelerate our progress.

**SCIENTIFIC IMPEDIMENTS**

**Current state of the art for islet transplantation in humans.** Some forget that islet transplants are now being provided to a relatively small number of people with diabetes in the form of pancreas transplants and islet allografts or autografts. Recipients of these transplants can sometimes maintain perfectly normal glucose levels without insulin therapy for years and have essentially been cured of their diabetes. These pioneering efforts not only have provided hope and an example of what is possible, but have also furnished an important scientific foundation for the future.

**Pancreas transplantation.** Pancreas transplants, which are a form of islet transplantation, began as experiments in the mid 1960s and by the late 1980s became an accepted therapy now provided by many medical centers (3,4). These are mostly simultaneous kidney-pancreas transplants, provided to patients who would otherwise be receiving a kidney alone. Good graft function with insulin independence 1 year after surgery can be expected in ~80% of patients, and after 5 years, almost 50% of the recipients maintain their euglycemia. The results obtained with pancreas transplantation alone are not quite as good (5). Because so many of these patients already have advanced complications, it is not surprising that this treatment at best has only a stabilizing effect on the complications. Of concern, there is growing awareness that this surgery is associated with a considerable amount of morbidity and even a likely excess of mortality compared with patients with diabetes who receive a kidney alone (6). However, the quality of life for successful recipients is clearly enhanced (7). Recently, increased attention has been paid to patients without kidney failure who have serious problems, such as hypoglycemia unawareness, that make their lives miserable. For this small number of patients, the risk of immunosuppression and the complications of surgery are rational exchanges for good glycemic control. Although the results of pancreas transplantation should improve as surgical techniques become further refined and immunosuppression regimens become less toxic, an unavoidable limitation will be the finite number of pancreases available for transplantation.

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From the Research Division, Joslin Diabetes Center; the Departments of Medicine of Beth Israel Deaconess Medical Center and Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts.

Address correspondence and reprint requests to Dr. Gordon C. Weir, Research Division, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215. E-mail: weirg@joslab.harvard.edu.

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ADA, American Diabetes Association; AIDS, acquired immunodeficiency syndrome; IL, interleukin; JDFI, Juvenile Diabetes Foundation International; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health.
Human islet allografts. After years of research developing methods to isolate islets from large animals and exploring different transplant sites, it finally became possible to begin serious islet transplants in the late 1980s. Islets obtained from cadaver donors were transplanted into the liver via the portal vein of immunosuppressed patients with kidney transplants (8–12). In many cases, islets from more than one pancreas were used, an advantage provided by islet cryopreservation (13). The first reports of insulin independence were exciting, but the results turned disappointing as it became apparent that most recipients remained hyperglycemic. By the end of 1995, of 270 type 1 diabetic patients with adult islet allografts reported to the International Transplant Registry (14), only 27 (10%) became insulin independent for >1 week, 14 (5%) were insulin independent at ≥1 year after the transplant, and 1 patient had been insulin independent for 4 years. Instructive results have emerged from patients who have had pancreatectomy and hepatectomy for extensive abdominal cancer, followed by simultaneous islet and liver grafts: 9 of 15 (60%) have become insulin independent (14). Eventually, all of the patients in this group succumbed to their malignancy, although one remained insulin independent for 5 years until her death. The reasons for the improved results are uncertain, but the islets faced only transplant rejection and not autoimmunity, and the cotransplantation of the liver may have modulated the rejection process.

In spite of this apparent lack of success with allografts, there are important positive aspects to these results. First, insulin independence is not the only definition of success; many of those still dependent on insulin have had persisting C-peptide secretion, a reduction of insulin dose, and improvement in stability of glycemic control, which often has meant less danger of serious episodes of hypoglycemia. Second, with experience, the results have been improving as more attention is paid to the characteristics and quantity of the transplanted islets, the type of immunosuppression, and various other details. Third, even partial success must be considered important progress. Although these transplants might still be considered to be experimental, as more patients obtain benefits, human islet allografts should soon be considered a bona fide treatment option for a small number of patients.

Human islet autografts. The experience with autografts, which are mostly done for painful pancreatitis, has been even more impressive (3,15,16). The introduction of islets into the liver through the portal vein is the same as with allografts, but the islet preparations are typically less pure, containing various exocrine and ductal elements. Of 31 well-documented cases, 24 (77%) became insulin independent, with 1 patient remaining so for over 13 years (14). Remarkably, as few as 65,000 islets can produce insulin independence, while the more than 600,000 islets typically used for autografts usually fail (3). These superior results are presumably attributable to the lack of immune attack and drug toxicity and provide reassurance about the value of the liver as a transplant site.

Limited supply of human islet tissue. A major barrier to the future of islet transplantation is the limited availability of human islet tissue. Each year in the U.S., ~5,000 brain-dead donors with intact circulation become available, and only a portion of these are suitable for islet or pancreas transplantation (17). Yet there are ~30,000 new cases of type 1 diabetes each year (18), not to mention the huge number of people with type 2 diabetes, some of whom might be candidates for transplants. The possibility of using islets donated by living donors is not an attractive option, in part because of the risk of the donor developing diabetes (19).

Fetal human islets. The limitation in the supply of adult islet tissue could theoretically be alleviated by exploiting the growth capacity of fetal tissue. Many transplants of human fetal pancreases have been carried out in China and Russia and some even in the U.S., but evidence of success from these transplants has yet to emerge (20,21). Typically, transplants have employed several fetal pancreases placed in subcutaneous or intramuscular sites, usually without any form of immunosuppression. Relatively little is known about the behavior of human pancreatic tissue in vivo or in vitro, but the problem is now being studied in several laboratories (22,23). Although the potential of using the human fetal endocrine pancreas continues to be tantalizing, its future is clouded by a variety of practical, political, and ethical concerns.

Xenografts. The limited availability of human tissues is an issue not only for islet transplantation, but also for the transplantation of hearts, livers, and various other organs, which helps provide momentum for the diabetes effort. All of these disciplines will benefit from research advances in the area of xenograft biology and from the selection of special strains of donors, the evolution of testing and production practices to minimize the risks of infection, and the development of regulations for industry. At present, there is a great deal of anxiety about the potential for introducing unknown infectious agents into humans, as is discussed later in this perspective. Although xenotransplantation was considered unthinkable only a few years ago, skepticism is declining as more is learned about its potential and feasibility.

Porcine islets. A variety of animal species have been considered as islet donors, but pigs and cows, which are part of the food chain, seem to hold the most promise. Pigs seem especially appealing for a variety of reasons (24,25): Porcine insulin differs from human insulin by only one amino acid and has been used to treat people with diabetes for decades. Moreover, pigs are omnivores, and their glucose levels are similar to those of humans. Another attractive feature is that pigs can be subjected to genetic manipulation, which means that transgenic pigs can be developed with genes expressed in their β-cells that could help resist immune attack and even enhance insulin secretion. There are complex arguments about the optimal source of porcine islet tissue, with various reasons being put forth to support the use of mid-fetal, late-fetal, neonatal, market-weight, and older pigs. Although most find that better islet yields are obtained from older pigs, improvements are being made in harvesting islets from younger market-weight pigs, which would be a more practical and less expensive source of tissue. In spite of the advances, there continue to be serious problems obtaining healthy adult pig islets, in part because of their fragility and poor survival in tissue culture (25,26).

The potential use of porcine fetal pancreas tissue is attractive because of the capacity for growth and the ease of maintaining sterility. In addition, the procedure for obtaining this tissue is less traumatic than that used for adult pancreases, so the cells are harder when placed into culture or transplanted. These fetal pancreatic cell preparations are very complex; fortunately, the exocrine cells spontaneously die off...
when cultured or transplanted, but the surviving population consists of a mixture of mesenchymal, precursor, protodifferentiated, and mature islet cells. There is a great need to learn more about how these cells develop so as to maximize growth capacity and optimize function when they are transplanted. Much work has been done on pancreases removed at the mid-fetal stage of 60–90 days' gestation, which can normalize glucose levels in recipient mice with diabetes (27,28). Although the wait for the maturation of the islet tissue is problematic and the final yield of β-cells limited, neither of these impediments seems insurmountable. Recent attention has been paid to the potential of pancreatic cells obtained from the late-fetal and neonatal periods (29). They have the advantage of being more mature and yet maintaining considerable capacity for growth.

**β-cell expansion strategies.** Much attention is focused on the general problem of β-cell growth, development, and function in the hope of finding new sources of insulin-producing cells for transplantation. Because β-cell mass cannot be expanded in a meaningful way either in vivo or with tissue culture, an increasing number of investigators are working on such basic problems as embryology of the endocrine pancreas (30), differentiation of duct cells (31), mechanisms of β-cell replication (32), and apoptosis of β-cells (33). Even in adulthood, new β-cells are constantly produced either by differentiation of pancreatic duct cells or through replication of preexisting β-cells (31). The hope is that with the right combination of growth and differentiation factors or with some genetic manipulation, β-cell expansion could provide cells for transplantation.

One approach to expansion is to create β-cell lines. Considerable progress has been made with rodent islet cells (34,35), but the quest to obtain similar lines of human cells has proved to be more difficult (36). Even the best rodent cell lines have deficiencies limiting their value for transplantation: there are concerns about their neoplastic nature; their capacity to produce insulin is low; and even though some can secrete insulin when exposed to glucose, their performance still falls far short of that of normal β-cells. Efforts are underway to use the powerful tools of genetic engineering to improve the performance of some of these cell lines so that they might be useful. Not only can insulin production be improved by transferring human insulin promoter sequences into rodent cell lines, but glucose responsiveness can be enhanced by transfection of the glucose transporter GLUT2 and use of antisense RNA for hexokinase, which can bring the glucokinase-to-hexokinase ratio closer to that of normal β-cells (37,38). However, the mechanisms responsible for physiological insulin secretion from normal β-cells are turning out to be so complex and sophisticated that it may be very difficult to mimic this machinery by changing the expression of a few genes. It will probably be necessary to alter differentiation in a more fundamental way, such as through expression or repression of transcription factors, that will take into account ion channels, energy handling, lipid metabolism, and more.

A molecular approach that might lead to a more "normal" β-cell is the manipulation of oncogenes by controlling gene expression with a tetracycline response element. Valuable cell lines have been generated in transgenic mice using the oncogene T-antigen driven by the insulin promoter, so that the β-cells of these mice are hyperplastic (because of the specificity of the insulin promoter; the oncogene is not expressed in any other cell type) (34). With additional genetic engineering using the bacterial tetracycline resistance operon regulatory system, the T-antigen can be turned off either in vitro or in vivo with very low concentrations of tetracycline or one of its analogs, allowing the cells to redifferentiate and function like normal β-cells (39). This approach makes it theoretically possible to expand β-cell mass to whatever level might be required and then, by turning off the oncogene, be left with a useful population of cells. Mice may not be an ideal species for xenotransplantation, but the same technology might be used to make similar cells in transgenic pigs.

**Lack of knowledge about the cell biology and pathophysiology of islet transplantation.** There are still important unanswered questions about the ability of islet transplants to control carbohydrate, fat, and protein metabolism. Recipients of transplanted pancreases often, and allogenic islets sometimes, have normal glycohemoglobin levels, which provide reassurance that metabolism is at least near normal. Discussions about the potential dangers of insulin being delivered into the circulation peripherally instead of via the portal vein (40) continue because of concerns that hyperinsulinemia might somehow promote atherosclerosis and/or hypertension (41). At present, the evidence seems only circumstantial, but the debate is likely to persist. Another question is whether islets function normally when transplanted into an unnatural site, such as the liver, peritoneal cavity, or subcutaneous space (42,43). We know little about how much β-cell mass is needed for successful transplantation, the repercussions of transplants of excess islet mass, the optimal ratios of β-cells to non-β-cells, and the vulnerability of transplanted islets (44–47). In their normal location in the pancreas, islets have a specialized vasculature in which arterioles break into capillaries within the β-cell core and then exit through the islet mantle, which contains glucagon-secreting α-cells (48,49). When transplanted islets are revascularized, the normal relationship between β- and non-β-cells may not be reestablished (50), so some β-cells not normally exposed to local glucagon secretion could be downstream from this potent insulin secretagogue, which might make these β-cells more responsive to glucose (51) and cause hypoglycemia. The exposure of β-cells to excessive amounts of glucagon could be even more of a concern for islets contained within immunobarrier devices. Other questions can be raised about whether the set point of porcine β-cells for glucose-induced insulin secretion is similar enough to human β-cells not to cause problems.

**Immunooprotection of insulin-producing cells.** The vulnerability of islets to immune attack continues to be one of the major barriers to successful islet transplantation. Transplanted islets face not only rejection but also the threat of recurrent autoimmunity. In this short perspective, it will only be possible to mention some of the more vexing obstacles.

**Allograft rejection and autoimmunity.** Although transplanted islets are subject to classic allograft rejection, it must be remembered that islets are more a cell transplant than an organ transplant. For example, islets can be largely depleted of antigen-presenting cells in tissue culture, which can attenuate the rejection process (32). There are practical problems in monitoring the rejection of transplanted islets because of the lack of good markers, which is particularly a problem...
because of the several-month period of time usually required for allografted islets to produce normoglycemia. Autoimmunity may also cause difficulties, as has been dramatically demonstrated by the rapid destruction of islets after segmental pancreas transplantation between identical twins (53). We have much to learn about the determinants of the severity of autoimmunity during transplantation. It is not clear that autoimmunity will be a problem at all with discordant xenografts or even with some allografts. The contention that the antigenicity of insulin is important for the pathogenesis of autoimmunity has not been proven (54,55). Fortunately, results from pancreas allografts tell us that both rejection and autoimmunity can be kept in check for many years with conventional immunosuppression.

**Xenograft rejection.** The mechanisms responsible for xenograft rejection are complicated, but are being rapidly elucidated because of the drive to use xenografts for heart, liver, and islet transplantation. With organ transplants, hyperacute rejection occurs, mediated by preformed antibodies that bind the Gal alpha(1,3)Gal epitope (also known as the Gal epitope) of transplanted cells and act with complement to cause rapid cell death, with the most serious target being endothelial cells (56–58). This hyperacute rejection phenomenon may be less of a problem with islet transplantation because islet cells seem to have very little of the Gal epitope (59) and because the vascularization of transplanted islets seems to come entirely from recipient endothelial cells (60). Hyperacute rejection may be more of a problem for fetal or neonatal pancreas cells because duct cells, which are precursor cells for islet formation, appear to express the Gal epitope (61). Unfortunately, the xenograft rejection process is far more complex than just Gal epitope−dependent hyperacute rejection; there seem to be other antibody- and complement-mediated reactions, as well as a variety of cell-mediated assaults that provide a serious challenge to the success of these transplants (56,57). The possibility that xenografted islets are subject to autoimmune attack is unanswered.

**Improved immunosuppression and the induction of tolerance.** Although present-day immunosuppression is dangerous, extraordinary advances are being made in the field of immunology that should lead to the development of more-selective and safer approaches. The well-documented risk for developing neoplasms is of special concern (62). Glucocorticoids are particularly toxic and have adverse effects on islet function (63), so there is hope that some steroid-sparing regimens, using such promising drugs as 15-deoxyspergualin, lefunomide, mycophenolate mofetil, and rapamycin, will turn out to be useful. Immune reactions against islets may differ from those found with solid organ transplants and thus may require specially tailored drug regimens. It may even be possible to induce tolerance to transplanted tissue by using drugs before or at the time of the transplant (64) by transplanting islets into the thymus (65), by simultaneously transplanting bone marrow along with the islets (16), or by using such immunoprivileged sites as the testes (66). Some of these strategies may need to be combined with immunosuppression.

**ImmunobARRIER approaches.** Work continues on the possibility that islets could be protected by a semipermeable membrane. The principle is that the permeability of the membrane would be open enough to allow nutrients and oxygen to reach the islets and for insulin to be released into the bloodstream, but restrictive enough to exclude immune cells and even antibodies (52,67–69). Remarkably, islets completely separated from their normally rich blood supply and innervation can survive and function well inside such devices. There are three major approaches to immunobarrier protection.

**Microencapsulation.** The most widely used approach is to contain islets within a bead of alginate gel and then coat the bead with poly-L-lysine or some other material to provide permselectivity and strength (70–75). These capsules were originally made with a diameter of ~800 μm, but can now be produced in the range of 300 μm or even as a conformal coating adherent to the surface of the islet. Another promising approach is to use polyethylene glycol as a conformal coating photopolymerized to the surface of the islet with eosin Y (76). The possibility of using other materials is also being explored (75). Interest in the potential of microencapsulation has been enhanced by a recent report in which monkeys with spontaneous diabetes given adult porcine islets contained in alginate/polylysine capsules were cured for periods as long as 803 days without immunosuppression (70). This striking finding should accelerate efforts to use the same approach in future monkey and human trials. In spite of this apparent success, there are still major questions about how best to design microcapsules; some of the issues that must be taken into account include biocompatibility of material with host tissue and the contained islets, amount of permselectivity required, and distance from the surface of the capsule to the islet, which not only will influence delivery of oxygen and nutrients but may also determine susceptibility to toxic cytokines. There are other concerns, such as release of antigens and debris of the capsular material in the peritoneal cavity, which could cause an inflammatory reaction that would be difficult to stop because the capsules cannot be easily retrieved.

**Macroencapsulation dependent on diffusion.** Islets in hollow fibers, planar envelope devices, and devices with other configurations can be transplanted into a variety of tissue sites. Some of the materials used to make these devices include polytetrafluoroethylene (PTFE), acrylate copolymers, polysulfone, polycrylonitrile-polyvinyl chloride copolymers, and cellulose acetate (68,69,77–83). A potential advantage of this approach is that the devices can be retrieved or even reloaded. As with the microcapsules, there are many factors that determine survival and function of the contained islets, with oxygen delivery being at the forefront. The membranes of these devices must be very thin because at best a tissue layer of only 8–10 cells thick could receive enough oxygen from surrounding capillaries to survive. Relatively open membranes will be valuable for optimal penetration of oxygen and nutrients, but will be more likely to allow shed antigen to elicit an immune response on the surface of the device. Such an inflammatory response not only might produce penetrating toxic cytokines, but also will consume oxygen, thus preventing it from reaching the islets. On the other hand, a membrane that is so tight as to limit release of shed antigens would be more likely to suffocate the islets. Because of such constraints, there are problems obtaining good enough packing density in these devices for easy surgical implantation. One approach is to find ways to prevascularize devices before the introduction of the islets, which could be accomplished by membrane materials or diffusible growth factors that promote angiogenesis. Even so, questions remain about the function of islets within these devices, such
as how long β-cell mass can be maintained, whether the insulin secretion from β-cells has a normal dose-response to glucose, and how much lag occurs between glucose and insulin changes in plasma.

**Macroencapsulation using vascular access.** With this approach, islets are kept on the outside of hollow fibers through which the blood of the recipient flows. Thus, a device with many parallel hollow fibers is fed by an artery and drained by a vein. One group has tested this approach extensively in dogs and has been able to normalize glucose levels with allografted islets for prolonged periods of time without immunosuppression; they have even had partial success with porcine islets (84). These important experiments provide proof for the principle that immunobarrier membranes can protect islets from xenograft rejection. Nonetheless, there are still concerns about the safety and practicality of this approach, such as development of thromboemboli, rupture of the device, and the stress of arteriovenous shunting.

**Gene therapy approaches to protect islets from immune attack.** The rapid advances in gene transfer technology hold great promise for the field of islet transplantation (85, 86). A variety of methods, such as the use of retroviral vectors, can be used to introduce genes into dividing cells, which makes gene transfer useful for cell lines but not for slowly dividing islet cells. For stable cell types, genes can be transduced with adenoviral vectors (87), but the genes can only produce proteins in vivo for a limited period of time, with the exact reasons for failure being uncertain. Fortunately, there are some new approaches, such as the use of a lentivirus vector, that allow incorporation of DNA into the genome of nondividing cells without expression of viral proteins (88). Even though adenoviral vectors may turn out to be of limited utility for clinical application, they can be of great value for establishing proof of principle. For example, through the use of adenoviral vectors, various genes can be tested in rodent or porcine islets for their ability to protect against rejection and autoimmune attack. When a positive result is obtained, its potential can be further explored in transgenic mice and pigs.

There are many ways in which genetic modification of β-cells could provide resistance against immune attack. Cellular antigens can be modified to reduce recognition by the immune system (89). Immunomodulatory cytokines, such as interleukin (IL)-4, IL-10, IL-12, or TGF-β (transforming growth factor-β), can be released locally to alter cellular responses (90). Co-stimulation pathways for T-cell activation can be blocked with CTLA4 or other proteins (91). Protection against cytokines could be provided by the IL-1 receptor antagonist (92) or by the soluble TNF (tumor necrosis factor) receptor protein (93). Expression of Fas ligand in the vicinity of the graft or by β-cells could promote apoptosis of invading T-cells (94, 95). Proteins such as Bcl-2 or A20 could be expressed within β-cells to protect them against apoptosis (96, 97), and other proteins could bolster defenses against oxidant injury (98). Attack by complement could be blunted by overexpression of complement regulatory proteins such as decay accelerating factor (DAF) and CD69 (99, 100). Several of these approaches could be combined and even used with immunobarrier devices and/or selective immunosuppression. As we learn more about the mechanisms of immune injury and cell death, the number of possible therapeutic options should continue to expand.

**POLITICAL IMPEDIMENTS**

Although a discussion of the political impediments to islet transplantation could be a separate perspective, we feel that the political and scientific issues are so entwined that juxtaposition of the two is needed to provide full appreciation of the problem.

**Expressions of growing frustration.** Vocal members of the diabetes community are becoming increasingly strident in expressing their frustration and impatience about the limited tangible success of islet transplantation. Some of these concerns have been clearly articulated in a recent article in *Diabetes Interviews* (101). Strategies for research funding are being reassessed by the Juvenile Diabetes Foundation International (JDFI) as their "Decade of the Cure" nears its end with the cure still too far off. Many of those watching the process wonder why so few people are working on the problem, why so little is being spent, and why a more coordinated approach is not evident. They are correct in their contention that remarkably little is spent by conventional sources on the applied or even the more basic aspects of islet transplantation. Most diabetes research in the U.S. is funded by the National Institutes of Health (NIH), with the total funding for 1996 being about $300 million; yet according to the Financial Management and Analysis Office of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), only about $6.5 million of that spent by NIDDK is in the category of pancreas and islet transplantation. Close inspection of the titles and abstracts of these grants reveals that only about one-third of this is going to treatment-oriented approaches, with the rest going to more basic projects, which, while valuable, are unlikely to provide help for patients in the short-term. Of course, it must be pointed out that money from foundations and various other sources provides a patchwork of support for the problem and that important work is performed outside the U.S., but the magnitude of these efforts must be considered modest.

In this portion of the perspective, we will develop the argument that for complicated and understandable reasons, the field of islet transplantation has been badly neglected in recent years and that steps must be taken to remedy the situation. The basis for this argument is that insufficient planning, resources, and attention are being devoted to the problem. Good sense tells us that throwing money at a scientific problem is a dangerous proposition, but of course, the real issues are the following: Is the scientific problem ready for a targeted approach, and how should the money be thrown? What strategies are required to make β-cell replacement therapy readily available to people with diabetes as soon as possible? In our judgment, the problem of islet transplantation is ready for a serious commitment.

**High expectations can backfire.** The high expectations of the diabetes community have had damaging effects on progress in islet transplantation. Much of this stems from the apparent simplicity of islet transplantation: it seems that an approach so easy and successful in mice cannot be that difficult to perfect for humans, particularly now that the miracles of kidney, heart, and liver transplantation seem almost routine. At intervals, triumphant reports of breakthroughs for diabetes have appeared, but sadly, hopeful patients and family members have often found these to be mere mirages. These disappointments have led to a great deal of cynicism. Part of the problem is created by scientists who are willing
to have their work portrayed by the media as a breakthrough. It is easy to feel anger toward these individuals, but in most cases, a real advance has been made, and it is natural for hard-working investigators to be excited and proud of their accomplishments. Organizations whose mission is to support diabetes research face difficult challenges in raising funds, and at times they too have inadvertently raised false expectations. Some scientists working in the diabetes area have become cynical and even hostile, making such comments as: "Islet transplantation is getting nowhere," "Xenotransplantation will never succeed," or "Targeted research never works." This negativity seems to condemn a set of important hypotheses that have not yet been sufficiently tested. In summary, high expectations, combined with promises, exaggerated claims, and a failure to deliver tangible results, have raised questions about the credibility of the effort and have dampened enthusiasm for a full-fledged attack on the problem.

Why not focus on prevention instead of cure? The prospects for preventing or slowing the development of type 1 diabetes are improving. With the demonstration that a variety of interventions can prevent diabetes in rodent models of type 1 diabetes and because some pilot trials in humans suggest that progression of autoimmunity can be slowed (102), large prevention trials are underway (103,104). As frustration about the difficulties of islet transplantation grows, some individuals suggest that research should be focused more on prevention instead of cure, but there are several strong arguments for not neglecting islet transplantation:

1. There are many people with existing diabetes who cannot be helped by prevention.
2. Prevention trials are difficult and time consuming, so even an effective prevention strategy will take many years to implement.
3. If an intervention can be shown to prevent or delay the onset of diabetes in subjects with impaired \( \beta \)-cell reserve, there will be a great temptation to treat people with positive autoimmunity markers but apparently normal \( \beta \)-cell function, many of whom would never develop diabetes.
4. Even if prevention of autoimmune diabetes could be accomplished, most diabetes is not caused by autoimmunity. There is a common perception that islet transplantation will never be useful for the treatment of type 2 diabetes, largely because of old assumptions that this form of diabetes is purely the result of insulin resistance. Now it is recognized that type 2 diabetes develops in people with insulin resistance only when their \( \beta \)-cells fail (105). Therefore, euglycemia could be restored with islet transplantation, which should thus be considered one of many potential treatment options.

Controversy about targeted research. Depending on where one sits, the words "targeted research" can be met with suspicion, disdain, or enthusiasm. The misadventure of the War on Cancer in the 1970s is remembered as a conspicuous example of how well-intentioned directed research can be spectacularly unsuccessful. Nonetheless, everyone should be able to agree that there is good and bad targeted research. The discovery of insulin and the development of laser therapy for diabetic retinopathy must be regarded as high points of targeted research. In trying to place a value on targeting, we should be cautious about the definition, which in itself can lead to disagreement. The very existence of NIDDK means that funds are being targeted toward the problem of diabetes. Most investigators doing disease-related research agree that broad targeting is fine but narrow targeting becomes threatening, especially when their area is not being targeted. Judgments about when an area is ready for increased attention and funding are inevitably difficult and controversial. The area of islet transplantation is an excellent case in point. The first debate is whether this specific problem should be targeted, and if the decision is yes, the next debate is how it should be targeted, with there being predictable difficulty in sorting out how to balance the emphasis on the study of basic mechanisms versus applied approaches.

Basic and applied research in an academic setting: what is happening to the balance? Questions about why so little university-based research is focused on the applied aspects of islet transplantation can be partially answered by understanding the current funding situation. In the U.S., biomedical research supported by government and foundations is usually carried out in university laboratories, with funds typically being distributed through a peer-review system. Thanks to this structure, the U.S. research establishment has produced spectacular advances in medical knowledge and delivery of remarkable new treatments to patients. Advances can be expected when university-based scientific laboratories generate new knowledge about basic mechanisms and disease pathogenesis, and then industry, by using this new information for applied research, develops and introduces new therapies to the clinic. Although this model might be expected to be helpful for the development of islet transplantation, the actual efficacy of the approach is unclear.

One concern is whether university-based research has tilted too much toward undeniably important hypothesis-driven mechanistic research, with resultant neglect of valuable applied research. Research categorized as descriptive or applied is often regarded as second-rate, being thought to be less difficult, less elegant, and even less valuable; but obviously, medicine cannot advance without clinical trials, descriptions of clinical findings, development of new drugs, and application of new therapies. Some of this trend can be accounted for by a vicious cycle that leads to a dominance of basic research in universities. When there is competition for research dollars, it seems appropriate that the scientists with "excellent" research be successful, but one must be cautious about whether this kind of excellence can always be equated with value. Academic prestige and promotion, in both basic science and clinical departments, are more and more dependent on the production of excellent mechanistic research and on success in obtaining grant support through the peer-review system. Scientists who thrive in this environment and become recognized for their excellence are most likely to be invited to serve on scientific review committees for funding organizations such as the NIH, the JDFI, or the American Diabetes Association (ADA). This creates a situation where scientists whose research approach has conformed to the demands of the system are responsible for distributing the limited available funds. Because scientists are typically most comfortable with their own approach, it is easy to understand why valuable applied research might fare poorly in study sections. There may even be an admission that the work is important, but its priority cannot measure up to that of some elegant project employing molecular biology. Members of a study section may say "My task is to promote the best
science,” or “Yes this applied research is valuable, but it should be supported by industry, or at least by someone other than us.”

These considerations become important for the field of islet transplantation because so much of what needs to be done is descriptive and applied. For example, working out the best collagenase conditions for obtaining human islets is not likely to be valued by those who cherish mechanistic research, nor is much of the work required to develop immunobARRIER devices or to evaluate new transplantation sites, but this work needs to be done somehow. A historical review of grant submissions would almost certainly unearth a steady stream of proposals to work on these and similar problems that have received unfunded priority scores.

Why aren't more scientists working on islet transplantation? Visits to islet transplantation meetings reveal how few academic scientists are working on either applied or basic aspects of the problem. This should be highlighted as a major issue. What is being done to develop bright young scientists or to attract scientists from other disciplines such as biomaterials, embryology, gene therapy, xenotransplantation, and many other potentially useful areas? If more bright and creative people would focus on islet transplantation, new ideas and approaches would undoubtedly emerge. Many strategies could be used to attract such individuals; one is providing funding opportunities for multidisciplinary teams of investigators. Experience with acquired immunodeficiency syndrome (AIDS) tells us that excellent scientists can be attracted to a new area of investigation.

Funding decisions about islet transplantation. There are serious debates about how the limited amount of money available for diabetes research should be distributed. When funds have been dispersed by the NIH, and even the JDFI and the ADA, there has been considerable caution about directing the funds to specific areas in diabetes research, based on the assumption that excellent nondirected science will produce the greatest long-term benefit. Nonetheless, concerns can be raised about how well it is serving the challenge of islet transplantation. Four specific questions can be addressed.

Does islet transplantation receive an appropriate share of the funds allocated to university-based diabetes research? Somewhere, an annual expenditure of only $6.5 million by NIDDK for the problem of pancreas and islet transplantation seems woefully inadequate considering the magnitude of the diabetes problem. However, if a decision were made to spend a bigger piece of the pie on islet transplantation, there would be protests from the other areas of diabetes research that would necessarily receive less. The easy answer is that all areas of diabetes research shoulde have more funding; however, while true, this dodges questions about what areas of research are more important than others. These issues are hotly debated by organizations such as the JDFI and the ADA, as well as by other parts of the diabetes community.

Are dollars spent on islet transplantation appropriately balanced between hypothesis-driven and applied research? There is little to be gained in trying to sort out the relative importance of basic and applied research for islet transplantation when the total spent by NIDDK is only $6.5 million per year. Both approaches need more funding, but perhaps there should be some rational plan for ensuring that valuable approaches are not neglected because they are not fashionable. The NIH could develop mechanisms to foster research on islet transplantation, as they have for AIDS, breast cancer, and a variety of other diseases. Grant applications on islet transplantation are frequently assigned to study sections whose members know little about the problem of diabetes, much less the specific problems facing islet transplantation. However, mechanisms exist to request proposals for grant applications focusing on specific problems (RFAs), and special study sections can be formed to provide whatever expertise is required. Although there seem to be many ways for the NIH to direct attention and support to the problem of islet transplantation, the most fundamental questions are: What is NIH's plan for dealing with the islet transplantation area? Can the diabetes community and Congress be convinced that the wisest approach is being taken?

How much applied research should be performed in a university setting? In spite of current constraints, notable amounts of applied research are currently performed in universities by excellent individual investigators and groups of collaborating scientists who work best in that environment, so it is obviously an overstatement to suggest that applied work should be restricted to industry. A facet of this issue is that applied approaches may be necessary to perform mechanistic experiments. Take the case of hypothesis-driven "basic" experiments on xenograft rejection, which is best studied using human islets in rabbits. These experiments may depend on expensive and time-consuming developmental work to make the human islets, which, if evaluated by itself, might be dismissed as applied research. Applied work that is necessary for collaborative studies needs to be fostered somehow; as does valuable research that is not being done by industry. But how can such work find acceptance by the current peer-review system?

Who should make judgments about these questions, and how might changes be implemented? The search for wisdom in making judgments about scientific priorities is difficult. The obvious people to ask are the scientists themselves, but there are worrisome conflicts of interest and differences in judgment. There is always the risk that active scientists will conclude that whatever they and their friends are working on is especially important. It would be foolish to ignore the scientists entirely, because they are the true experts in their field, but somehow their knowledge and judgment must be utilized more effectively. A spectrum of people should be brought together, and it must include the scientists who work on diabetes along with others who are not active participants in the research. Such individuals might include scientists working in other areas, physicians, patients, and others who are knowledgeable about diabetes and the process of science.

Help from industry is welcome but complex. Involvement by industry takes many forms, including relatively small initiatives within large corporations, small companies supported by venture capital, and industrial support provided to scientists working in academic settings. Companies can usually move much faster on applied research than can university research groups for a number of reasons. They may be able to focus on a single problem with much more financial support and can employ fully trained scientists rather than rely on scientists in training; moreover, they need not spend as much time writing grants and papers, nor worry about whether their work is mechanistic or hypothesis-driven. On the other hand, they are under tremendous pressure to produce a product, which has already led to problems for some
companies. Several ventures have failed because of the combination of inappropriately high expectations and failure to appreciate the scientific complexity of islet transplantation.

Despite all of the positive contributions from industry, some of industry's inherent characteristics can be exasperating. The need to keep trade secrets and patent information confidential is understandable because of the need for companies to maintain a competitive advantage. However, secrecy is often so tight that important information that might help the field as a whole is not made available to academic laboratories. Even work in academic laboratories supported by industry is often proprietary and unavailable to the scientific community. For example, the publication of valuable research manuscripts is often significantly delayed by industry (106), and papers often leave out key details of methods that are required for the work to be reproducible. There are no easy solutions to these problems, but academic scientists, journal editors, and meeting organizers should continue to remind industry of its moral obligations to the scientific community.

Anxiety about xenotransplantation. The obstacles facing xenotransplantation are more than scientific. Although there will be psychological discomfort about the prospect of using tissues from other species, the more problematic issue is the potential danger of viral, prion, or some other type of disease process being transmitted to humans (107,108). Anxieties about pigs have been fueled by a recent report of a retrovirus transmission to humans (109). The problem certainly deserves careful study and caution about if, when, and how to start human trials.

Lessons from the last 25 years. The past 25 years have provided many sobering lessons about the difficulties of islet transplantation. The most important lesson is the realization that the problem is truly difficult; most of the challenges could never have been predicted, which means we must continue to be wary of what lies ahead. In retrospect, it was naive to think that the problem could have been solved by a small number of investigators and modest support. Another lesson is that we must be very cautious about predictions of success, mainly because of the emotional and practical repercussions of unfulfilled promises. Although not generally appreciated by those outside the field, a tremendous amount has been learned about islet transplantation, and these scientific lessons are essential for future progress. Finally, it is necessary that the importance, potential, and feasibility of islet transplantation be better appreciated so that the need to develop this urgently needed therapy be more accepted.

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