Transplantation and Islet Topics

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Posttransplantation diabetes

The American Society of Transplantation (www.a-s-t.org) held a symposium at the June ADA meeting addressing the importance of diabetes following transplantation (1). Martha Pavlakis (Boston, MA) introduced the symposium, pointing out the importance of "long-term management, now that our focus is no longer [merely] getting the patient to survive 1 year." Among the risks of transplantation are those of the surgery itself, those of chronic immunosuppression, and now those of new-onset diabetes, which "definitely affects graft and patient survival."

Fernando G. Cosio (Rochester, MN) gave an overview of new-onset diabetes after transplantation in the U.S. Defining posttransplant diabetes mellitus (PTDM) as new onset of abnormal glucose metabolism following transplantation, he noted that it is common, that the incidence is increasing, and that the pathogenesis is complex. PTDM is associated with unexpectedly high risk of patient death, as well as with risk to the graft. One important question is whether this is "really new onset," as the level of glucose tolerance of many patients is not carefully characterized before transplantation, and few studies assess patients for impaired glucose tolerance (IGT), or even for impaired fasting glucose (IFG). Indeed, rather crude diagnostic criteria are often used, such as the need for insulin administration, need for any glucose-lowering medicine, or assignment of billing codes for diabetes, so certainly many patients have diabetes that is not recognized. Given these reservations, the incidence of diabetes has been shown to increase with time after transplantation and appears to be higher among patients treated with tacrolimus than those treated with cyclosporine, at ~15 vs. 10% for kidney and 18 vs. 8% for liver transplantation. Cosio reviewed his studies, with a linear increase in PTDM following kidney transplant with cyclosporine treatment, ~7% during the first year, with increase to ~30% over 12 years. The incidence appeared to increase after 1995, with ~20% diabetes prevalence at 3 years vs. ~10% at 3 years before 1995, despite a reduction in the mean prednisone dose from 101 to 91 mg · kg^{-1} · $year^{-1}$. This appears to be related in part to the use of higher cyclosporine dosages, as well as to somewhat greater age and body weight of persons undergoing transplantation (2). In a similar study of persons who had renal transplant, PTDM was seen in 9, 16, and 24% of patients at 3 months and 1 and 3 years when use of glucose-lowering medications was the diagnostic criterion, with an additional 10% at 3 months and 1 year having evidence of IFG (3). Patient survival is reduced in persons with PTDM, although not to as great an extent as in those with pretransplant diabetes. Data from the Mayo Clinic experience suggest that patients with IFG or PTDM have more posttransplant heart disease than those who are euglycemic, and patients with glycemic abnormality have lipid and blood pressure abnormalities similar to those of persons with preexisting diabetes (4). Cosio et al. (5) noted that the rate of onset of diabetes in persons receiving chronic dialysis is ~6%/year, so that one should not overly blame the transplant. However, it seems certain that to some extent immunosuppressive medications contribute to the risk of diabetes and impede the control of glycemia, suggesting that it may be appropriate to modify these medications, for example by reducing steroid dosages, albeit with "a great deal of caution," as "the transplant is what keeps these patients alive. " It is not currently known whether abnormal glucose homeostasis posttransplant should be aggressively sought, and whether or how it should be treated, with Cosio proposing a trial of thiazolidinediones in persons with IFG following transplantation, addressing the issues of whether early alterations in glucose metabolism contribute to increased cardiovascular risk and whether treatment would modify the cardiovascular risk.

Alan Wilkinson (Los Angeles, CA) further discussed the definition of PTDM, and Pavlakis discussed the effects of immunosuppression on PTDM. Rates of diagnosis and treatment "have been abysmal," Wilkinson commented. Risk prevention strategies such as lifestyle modification and reduction of immunosuppressive medications (while not risking rejection) might appropriately be employed in patients with IFG or in those characterized by novel risk factors such as low levels of adiponectin. PTDM is seen in ~4% of Caucasians and ~20% of African-American and Hispanic-American patients, with incidence ~5% for persons <45 years of age and ~35% above this age and ~5 vs. ~20% for persons with body weight <70 vs. >70 kg (6). Additional risk factors for PTDM include age, pretransplant glycemia (7), steroids, cyclosporine, tacrolimus, obesity, and hepatitis C (HVC) infection (3). Another risk factor is cadaveric as opposed to living donor kidney, perhaps because of more frequent rejection with the former and hence need for greater dosages of immunosuppressive agents. Steroids cause both peripheral insulin resistance and decreased insulin secretion (8), and diabetes incidence correlates most strongly with the cumulative dose administered, with rates of PTDM following high-dose methylprednisolone courses for acute rejection being as high as 10–30%. The calcineurin inhibitors (CNIs) cyclosporine and, in particular, tacrolimus appear most detrimental, with evidence that PTDM rates increased following introduction of the latter (9) and histologic evidence of islet damage by both agents (10,11). They are, however, highly effective immunosup-

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Abbreviations: CNI, calcineurin inhibitor; HVC, hepatitis C; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL, interleukin; IRS, insulin receptor substrate; MMF, mycophenolate mofetil; NF, nuclear factor; PTDM, posttransplant diabetes mellitus; TNF, tumor necrosis factor.

pressive agents. Although tacrolimus was associated with a 50% increase in PTDM, it was also associated with 35% reduction in overall mortality when compared with azathioprine and mycophenolate mofetil (MMF) (3), a dilemma facing the transplantation physician concerned about PTDM. Tacrolimus-induced diabetes appears to be reversible with a switch to cyclosporine in pediatric transplants, but the diabetes does not always resolve in adults with this maneuver. Furthermore, virtually all immunosuppressive agents currently used may have adverse glycemic effect, including azathioprine, MMF, and sirolimus, although not rapamycin (12 and vide infra). An interesting question is whether ACE inhibitors and angiotensin receptor blockers might have an ancillary protective role in reducing PTDM as well as having nephroprotective effects, although caution must be paid to renal function and potassium with these agents following renal transplantation, and many centers avoid their use. Clearly, minimization of steroid and CNI use is particularly important in islet transplantation, with the Edmonton protocol steroid free and using an interleukin (IL)-2 receptor antibody, tacrolimus, and rapamycin. Several centers are employing modifications of this approach, replacing tacrolimus with agents having less adverse islet effect. A further promising approach being evaluated in nonhuman primate models involves adjustment of the balance between cytotoxic and regulatory T-cells to induce transplantation tolerance (13).

Roy Bloom (Philadelphia, PA) discussed HVC as a novel risk factor for new-onset diabetes following transplantation. HVC affects ~200 million persons worldwide, 4 million in the U.S., 12–15 million in South America, 30–40 million in Africa, 10–15 million in Europe, and 90–100 million in Asia. The virus has, Bloom pointed out, been found to be associated with diabetes in the general population. Between 30 and 50% of persons receiving liver transplant and 10 and 40% of those receiving kidney transplants have HVC. In the NHANES III (Third National Health and Nutrition Examination Survey), which studied 9,841 persons >20 year of age representative of the overall U.S. population, those with HVC antibodies had a 3.77-fold increased risk of diabetes (14). Bloom showed studies of kidney transplant recipients, with 40 vs. 10% of HVC-positive versus -negative persons developing PTDM. "The milieu of transplantation," he said, "strongly increases the risk of diabetes." Additional risk factors were tacrolimus treatment and obesity. Among HVC-negative patients, ~10% of patients receiving either cyclosporine or tacrolimus developed diabetes, but among HVC-positive patients, PTDM developed in 10% of those receiving cyclosporine, but diabetes developed in 50% of those treated with tacrolimus. Male sex and obesity were additional risk factors (15).

In a study of 278 liver transplant recipients, 266 treated with cyclosporine, 30–40% of those with HVC developed diabetes as opposed to 10–20% of those with hepatitis B virus and ~5% of those with chronic liver disease of other etiology. In nontransplanted patients, insulin resistance is associated with liver disease severity, as assessed by the degree of liver fibrosis, with those persons having HVC genotype 3 having lower diabetes risk than those with other genotypes. Increasing viral load also may be associated with worsening risk. The mechanism of HVC in worsening glycemia may involve effects on insulin sensitivity, decreased hepatic glucose uptake or glycogen formation, possible viral β-cell damage, or immune-mediated β-cell damage. In HCV-infected liver tissue extracts incubated with insulin, insulin receptor and insulin receptor substrate (IRS)-1 were present at higher levels than in noninfected tissues, but the association of the insulin receptor with IRS-1 appeared to be impaired and phosphatidylinositol 3-kinase activation by IRS-1 was diminished (16). In a study comparing the effects of a 14-day course of cyclosporine versus tacrolimus in 20 patients awaiting renal transplantation, among those who were HCV positive, insulin secretion increased with cyclosporine while decreasing with tacrolimus, suggesting the latter to have adverse β-cell effects. Bloom noted that HCV-positive patients who develop diabetes after liver transplant have a 6.5-fold increase in mortality (17). Thus, the question of approaches to treatment of new-onset diabetes in HCV-positive transplant recipients is of great potential importance, with immunosuppressive regimen modification not appearing to be effective. Interferon may improve glycemia and is safe for liver transplant recipients, but it is associated with unacceptably high risk of kidney transplant rejection, leading to the suggestion that interferon treatment may be needed before kidney transplantation. In a study of 55 patients treated with interferon, 21 had sustained virologic response, of whom 16 were transplanted, 13 treated with cyclosporine, all remaining HCV negative, and none developing PTDM (18).

Robert Woodward (Durham, NH) discussed the economics of PTDM, noting that U.S. Renal Database System data from 2000 show each transplant to cost $1,000–2,000 extra because of the risk of diabetes. In a set of 11,319 patients aged 20–64 years with nondiabetic renal disease transplanted after 1996, 62% of whom were treated with cyclosporine, diabetes developed in 9–12% of patients over 2 years, with somewhat greater incidence among persons who had received hemodialysis. At 1 year, the cost for persons who developed diabetes was $13,000–15,000 greater than that for persons without PTDM. As the incidence of diabetes was greater for persons treated with tacrolimus than for those receiving cyclosporine, the incremental cost was greater with the former agent. Kristina I. Rother (Bethesda, MD) discussed therapeutic options for PTDM, mentioning the potential for prevention with lifestyle modification and avoidance of tacrolimus and the importance of aggressive treatment of hypertension and hypercholesterolemia. In islet cell transplants, both tacrolimus and rapamycin blood levels correlate with blood glucose. Animal studies of tacrolimus show increased glucose levels, with rapamycin increasing insulin levels suggesting reduction in insulin sensitivity. Renal and cardiac dysfunction often preclude metformin and thiazolidinedione use after transplantation, with there being a potential drug interaction of pioglitazone increasing rapamycin and tacrolimus levels and requiring dose reduction. A study of treatment with rosiglitazone showed a decrease in HbA_{1c} in persons with diabetes after transplantation, although there was a trend to increased tacrolimus levels (19). Rother commented that early use of insulin may be the most appropriate approach for PTDM. Two studies presented at the ADA meeting gave further insight into the use of rosiglitazone for PTDM. Villanueva and Baldwin (abstract 300) treated 32 and 8 persons with PTDM following liver and kidney transplantation

with NPH and regular insulin twice daily and rosiglitazone 4 mg daily, with a subsequent increase to 8 mg daily and with addition of sulfonylureas in 26 patients. After a mean of 11 weeks of rosiglitazone, insulin was discontinued in 36 of the 40 patients. Five patients developed edema, and none developed pulmonary congestion. Srikanthan et al. (abstract 615) reviewed nine persons with PTDM following cardiac transplantation, showing a suggestion of decrease in development of coronary artery disease, suggesting that there may be antiatherogenic and -immunomodulatory effects of rosiglitazone.

Pancreas transplantation

At a symposium on pancreas transplantation, David Sutherland (Minneapolis, MN) discussed approaches to immunosuppression, noting that existing agents, CNIs, antimetabolites, and steroids, cause infections, lymphoproliferative disease (in part caused by Epstein-Barr virus), and nonimmune side effects and that lifelong immunosuppression is required because we currently lack the ability to produce graft tolerance. Steroid side effects include osteoporosis, diabetes, and dermopathy, and their withdrawal is highly desirable, with Sutherland's program not using steroids after the first week. CNI side effects are second only to those of steroids, with neural, renal, and diabetogenic effects, so that withdrawal is desirable, although the efficacy of these agents has led to extensive use for kidney transplantation and essentially universal use for pancreas transplantation. Antimetabolites such as azathioprine and MMF often cause gastrointestinal effects, and sirolimus commonly causes oral ulcers and dyslipidemia, a side effect also encountered with rapamycin plus cyclosporine.

Effective prophylactic treatment has greatly reduced the likelihood of opportunistic infection, with gancyclovir, which Sutherland termed the most effective drug developed for transplantation over the past 30 years, decreasing cytomegalovirus rates to 5%, and pneumocystic and *Nocardia* occurring following <1% of transplants with trimethoprim-sulfamethoxazole administered as infrequently as once weekly. Nonimmune side effects are less readily countered, leaving the transplant physician to choose accepting these adverse consequences, reducing the dose, or discontinuing and substituting. By developing combination treatment approaches with additive, although unfortunately not synergistic, immunosuppressive effects, while not having additive nonimmunosuppressive side effects, it may be possible to optimize outcome, with Sutherland's group at the University of Minnesota trying to develop approaches using neither steroids nor CNIs.

Sutherland reviewed the use of biological anti–T-cell agents. Depleting agents, such as thymoglobulin (a polyclonal anti-human thymocyte globulin), monoclonal OKT3 (an anti-CD3 monoclonal antibody exerting immunosuppressive effects by inducing peripheral T-cell depletion and modulation of the T-cell receptor complex), and campath (a therapeutic antibody directed against the CDw52 antigen expressed by lymphocytes with lytic abilities), are effective, although they have the potential to induce lympholysis-related cytokine release side effects. Nondepleting agents include anti-CD25 monoclonal antibodies and IL-2 receptor blockade with daclizumab, which, rather than causing lympholysis, downregulate the immune response. The anti–T-cell agents do not cause nonimmune side effects and, although usually used for induction, could conceptually be used for maintenance as well, although the need for intravenous administration is inconvenient. Sutherland described a pilot study begun in 2003 of pancreas transplantation with three initial Campath doses followed by repeated dosing when the lymphocyte count exceeds 200. MMF or rapamycin are also administered in this protocol. CNI-free maintenance with MMF or sirolimus has been achieved in other patients with a course of Campath. His group has performed ~130 living related donor segmental pancreas transplants, usually simultaneous with kidney transplantation. These patients usually receive thymoglobulin induction, followed by tacrolimus and MMF maintenance. In May 2003, a study was initiated using Campath plus a single dose of thymoglobulin as induction with campath maintenance, using steroids only to prevent the initial cytokine release reaction. The outcome has been similar to that of other protocols, with similar early rejection, infection, and malignancy rates. Patients with prior transplant who had increased creatinine were also converted to the new protocol, with evidence of preservation of renal function.

In a related study presented at the ADA meeting, David et al. (abstract 91-LB) compared data from the Scientific Registry of Transplant Recipients on all U.S. adult renal transplants performed between June 1995 and June 2002 to assess differences in outcome between 14,144 diabetic persons receiving MMF and 3,001 treated with azathioprine, showing the former to be associated with 20% less CVD mortality, with acute rejection in 24 vs. 28% and malignancy occurring in 2.2 vs. 3.7%, suggesting the former agent to be preferable. Luzi et al. (abstract 1901) presented evidence that insulin-mediated glucose clearance improves in rapamycin (plus statin)-treated patients following islet transplantation, noting that rapamycin has been recommended for its steroid-sparing effect. To assess whether this was an effect of glycemic improvement from the transplant, four persons with type 1 diabetes who were candidates for islet transplantation received rapamycin plus statins and were also found to have improvement in the glucose-lowering effect of insulin.

Stephen Bartlett (Baltimore, MD) gave an update on pancreas transplantation, recalling that the first was performed in 1966 at the University of Minnesota, with the patient dying after 2 months. In 1983, there was 67% 1-year patient survival and 21% graft survival. With the development of bladder drainage in 1983, the number of pancreas transplants increased, with 1-year graft survival 84% after simultaneous kidney and pancreas and 72% with pancreas after kidney transplantation. After the DCCT (Diabetes Control and Complications Trial) report, Bartlett stated, the rationale for pancreas transplantation was strengthened, and although the mortality of type 1 diabetes has decreased substantially over the past two decades (20), it is noteworthy that 10% of the intensive group of the DCCT experienced five or more episodes of coma or seizure, with persistent hypoglycemia unawareness increasing the risk of hypoglycemia and associated with cognitive dysfunction and arrhythmias, leading Bartlett to believe "it is something more than just an inconvenience," so that pancreas transplantation remains important. Currently, pancreas transplantation utilizes portal venous drainage, which reduces hyperinsulinemia and dyslipidemia

while allowing pancreas biopsy for rejection evaluation, recent evidence showing that 4-year pancreas survival has increased from 81 to 85%, far better than the 4-year graft survival of 33% reported with the Edmonton Protocol for islet cell transplantation. Complications of pancreas transplantation include early thrombosis in 1–8%, peripancreatic sepsis in 15%, and hemorrhage in 2–10% of patients, with indications for biopsy including elevations in amylase, lipase, or glucose (although as discussed above this is more likely to reflect PTDM than rejection), or unexplained fever. The number of solitary pancreas transplants (alone or after kidney transplantation) has increased greatly, although Bartlett referred to the somewhat controversial recent report that this may be associated with increased mortality (21), with D. Harlan, the senior author of this article (who was in the audience) stating that "the majority of patients with type 1 diabetes never have a decrement in renal function, " so that he believed that transplantation is appropriate for persons with renal disease but that the risks outweigh the benefits for those with normal renal function. In addition, there is evidence that the rate of decline in renal function worsens with pancreas transplant alone or islet after kidney transplant, perhaps because of CNI effects. In an analysis of ~100 persons following pancreas transplantation, 30 with ≥5 years of follow-up, creatinine clearance decreased from 90 to 65 at 36 months, and 6 developed end-stage renal disease and required renal transplants. In contrast, Bartlett noted, pancreas transplantation may improve renal survival after kidney transplantation. He suggested further that pancreas transplantation alone might offer benefit to diabetic persons with autonomic neuropathy, as there is evidence both that transplantation reverses this and that their CVD risk is markedly increased, causing disruption in the quality of life of persons with recurrent severe hypoglycemia (22,23). In a study presented at the meeting, Giannarelli et al. (abstract 295) presented an experience regarding pancreas transplantation alone with 32 type 1 diabetic persons followed for 1–3 years. A quadruple immunosuppressive regimen used basiliximab or antithymocyte globulin for induction and steroids, MMF, and tacrolimus for maintenance, reporting 100 and 93.5% patient and graft survival, respectively. The procedure normalized glycemic control, with HbA_{1c} 5.5 vs. 9.4% pretransplantation and with improvement in LDL cholesterol, blood pressure, neuropathy, proteinuria, and retinopathy. Pugliese et al. (abstract 297) described findings in 33 persons with type 1 diabetes whose hyperglycemia recurred on average 5.6 years following pancreas transplantation, out of ~250 pancreas grafts at their centers, with selective loss of insulin secretion in 7 persons, chronic pancreas rejection in 13, and evidence of IGT or type 2 diabetes in 13. Autoantibodies to GAD or IA-2 (transmembrane protein tyrosine phosphatase, a precursor of 40-kDa islet cell autoantigen) were present in 5 of those with selective insulin secretory defect and 9 of those with chronic rejection, but only in 2 of those with type 2 diabetes/IGT and in 3 of 14 randomly selected simultaneous pancreas and kidney transplantation (SPK) patients with normal glucose tolerance. GAD557I tetramer–positive CD4+ CD25+ T-cells were found in three of five of those with selective insulin secretory loss. Recurrence of autoimmunity may be an important cause of diabetes following pancreas transplantation despite ongoing immunosuppressive treatment, suggesting that monitoring for markers of autoimmunity may be appropriate.

Osama Gaber (Memphis, TN) further discussed indications for pancreas transplantation. He noted the high mortality of persons with glomerular filtration rate 15–29 ml/min while awaiting renal transplantation, stating that earlier referral improves outcome. Mortality rates are, Gaber stated, 45% lower and graft loss is 25–30% lower among persons having transplantation before dialysis is required. Overall life expectancy is 11 years longer for persons having transplantation than those electing chronic dialysis, recognizing that there may be many differences between the two groups determining their choice of treatment. Simultaneous pancreas and living donor kidney transplantation leads to the best life expectancy, with, for example, diastolic dysfunction and left ventricular hypertrophy improving more with pancreas plus kidney than with kidney transplantation alone. Primary living donor kidney transplantation has progressively improved outcome (24). Gaber suggested that pancreas transplantation alone leads to acceptable outcome (25) and that new approaches to immune suppression will avoid nephrotoxicity, agreeing with Bartlett that symptomatic autonomic neuropathy and hypoglycemia unawareness are indications and suggesting that persons with unstable glucose control or adverse effect of hyperglycemia on quality of life, those who will require immunosuppression for any indication, those with serious complications or wishing prevention of secondary complications, and perhaps certain persons with type 2 diabetes may also be candidates for the procedure.

Jimmy A. Light (Washington, DC) addressed the use of pancreas transplants for persons with type 2 diabetes, pointing out that there is little evidence on which to base the recommendation that persons with type 2 diabetes not be considered candidates, further pointing out that the use of C-peptide for determination of insulin deficiency is flawed by the elevation in C-peptide levels seen with decreased renal function and that the exacerbation of glycemic control commonly occurring following renal transplantation suggests there may be as great a benefit for insulin-requiring persons with type 2 as for those with type 1 diabetes. During the decade from 1989, his group performed 135 SPKs using systemic venous and bladder drainage, finding similar 4-year outcome regardless of C-peptide or race (26). Most insulin-dependent persons with type 2 diabetes at their center are African Americans whose mean age at first insulin use was 24 years, with transplantation at age 41. The mean pretransplant BMI was 25 kg/m^2, with a striking posttransplant weight gain to 32 kg/m^2 and weight gain particularly occurring in females. Patient and pancreas and kidney graft survival was similar for persons with type 1 and type 2 diabetes, leading Light to conclude that the diabetes type is irrelevant and to suggest that candidates <50 years of age who are not obese at transplantation may be particularly good candidates, particularly if glycemic control is difficult, with steroid-free regimens offering the potential for avoidance of weight gain.

Islet transplantation

James Shapiro, Edmonton, Canada (abstract 1904) presented results of the international multicenter islet transplantation study utilizing the Edmonton protocol at nine sites in Canada, the U.S., and Europe, with 36 patients undergoing the

procedure in an effort to duplicate the Edmonton experience of 64 patients. Patients weighing ≤70 kg and with creatinine clearance >80 ml · min^{-1} · 1.73 m^{-2} were studied, with 64% now 1 year posttransplant. Five patients had a single transplant, with a trend to pretransfusion HbA_{1c} being lower in those patients who had single donor success. Up to three transplants were used per patient, as in Edmonton. Nineteen patients are insulin independent at 1 year. Of the remainder, four withdrew from the study, six had primary nonfunction, and the rest are C-peptide producing but insulin requiring, so that, in total, persistent secretion of C-peptide was seen in 72% at 1 year. Islet cell autoantibodies were higher in persons who failed to achieve islet function, while 70% of those without measurable autoantibodies became insulin independent. Among patients with primary islet nonfunction, 60 and 40% failed to achieve adequate sirolimus and tacrolimus levels within 5 days, respectively, suggesting another important cause. Fiorina et al. (abstract 298) compared 17 patients with long-term function following islet transplantation to 20 patients losing >50% of C-peptide secretion within 6 months, similarly noting the latter to develop anti-GAD and –IA-2 antibodies, as described above for loss of whole pancreas insulin secretory function.

There was tremendous intrasite variability, from 0 to 100% success. Mean islet purity was 57% and viability 91.5%, with mean islet yield 6,299 islet equivalents/kg recipient: a tissue volume of 3.4 ml. Islet yield, although not purity or viability, showed a strong relationship to outcome. Those becoming insulin independent had a mean of 7,827 islets per transplant, while primary nonfunction had a mean yield of 5,880, with the number of islets infused 458,000 vs. 340,000 for single donor success versus primary failure. The engraftment index, an index based on the acute C-peptide response from each transplant, was 0.93 for persons becoming insulin independent, 0.59 for those with partial restoration of insulin response, and 0.05 for nonengraftment; the respective daily mean insulin requirements decreased from 30 to 0, decreased from 36 to 21, and increased from 33 to 39.

Before transplantation, the mean glucose exceeded 200 mg/dl in 72%, while at 1 year, 75% of patients had a glucose average of 60–139 mg/dl. The HbA_{1c} decreased from 6.5 to 5.6% in the insulin-independent group and improved in the insulin-dependent group. IGT was, however, found in most of the insulin-dependent group. No patients developed clinical acute cytomegalovirus infection, although three had serologic evidence of infection. Serious adverse events included neutropenia in 86%, mouth ulceration in 92%, abnormal liver function in 83%, anemia in 83%, and diarrhea in 58% of patients. Three patients required transfusion, two had partial portal vein thrombosis, and one had a bile leak requiring laparotomy and abdominal lavage. The mean portal pressure rose significantly but only modestly with the procedure. Lipid-lowering treatment was required prior to transplantation in 20%, with sirolimus leading to an additional 44% to require this subsequently. Creatinine did not increase significantly, macroalbuminuria did not occur, and there were no malignancies, opportunistic infections, or deaths.

In a presentation at the meeting, Hering et al. (abstract 1899) noted that a Collaborative Islet Transplant Registry has been created to follow the progress of clinical treatment in this area. Rilo et al. (abstract 154) reported the use of islet autotransplantation following total pancreatectomy for incapacitating painful chronic pancreatitis in 14 persons. Although all developed impairment in glucose tolerance, β-cell function was partially preserved, with four not requiring diabetes treatment, suggesting this to be an important approach to treatment of this illness. Cagliero et al. (abstract 1894) discussed their experience with 13 islet transplants in seven C-peptide–negative type 1 diabetic patients who had had renal transplantation and who were receiving sirolimus and tacrolimus. All patients became C-peptide positive, with a decrease in HbA_{1c} from 8.6 to 6.9%, and all patients were able to stop chronic insulin therapy, suggesting that persons already tolerating immunosuppression therapy with sirolimus and tacrolimus for a prior kidney transplant may be ideal islet transplant recipients. This may be particularly relevant in view of an analysis by Senior et al. (abstract 296) of the Edmonton experience of the effect of sirolimus plus low-dose tacrolimus on the kidney in 45 persons with type 1 diabetes receiving islet transplantation. HbA_{1c} decreased from 8.1 to 6.1% through 12 months, but creatinine clearance decreased from 98 to 91 ml · min^{-1} · 1.73m^{-2} during this period. In 27, 11, and 5 patients studied at 24, 36, and 48 months, respectively, the creatinine clearance decreased further to 85, 74, and 61 ml · min^{-1} · 1.73m^{-2} despite HbA_{1c} levels of 6.6, 6.6, and 6.4% and no increase in blood pressure. Fourteen of 38 initially normoalbuminuric persons progressed to microalbuminuria. Although the authors suggest that "restriction of islet alone transplants to those with preserved renal function seem prudent," one could also rationally argue that the benefit of improved glycemia may be entirely outweighed by this adverse consequence.

Vahl et al. (abstract 299) studied a canine islet autotransplantation model, showing variable C-peptide response to arginine administered via the hepatic artery and portal vein, suggesting that the blood supply of pancreatic islets transplanted into the liver is derived to differing degrees from the two sources, a potential source of variation in β-cell function. Ihm et al. (abstract 149) compared the insulin secretory function of human islets isolated from cadaveric donors age 16–70 years, showing that the glucose-stimulated insulin response was almost threefold greater in islets isolated from persons <40 than those >40 years of age at death, with strong correlation between the C-peptide response to glucose and the donor age. Hirshberg et al. (abstract 150) studied three patients who were insulin independent for at least 18 months after islet transplantation. Portal, hepatic, and central sampling after arginine-stimulated insulin release showed that portal C-peptide concentrations exceeded those obtained from central venous sampling in two of the patients, suggesting that improvement in endogenous insulin production occurs, perhaps either due to improved glycemia or to the immunosuppressive treatment itself.

Islet regeneration

Denise L. Faustman (Boston, MA) discussed studies suggesting the possibility of islet regeneration in the NOD mouse model of type 1 diabetes. Autoimmunity, she stated, manifests as many different diseases, such as type 1 diabetes, Hashimoto's thyroiditis, rheumatoid arthritis, and Crohn's disease. Persons with autoimmunity often develop an additional au-

toimmune disease, but the situation is complex and inconclusive, as even identical twins are concordant for an autoimmune disease less than half of the time. Our current concept of autoimmune disease involves the notion that the bone marrow produces many millions of different T-cells, the vast majority of which are negatively selected by a process of T-cell education to self-peptides, with autoimmunity a set of conditions in which "bad cells" escape. The major histocompatability complex class I "groove" is a recognition site for self- as well as viral peptides that acts as an educational complex for the process of self-selection. The ideal immune suppressive treatment would target only the disease-causing population of T-cells. In the NOD mouse model and in the majority of human autoimmune diseases, two different receptors exist leading to T-cell death, the T-cell receptors and tumor necrosis factor (TNF)-α receptors. The memory T-cells are insensitive to self-selection–induced cell death but exquisitely sensitive to TNF receptor–induced cell death. Both receptors are linked to nuclear factor (NF)-κB. Signals such as TNF-α and IL-1 lead to translocation of NF-κB into the nucleus, which promotes cell survival, while the inhibitor of NF-κB is involved in proteasome-dependent NF-κB degradation. TNF-α does not induce NF-κB to a normal extent in the NOD mouse, and NF-κB precursor proteins are improperly processed in NOD mice, with proteasomes from NOD mice not cleaving the NF-κB precursors. The NOD mouse proteasomes are missing the LMP2 subunit, which is involved in NF-κB processing in T-cells but not in macrophages. This could be exploited for specificity of potential therapeutic approaches. Faustman stated that defects in NF-κB and LMP2 are not present at birth in NOD mice but are acquired around 12 weeks in T–memory cells, although not in monocytes or B-cells, further suggesting the potential for a selective intervention. Defects in NF-κB have been shown in human autoimmune diseases including Crohn's disease and Lupus. With low-dose TNF-α administration at the earliest stages of diabetes in NOD mice, apoptosis of disease-causing cells can be demonstrated.

Two populations of diabetes-causing cells are present in the NOD mouse, T–memory cells and major histocompatability complex class I and self-peptide matched cells. Faustman described a therapeutic approach to NOD mice in which evidence of pancreatic islet regeneration could be demonstrated following a "cure" with islet transplantation and immunosuppression. Faustman described studies (27) in which permanent reversal of diabetes in the NOD model could be demonstrated, using two different approaches to treatment, one which destroyed memory T-cells and the other using TNF-α. Splenocytes were better than bone marrow cells in reversing disease. Both irradiated and living splenocytes were used, with remission of diabetes in ~90 and 40 days with the two approaches and with intense peri-islitis using the irradiated cells but no inflammatory infiltrate with the live splenocytes. She noted the importance of normalization of blood glucose in her model to allow the islet regenerative process to occur, suggesting that this helps to preserve islet creation and normal β-cell function; therefore, immunomodulatory therapy may not succeed in the hyperglycemic state.

The source of the islets may differ in the two experiments. Those animals that had received live splenocytes showed islet differentiation, with approximately half of cells derived from the donor, shown by gene markers, and also showed some duct cells derived from the donor cells. The source of the cells that developed into islets is uncertain, with Faustman suggesting that pancreatic islets can be derived from splenocytes. She noted that following surgical partial pancreatectomy with removal of the head of the pancreas alone, regeneration is typically seen and development of diabetes unlikely, but that removal of the tail of the pancreas with splenectomy appears to prevent pancreatic regeneration and that persons with β-thallasemia may develop ketosis-prone diabetes following splenectomy. She concluded that severe end-stage NOD diabetes can be permanently reversed, with islet regeneration either from endogenous cells (associated with peri-islitis, with pancreatic inflammation appearing to be important in promoting β-cell–to–β-cell regeneration) or from splenocytes. Asked about the malignant potential of administering splenocytes, she agreed that any preparation including stem cells could cause tumors, further suggesting that the optimal approach is to cause differentiation of endogenous cells. She noted that the question of islet regeneration is highly controversial, with a number of authors reporting findings to some extent at variance with those of her studies (28–30).

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