Context Islet allografts from 2 to 4 donors can reverse type 1 diabetes. However, for islet transplants to become a widespread clinical reality, diabetes reversal must be achieved with a single donor to reduce risks and costs and increase the availability of transplantation.

Objective To assess the safety of a single-donor, marginal-dose islet transplant protocol using potent induction immunotherapy and less diabetogenic maintenance immunosuppression in recipients with type 1 diabetes. A secondary objective was to assess the proportion of islet transplant recipients who achieve insulin independence in the first year after single-donor islet transplantation.

Design, Setting, and Participants Prospective, 1-year follow-up trial conducted July 2001 to August 2003 at a single US center and enrolling 8 women with type 1 diabetes accompanied by recurrent hypoglycemia unawareness or advanced secondary complications.

Interventions Study participants underwent a primary islet allotransplant with 7271 (SD, 1035) islet equivalents/kg prepared from a single cadaver donor pancreas. Induction immunosuppression was with antithymocyte globulin, daclizumab, and etanercept. Maintenance immunosuppression consisted of mycophenolate mofetil, sirolimus, and no or low-dose tacrolimus.

Main Outcome Measures Safety (assessed by monitoring the severity and duration of adverse events) and efficacy (assessed by studying the recipients’ insulin requirements, C-peptide levels, oral and intravenous glucose tolerance results, intravenous arginine stimulation responses, glycosylated hemoglobin levels, and hypoglycemic episodes) associated with the study transplant protocol.

Results There were no serious, unexpected, or procedure- or immunosuppression-related adverse events. All 8 recipients achieved insulin independence and freedom from hypoglycemia. Five remained insulin-independent for longer than 1 year. Graft failure in 3 recipients was preceded by subtherapeutic sirolimus exposure in the absence of measurable tacrolimus trough levels.

Conclusions The tested transplant protocol restored insulin independence and protected against hypoglycemia after single-donor, marginal-dose islet transplantation in 8 of 8 recipients. These results may be related to improved islet engraftment secondary to peritransplant administration of antithymocyte globulin and etanercept. These findings may have implications for the ongoing transition of islet transplantation from clinical investigation to routine clinical care.

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METHODS

Study Design

Our study was a prospective, single-center, 1-year follow-up pilot trial conducted from July 2001 to August 2003. The primary efficacy end point was the proportion of recipients who achieve insulin independence in the first year after a single-donor islet transplant. We defined recipients as insulin-independent if they maintained fasting blood glucose levels below 126 mg/dL (7.0 mmol/L) and 2-hour postprandial levels below 180 mg/dL (10.0 mmol/L) after discontinuation of insulin.

A total of 8 patients (coincidentally all women) were enrolled. Eligibility criteria are detailed in the Box and detailed recipient characteristics are shown in Table 1. Our study protocol was approved by the local institutional review board, and written informed consent was obtained from all participants.

Islet Product Preparation

Eighteen consecutive donor pancreases were procured from cadaver donors younger than 50 years with a body mass index (calculated as weight in kilograms divided by square of height in meters) of 27 or greater; the pancreases were preserved for 8 hours or less using the 2-layer method. ABO compatibility and a negative serum crossmatch for T cells were required, but HLA antigen matching was not. Islets were isolated as previously described. Briefly, preserved pancreases were perfused with cold Liberase (Roche Diagnostics Corp, Indianapolis, Ind). Islets were isolated by the automated method, purified with continuous iodixanol density gradients in a Cobe 2991 cell separator (Gambro BCT, Lakewood, Colo), and cultured free-floating in supplemented CMRL 1066 for 1 day at 37°C and 1 day at 22°C. Of the 18 consecutive cadaver donor pancreases processed for this study, preparations from 8 were transplanted (detailed donor and graft characteristics for those 8 are shown in Table 2). Islet preparations from the remaining 10 donor pancreases were not transplanted because of inadequate islet yield for single-donor islet transplantation. The mean islet yield of 7 of those 10 preparations was 30,428 (SD, 59,780) IEs.

Transplant Procedure

After establishing access to the portal vein via minilaparotomy or percutaneous transhepatic portal venous catheterization, we infused 7271 (SD, 1035) IEs/kg of recipient body weight by gravity, along with heparin, 70 U/kg, on day 0 into 8 consecutive participants. Prophylactic anticoagulation was continued with intravenous heparin (target partial thromboplastin time, 50-60 seconds) for 48 hours, followed by enoxaparin (30 mg subcutaneously twice daily) through day 7.

Immunosuppression

Induction immunosuppression, initiated on day –2, consisted of rabbit antithymocyte globulin (RATG) (0.5 mg/kg of recipient body weight [day –2], 1.0 mg/kg [day –1], 1.5 mg/kg [days 0 through +2]), methylprednisolone (on day –2 only, 2 mg/kg), daclizumab (5 doses of 1 mg/kg every 2 weeks starting on day 0), and etanercept (50 mg intravenously 1 hour pretransplantation, followed by 25 mg subcutaneously on days 3, 7, and 10). Premedication for RATG included acetaminophen and diphenhydramine as well as pentoxyfylline, which was extended through day 7 posttransplantation. Maintenance immunosuppression was initiated with sirolimus (0.2 mg/kg starting on day –2, followed by 0.1 mg/kg daily; target whole blood trough levels, 5-15 ng/mL, as tolerated) and reduced-dose tacrolimus (0.015 mg/kg twice daily, starting on day 1; target whole blood trough levels, 3-6 ng/mL). At 1 month posttransplantation, tacrolimus was gradually replaced with mycophenolate mofetil (750-1000 mg, twice daily); tacrolimus was either discontinued or dosed to a target trough level of less than 3 ng/mL. If target levels of sirolimus could not be achieved or maintained, however, tacrolimus (target level, 3-6 ng/mL) was continued.

Box. Study Eligibility Criteria

**Inclusion Criteria**

1. Age 18 years or older
2. C-peptide–negative* type 1 diabetes for >5 years complicated by 1 of the following:
   - Advanced secondary complications including proliferative retinopathy or clinically significant macular edema or photocoagulation, urinary albumin excretion >300 mg/d but proteinuria <3 g/d, or symptomatic autonomic neuropathy
   - Metabolic lability/instability (≥2 episodes of severe hypoglycemia or ≥2 hospital admissions for ketosis in the past year)
   - Hypoglycemia unawareness (≥4 “reduced” responses in the Clark “hypoglycemia questionnaire”)

**Exclusion Criteria**

1. Body weight >70 kg
2. Insulin requirements >40 U/d
3. Previous islet transplant
4. Abnormal renal function (creatinine clearance <60 mL/min [1.002 mL/s] per 1.73 m²)
5. Portal hypertension, abnormal liver enzyme test results, or history of significant liver disease

*Defined as C-peptide level <0.2 ng/mL after administration of 5 g of intravenous arginine.
Concomitant Therapy
Antimicrobial and antiviral prophylaxis with imipenem, vancomycin, trimethoprim/sulfamethoxazole, and valganciclovir was administered. Glycemic control was achieved with intravenous insulin from day –2 to day +2 relative to transplant and with subcutaneous insulin for at least 3 additional weeks.

Safety and Efficacy Assessments
Safety of the transplant protocol was assessed by monitoring the severity and duration of procedural complications, serious infections, or islet- or immunosuppression-related adverse events. Self-measured blood glucose concentrations (5 or more times daily), hypoglycemic episodes, basal C-peptide levels, and levels of glycosylated hemoglobin (by high-performance liquid chroma-

Table 1. Recipient Characteristics for Each of 8 Female Pretransplant C-Peptide–Negative Islet Recipients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recipient No.</th>
<th>1†</th>
<th>2</th>
<th>3</th>
<th>4†</th>
<th>5†</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>Overall Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td>31</td>
<td>38</td>
<td>36</td>
<td>36</td>
<td>38</td>
<td>38</td>
<td>43</td>
<td>39</td>
<td>37 (3)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td></td>
<td>52.6</td>
<td>55.3</td>
<td>65.2</td>
<td>42.1</td>
<td>63.4</td>
<td>64.7</td>
<td>67.2</td>
<td>66.9</td>
<td>59.7 (8.9)</td>
</tr>
<tr>
<td>Body mass index‡</td>
<td></td>
<td>20.3</td>
<td>21.9</td>
<td>23.8</td>
<td>18.3</td>
<td>25.8</td>
<td>24.4</td>
<td>24.7</td>
<td>24.6</td>
<td>23.0 (2.6)</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td></td>
<td>20</td>
<td>16</td>
<td>31</td>
<td>25</td>
<td>35</td>
<td>32</td>
<td>34</td>
<td>31</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Anti-GAD65</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Anti-ICA512</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Daily insulin, U/kg</td>
<td></td>
<td>0.50</td>
<td>0.51</td>
<td>0.55</td>
<td>0.76</td>
<td>0.54</td>
<td>0.37</td>
<td>0.54</td>
<td>0.69</td>
<td>0.56 (0.12)</td>
</tr>
<tr>
<td>HbA1c range, %§</td>
<td></td>
<td>4.6-6.8</td>
<td>8.1-8.9</td>
<td>7.0-7.9</td>
<td>6.1-7.5</td>
<td>7.6-9.4</td>
<td>6.9-8.1</td>
<td>5.9-7.9</td>
<td>6.6-10.2</td>
<td>7.8 (5.9)</td>
</tr>
<tr>
<td>SEH 1 y pretransplantation, No.</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>0</td>
<td>18</td>
<td>3</td>
<td>2</td>
<td>12</td>
<td>7.8 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Diabetes complications</td>
<td>NR, MA</td>
<td>None</td>
<td>NR, MA</td>
<td>PR, MA</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>None</td>
<td>MA</td>
<td></td>
</tr>
</tbody>
</table>

**Recipient characteristics for each of 8 female pretransplant C-peptide–negative islet recipients.**

†Recipient resumed exogenous insulin therapy posttransplantation.
‡Calculated as weight in kilograms divided by square of height in meters.
§Range based on 4-8 measurements over 2 years pretransplantation.

Table 2. Donor and Graft Characteristics for Each of 8 Female Islet Recipients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recipient No.</th>
<th>1*</th>
<th>2</th>
<th>3</th>
<th>4*</th>
<th>5*</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>Overall Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age, y</td>
<td></td>
<td>19</td>
<td>47</td>
<td>48</td>
<td>50</td>
<td>47</td>
<td>42</td>
<td>31</td>
<td>24</td>
<td>39 (12)</td>
</tr>
<tr>
<td>Donor weight, kg</td>
<td></td>
<td>115</td>
<td>94</td>
<td>84</td>
<td>78</td>
<td>127</td>
<td>76</td>
<td>136</td>
<td>95</td>
<td>100.6 (22.8)</td>
</tr>
<tr>
<td>Donor body mass index†</td>
<td></td>
<td>32.2</td>
<td>35.7</td>
<td>29.0</td>
<td>26.9</td>
<td>45.3</td>
<td>28.9</td>
<td>48.5</td>
<td>27.6</td>
<td>34.3 (8.3)</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Trauma, ICH, Stroke, Stroke, ICH, Stroke, Trauma, Trauma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose during hospitalization, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>96</td>
<td>129</td>
<td>126</td>
<td>141</td>
<td>148</td>
<td>154</td>
<td>136</td>
<td>122</td>
<td>132 (18)</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>158</td>
<td>310</td>
<td>284</td>
<td>237</td>
<td>245</td>
<td>307</td>
<td>267</td>
<td>236</td>
<td>256 (49)</td>
<td></td>
</tr>
<tr>
<td>Elevated vasopressors</td>
<td>No, No</td>
<td>No, No</td>
<td>No, No</td>
<td>No, No</td>
<td>No, No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac/respiratory arrest</td>
<td>No, No</td>
<td>No, No</td>
<td>No, No</td>
<td>No, No</td>
<td>No, No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-A/B matches</td>
<td>1, 1</td>
<td>0, 1</td>
<td>1, 1</td>
<td>1, 1</td>
<td>1, 2</td>
<td>1, 1</td>
<td>1, 2</td>
<td>1, 1</td>
<td>1, 0 (0.5)</td>
<td></td>
</tr>
<tr>
<td>HLA-DR matches</td>
<td>0, 0</td>
<td>0, 0</td>
<td>0, 0</td>
<td>0, 0</td>
<td>0, 0</td>
<td>0, 0</td>
<td>0, 0</td>
<td>0, 0</td>
<td>0, 1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Graft</td>
<td>Cold storage time, h</td>
<td>7.0</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>8.0</td>
<td>5.0</td>
<td>7.3</td>
<td>3.0</td>
<td>6.6 (1.7)</td>
</tr>
<tr>
<td>Tissue volume, mL</td>
<td>2.0</td>
<td>1.8</td>
<td>2.8</td>
<td>1.3</td>
<td>1.2</td>
<td>2.0</td>
<td>1.0</td>
<td>4.5</td>
<td>3.2</td>
<td>2.5 (1.7)</td>
</tr>
<tr>
<td>Islet equivalents per kg body weight</td>
<td>7478</td>
<td>6996</td>
<td>5936</td>
<td>6536</td>
<td>7720</td>
<td>6222</td>
<td>8553</td>
<td>8724</td>
<td>7271 (1035)</td>
<td></td>
</tr>
<tr>
<td>Beta cells/kg, ×10³‡</td>
<td>2.7</td>
<td>3.7</td>
<td>5.3</td>
<td>4.2</td>
<td>1.2</td>
<td>3.7</td>
<td>10.9</td>
<td>10.3</td>
<td>5.3 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Islet purity, %</td>
<td>67.5</td>
<td>70.0</td>
<td>60.0</td>
<td>62.5</td>
<td>67.5</td>
<td>60.0</td>
<td>60.0</td>
<td>67.5</td>
<td>64 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Islet viability, %§</td>
<td>93.1</td>
<td>91.4</td>
<td>98.2</td>
<td>94.9</td>
<td>100.0</td>
<td>99.1</td>
<td>95.7</td>
<td>95.0</td>
<td>96 (3.0)</td>
<td></td>
</tr>
<tr>
<td>GSIR index</td>
<td>3.70</td>
<td>3.79</td>
<td>3.18</td>
<td>3.98</td>
<td>1.39</td>
<td>2.33</td>
<td>2.76</td>
<td>5.66</td>
<td>3.4 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Endotoxin, EU/kg</td>
<td>0.48</td>
<td>0.36</td>
<td>0.18</td>
<td>&lt;0.24</td>
<td>&lt;0.65</td>
<td>&lt;0.63</td>
<td>2.01</td>
<td>0.62</td>
<td>0.7 (0.6)</td>
<td></td>
</tr>
</tbody>
</table>

**Recipient characteristics for each of 8 female islet recipients.**

*Recipient resumed exogenous insulin therapy posttransplantation.
†Calculated as weight in kilograms divided by square of height in meters.
‡Derived from the total DNA content and the percentage of beta cells in the graft, elevated vasopressor levels, dopamine >20 µg/kg per min, and/or norepinephrine at any dose.
§Based on analysis of islet aliquots stained with fluorescein diacetate and propidium iodide.

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HbA1c range, % 4.7–5.1 5.7–6.3 5.1–5.4 5.7 5.8–6.4 4.4–5.8 5.4–5.7 5.5–5.6

Days to return to PTIR

Days to graft failure

Days of insulin independence† 56 to 177 56 to 177 56 to 330 247 366 NA NA NA

§Mean of the 3 peak levels minus mean prechallenge level. Normal controls without diabetes showed a mean (SD) response to arginine of 29.1 (5.3) µU/mL and a mean (SD) response to glucose of 1.04 (0.17) ng/mL.

‡Number of episodes of severe hypoglycemia for the duration of islet graft function through 1 year posttransplantation.

†Relative to islet transplant performed on day 0.

*Recipient resumed exogenous insulin therapy posttransplantation.

**Mean of the 3 peak levels minus mean prechallenge level. Normal controls without diabetes showed a mean (SD) response to arginine of 29.1 (5.3) µU/mL and a mean (SD) response to glucose of 1.04 (0.17) ng/mL.

Acute insulin response, µU/mL§

OGTT 2-h glucose, mg/dL NA 208 120 NA NA 120 90 129 133.4 (44.2)

To arginine NA 11.7 13.3 NA NA 14.8 16.2 21.3 15.5 (3.7)

To glucose NA 8.0 15.7 NA NA 17.0 21.6 21.3 16.7 (5.5)

Basal C-peptide, ng/mL 1.95 1.58 1.44 NA 1.22 2.36 1.90 2.28 1.82 (0.43)

Acute C-peptide response, ng/mL†

To arginine NA 0.90 1.17 NA NA 0.95 1.07 1.26 1.07 (0.15)

To glucose NA 0.48 1.25 NA NA 1.22 1.60 1.62 1.23 (0.46)

Abbreviations: HbA1c, glycosylated hemoglobin; NA, not applicable; OGTT, oral glucose tolerance test; PTIR, pretransplant insulin requirements.

SI conversion factor: To convert mg/dL of glucose to mmol/L, multiply values by 0.055.

*Recipient resumed exogenous insulin therapy posttransplantation.

†Relative to islet transplant performed on day 0.

‡Number of episodes of severe hypoglycemia for the duration of islet graft function through 1 year posttransplantation.

§Mean of the 3 peak levels minus mean prechallenge level. Normal controls without diabetes showed a mean (SD) response to arginine of 29.1 (5.3) µU/mL and a mean (SD) response to glucose of 56.1 (8.4) µU/mL.

¶Mean of the 3 peak levels minus mean prechallenge level. Normal controls without diabetes showed a mean (SD) response to arginine of 0.60 (0.07) ng/mL and a mean (SD) response to glucose of 1.04 (0.17) ng/mL.

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transplantation revealed 2-hour plasma glucose levels below 140 mg/dL (7.8 mmol/L). The 2-hour plasma glucose level in the fifth recipient was 208 mg/dL (11.5 mmol/L). These 5 recipients received daily mycophenolate mofetil doses of 1.5 to 2.0 g. They either achieved and maintained sirolimus trough levels greater than 9 ng/mL, with tacrolimus trough levels of 0 to less than 3 ng/mL, or achieved tacrolimus trough levels of 3 to 6 ng/mL in the absence of target sirolimus trough levels. The 3 recipients who resumed exogenous insulin therapy had received 1.5 g/d or more of mycophenolate mofetil but had subtherapeutic sirolimus trough levels (<9 ng/mL) in the absence of measurable tacrolimus trough levels (<3 ng/mL). For additional information, see Table 3 for metabolic monitoring and Table 4 for exposure to immunosuppressive drugs.

**Autoantibodies and Alloantibodies**

Of the 3 participants with graft failure, 2 tested positive for anti-GAD65 and anti-ICA512 in the pretransplantation period. In contrast, none of the 5 who remained insulin-independent tested positive for anti-GAD65 and anti-ICA512.

Graft failure was followed by allo sensitization in 2 recipients.

**COMMENT**

Our results mark a distinct advance in islet transplant efficacy. We not only achieved insulin independence using islets from only 1 donor pancreas (as compared with 2 to 4 in the Edmonton trial), we also achieved superior glycemic control (as evidenced by normal results of oral glucose tolerance testing in 4 of 5 recipients with sustained insulin independence) using significantly fewer islets (7271 [SD, 1035] IEs/kg vs 11 547 [SD, 1604] IEs/kg; P<.001). We had previously achieved insulin independence in 4 of 6 participants with type 1 diabetes who received an islet mass of 10 302 (SD, 2594) IEs/kg from 1 donor pancreas. However, transplantation of such an islet mass is only available from a limited number of donor pancreases and obviates assessment of the ability of a given protocol to permit reversal of diabetes with a lower islet mass retrievable from a larger subgroup of donor pancreases.

Determining the reasons for our high success rates with a lower islet mass from a single donor pancreas will have important ramifications for the advancement of the field. Previous studies by us and others have suggested that excluding pancreases from donors older than 50 years, limiting cold storage to less than 8 hours and using the 2-layer preservation method, avoiding use of Ficol during islet purification, and cultivating islets pretransplantation could conceivably preserve the potency of transplanted islets. Since pancreas procurement, preservation, islet processing, and culture protocols in the 2 studies were all identical, we assume that the potency was the same and therefore interpret the high efficacy of single-donor, marginal-dose islet transplants in our current trial as preliminary evidence of improved engraftment. In this study, induction therapy was with RATG, combined with daclizumab and etanercept. The resistance of islet-directed autoimmune responses to conventional immunosuppressive drugs and the immediate exposure of intraportally transplanted islets to primed autoreactive, islet beta cell–directed T cells have also provided a strong rationale for pretransplant initiation of RATG, which is known to cause selective depletion of activated T cells and dose-dependent depletion of resting T cells. Many of these effects are shared with the anti-CD3 monoclonal antibody, hOKT3y1 (Ala-Ala), used in our previous trial. Thus, they may not sufficiently explain the ability of the protocol used in our current trial to facilitate reversal of diabetes after single-donor, marginal-dose islet transplants. Therefore, the results are possibly related to the peritransplant administration of the soluble tumor necrosis factor receptor etanercept. Tumor necrosis factor α is cytotoxic to human islet beta cells. In murine models, selective inhibition of tumor necrosis factor α in the peritransplant period has promoted reversal of diabetes after marginal-mass islet transplants. Etanercept administration is a new addition to our protocol and distinguishes this trial from our previous trial, so it could have been a major factor allowing consistent diabetes reversal with a low islet dose.

Moreover, replacing or minimizing tacrolimus at 1 month posttransplantation, as we did in our current trial, may have enhanced the function of engrafted islets. Low-dose calcineurin inhibitor therapy, with no or minimal doses of steroids, has previously been associated with significantly reduced insulin sensitivity and beta cell secretory reserve, suggesting that even low-dose tacrolimus therapy may limit the ability of

### Table 4. Immunosuppressive Drug Exposure and Portal Venous Access Route for Each of 8 Female Islet Transplant Recipients

<table>
<thead>
<tr>
<th>Recipient No.</th>
<th>Drug exposure†</th>
<th>Portal venous access route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Mycophenolate mofetil, g/d 1.5</td>
<td>Minilaparotomy</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.5-2.0</td>
<td></td>
</tr>
<tr>
<td>4*</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>5*</td>
<td>1.0-1.5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.5-2.0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td></td>
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</tbody>
</table>

*Recipient resumed exogenous insulin therapy posttransplantation.
†Mean after day 30.
ISLET TRANSPLANTATION IN PATIENTS WITH TYPE 1 DIABETES

a reduced islet mass to reverse diabetes. Maintenance immunosuppression with mycophenolate mofetil and sirolimus, shown to be synergistic in experimental studies,12 is without diabetogenic or nephrotoxic adverse effects and is sufficiently potent, provided induction immunosuppression is administered and adequate sirolimus levels are achieved and maintained. In light of the results on exposure to immunosuppressive drugs (Table 4), it seems likely that the islet graft failure experienced by 3 recipients was caused by aloimmunity and/or recurrent autoimmunity. The observation that 2 of 3 recipients with graft failure, but none of the 5 who remained insulin-independent, tested positive for both anti-GAD65 and anti-ICA512 in the pretransplant period suggests a possible involvement of autoimmunity in graft failure. More detailed studies in a larger series of recipients will be needed to accurately ascribe islet graft loss to metabolic or immunologic reasons.

In conclusion, potent induction immunotherapy as used in this study may increase the ability of low-dose islet allografts to reverse diabetes and may minimize nephrotoxicity and cardiovascular toxicity by sparing calcineurin inhibitor dosing. While these findings may suggest a distinct advance in islet transplantation, further study in a larger population with longer follow-up will be critical to assess the risk-benefit ratio of this emerging therapeutic option.

Author Contributions: Dr Hering had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: Hering, Kandaswamy, Eckman, Matsumoto, Hunter, Sutherland. Acquisition of data: Hering, Kandaswamy, Ansite, Eckman, Nakano, Sawada, Matsumoto, Ihm, Zhang, Parkey, Hunter. Analysis and interpretation of data: Hering, Eckman, Sutherland. Drafting of the manuscript: Hering, Eckman, Sutherland. Critical revision of the manuscript for important intellectual content: Hering, Kandaswamy, Eckman, Sawada, Matsumoto, Ihm, Zhang. Obtained funding: Hering. Administrative, technical, or material support: Hering, Kandaswamy, Eckman, Nakano, Matsumoto, Zhang.

Study supervision: Hering, Sutherland. All authors contributed to the preparation of the report.

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REFERENCES


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institution. It is possible that the patient population of some institutions differs from the surrounding population in important ways. Despite these limitations, our study demonstrates that notices of privacy practices are lengthy and contain complex language that is unlikely to be understood by a considerable proportion of the populations served by top-ranked US health care institutions. If the purpose of the HIPAA legislation is to improve communication between patient and clinician, the documents used to do so need to be changed.

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CORRECTIONS

Incorrect Reporting: In the Original Contribution entitled “Association Between Cardiovascular Outcomes and Antihypertensive Drug Treatment in Older Women” published in the December 15, 2004, issue of JAMA (2004;292:2849-2859), the first sentence of the “Results” section of the Abstract should have read “Among 30,219 women with hypertension but no history of CVD, 19,889 were receiving pharmacological antihypertensive treatment, of whom 11,294 (57%) were receiving...” In Table 3 on page 2854, the number presented in the column heading for women receiving ACE inhibitor plus calcium channel blocker should have been 477, rather than 47. On pages 2855-2856, in the sentence beginning “The cumulative cardiovascular mortality rate for calcium channel blockers begins to diverge...,” the phrase “is lower than for ACE inhibitors.” should have read “is higher than for ACE inhibitors.”

Incorrect Data: In the Preliminary Communication entitled “Single-Donor, Marginal-Dose Islet Transplantation in Patients With Type 1 Diabetes” published in the February 16, 2005, issue of JAMA (2005;293:830-835), incorrect values were reported in the Table 3 footnotes on page 833. The last sentence of the last footnote should have read “Normal controls without diabetes showed a mean (SD) response to arginine of 1.80 (0.21) ng/mL and a mean (SD) response to glucose of 3.12 (0.51) ng/mL.”

Incorrect Byline Order: In the Research Letter entitled “Accessibility and Accuracy of Web Page References in 5 Major Medical Journals” published in the December 8, 2004, issue of JAMA (2004;292:2723-2724), the order of authors in the byline should have been reported as Renée Crichlow, MD, Nicole Wimbush, MD, and Stephanie Davies.

ANNOUNCEMENT
Online Submission and Peer Review System Available

The JAMA editorial office has introduced an online manuscript submission and peer review system developed by ejournalPress that will serve the needs of authors, reviewers, and editors. The new system will go live on April 12, 2005. See http://www.jama.com for more detailed information.