

## Glucose Homeostasis is Regulated by Donor Islets in Xenografts

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**A** FEW successful human islet allograft transplants allowing for prolonged insulin independence have demonstrated the feasibility of clinical islet cell transplantation in man.<sup>1-4</sup> The possibility to alter islet immunogenicity may allow for this procedure to be performed without immunosuppression in the future. One major obstacle to applying this technique to many patients would be a lack of donors. Pancreatic islet xenografts have recently been proposed as an alternative to allotransplantation in patients with type 1 diabetes. Trials of islet xenografts (pig to man) have been reported, resulting in an increased interest in this approach.<sup>5</sup> In the present study, we have used purified adult human islets to determine whether glucose homeostasis is regulated by xenogeneic donor islets.

### METHODS

Human islets were isolated from cadaveric donor pancreata obtained from multiorgan donors.<sup>6,7</sup> The islets were isolated using a modification<sup>8</sup> of the automated method previously described.<sup>9</sup> Athymic male nude mice (Sprague-Dawley) were made diabetic by a single intravenous injection of streptozocin (165 mg/kg) into the tail vein. Diabetes was confirmed if random plasma glucose following the injection was >300 mg/dL. Three to 5 days later, if diabetes was verified, each animal (n = 11) received an aliquot of approximately 600 (150- $\mu$ m) human islet equivalents that were transplanted beneath the left renal capsule.<sup>10</sup> Two weeks following the transplantation, the animals underwent a standard intraperitoneal glucose tolerance test (IPGTT).<sup>11</sup> Following an overnight fast, the animals were injected with 2 g/kg IP of a 25% dextrose solution. Samples were obtained for analysis of plasma glucose at 0, 15, 30, and 60 minutes following the injection. Non-streptozocin-injected male nude mice (n = 10) from the same litter served as controls for the IPGTT.

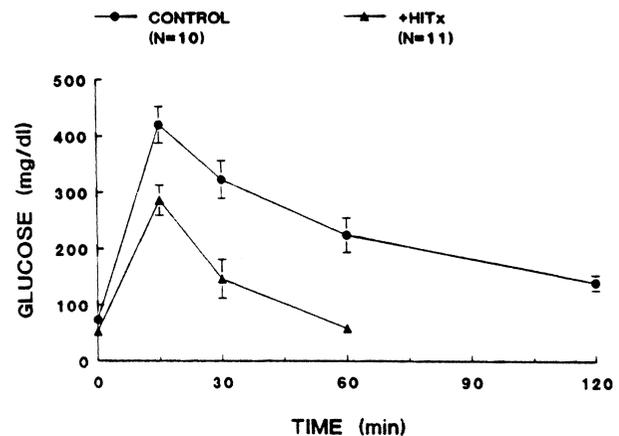
Statistics are presented as mean  $\pm$  SEM and significance of difference was assessed by the Student *t* test.

### RESULTS

Fasting glucose levels in the nude mice bearing human islet xenografts was  $52.4 \pm 4.1$  compared with  $73.6 \pm 4.4$  mg/dL ( $P < .05$ ). Plasma glucose at every time point was significantly lower than in control nude mice (Fig 1).

### DISCUSSION

There is evidence that pancreatic xenografts regulate glucose homeostasis in a recipient in a manner similar to that observed in the donor species.<sup>12</sup> In addition, there is evidence that donor human fetal pancreatic tissue<sup>13</sup> regulates glucose homeostasis recipient animals. Our data



**Fig 1.** Results of IPGTT in control nude mice and diabetic nude mice transplanted with human islets (HITx). All glucose values in the transplanted mice were significantly different than control animals ( $P < .05$ ).

confirm these findings with adult human islet grafts and suggest that the islet xenografts regulate the glucose levels to the donor levels and not to normal recipient levels. The source of xenogeneic islets for use in clinical trials should therefore be carefully selected based upon the donor species glucose tolerance and expected glycemic excursions desired in the recipient.

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