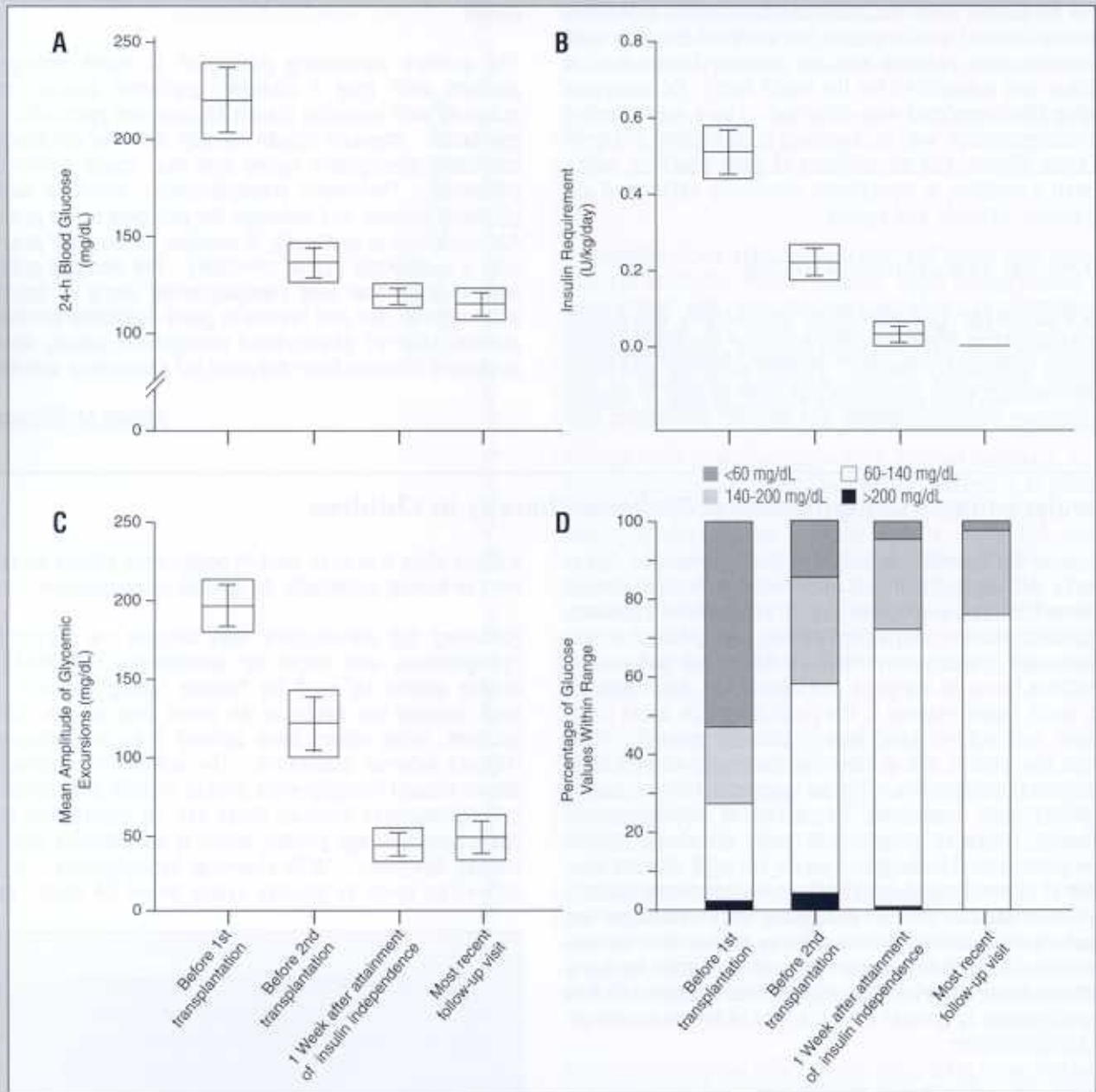


Islet Transplantation in Seven Patients With Type I Diabetes Mellitus Using a Glucocorticoid-Free Immunosuppressive Regimen

This very important study and report records a significant advancement in islet cell transplantation of tremendous potential. The apparent success of exceeding the usual limited success of islet transplantation is attributed by the authors, first, to transplanting an adequate number of islet cells and, second, to the replacement of glucocorticoids as the immunosuppressive agents with more recently designed nonsteroidal immunosuppressive agents.

The subjects were 7 consecutive patients with type I diabetes of more than 5 years who had essentially no stimulated C-peptide, whose glucose concentrations remained uncontrolled despite insulin therapy, and who had recurrent severe hypoglycemia. The new immunosuppressive agents that were used were *sirolimus* at the usual doses, low-dose *tacrolimus*, and *daclizumab*, which is a monoclonal antibody against the interleukin-2 receptor. The islet cell infusions required 2 sep-

Figure



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arate transplants in 6 patients, and 3 in 1 patient. The percutaneous transhepatic approach was used to gain access to the portal vein into which the islet cells were infused and transported into the liver. The quantity of insulin-producing cells transplanted is approximately double that reported previously.

Not only did the patients have essentially no insulin requirements for the time intervals of follow-up (4.5 to 15.0 months), but they also had no hypoglycemic episodes. The resultant 24-hour blood glucose, insulin requirements, mean amplitudes of glycemic excursions, and percentage of glucose values within normal range are demonstrated in the figure. Toxicity over the short term (up to 15 months) was limited to the requirement for blood transfusions following islet cell infusions (corrected by experience by developing a gel foam pad to be placed with the infusion) and minor superficial ulcerations of the buccal mucosa that resolved after the dose of *sirolimus* was reduced and the capsule formulation of *sirolimus* was substituted for the liquid form. No cytopenia resulting from *sirolimus* was observed. There was effective immunosuppression with no apparent diabetogenic or significant toxic effects, and no evidence of graft rejection, which has been a problem in transplants previously performed utilizing earlier methods and agents.

Shapiro AMJ, et al. *N Engl J Med* 2000;343(4):230-238.

Editor's comment: *This pilot study undoubtedly will lead to other studies that stand a good chance of confirming these rewarding preliminary results. Patient selection was such that the patients were desperately in need of help to control their diabetic symptomatology but had no significant sec-*

ondary complications such as significant renal disease. Hopefully, this procedure will lead to an acceptable and readily available method of treatment for type I diabetic patients regardless of various parameters associated with the basic disease. The utilization of an acceptable nonorgan transplant for adolescents and possibly preadolescents stands a good chance of stabilizing the erratic glucose levels that lead to so many problems in adolescent patients, whose self-images deter them from taking insulin on a regular basis. Endocrinologists are inundated when diabetic patients, for many different reasons, fail to adhere to their treatment regimen. The authors point out that availability of cadaver pancreases is greater than one might think. Fewer than one third of such available pancreases are actually transplanted. Therefore, islet cells can be made available to a significant extent.

The article's concluding paragraph is worth noting: "In patients with type I diabetes, glycemic control can be achieved with intensive insulin therapy and pancreatic transplantation. Intensive insulin therapy does not normalize glycosylated hemoglobin values and may cause severe hypoglycemia. Pancreatic transplantation provides excellent glycemic control, and although the outcome of the procedure has improved dramatically, it remains an invasive procedure with a substantial risk of morbidity. The findings published here indicate that islet transplantation alone is associated with minimal risk and results in good metabolic control with normalization of glycosylated hemoglobin values, and with sustained freedom from the need for exogenous insulin."

Robert M. Blizzard, MD

Hypoglycemia: A Complication of Diabetes Therapy in Children

Because of their erratic activity and eating behavior, hypoglycemia in diabetic children is much more difficult to predict and, therefore, to prevent than pediatricians wish to tolerate. The consequences of hypoglycemia are the greatest in this youngest age group, where these problems are paramount. The authors focus on the whys, the wherefores, and the treatment, since hypoglycemia is the most common acute complication in insulin-treated type I diabetic patients. The younger the patient, the greater the frequency of both mild and severe hypoglycemia. Tighter glycemic control also is associated with increased frequency of hypoglycemia. Conversely, however, people with poor metabolic control whose glycosylated hemoglobin levels are high also are susceptible to severe hypoglycemia. Does hypoglycemia matter? The authors answer with a resounding yes! Symptoms are uncomfortable and carry the fear of loss of control or unconsciousness. Morbidity occurs frequently, and mortality sometimes occurs. In addition, sometimes the patient's fear of hypoglycemia is greater than the fear of future microvascular complications.

Previous and repeated mild hypoglycemia can induce hypoglycemia unawareness, thereby leading to diminished warning symptoms and impaired hormonal counterregulation. The

authors state that even mild hypoglycemia should be considered as having potentially dangerous consequences.

Following this introduction, they discuss the prevalence of hypoglycemia and begin by establishing definitions they believe should be used for "severe hypoglycemia." Some have defined the entity as an event that causes coma or seizures, while others have defined it as any episode that requires external assistance. The authors recommend that severe clinical hypoglycemia should include only episodes of unconsciousness because these can be ascertained consistently across all age groups, which is not possible with a less intense definition. "Mild chemical hypoglycemia" has been defined by some as glucose values below 54 mg/dL but not

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