Letters to the Editor

Pancreatic islet transplantation for diabetes

Sir,

Taylor and Vandertrump\textsuperscript{1,2} have reviewed the recent advances in the management of diabetes. The concept of pancreatic islet transplantation was conceived as an alternative to vascularized pancreas transplantation because of the numerous complications of the latter procedure. Although many of the complications of vascularized pancreas grafting have now been resolved, islet transplantation remains an attractive alternative, as the procedure should be well tolerated by the patient. Islet tissue can be manipulated immunologically (in vitro) prior to transplantation and stored by cryopreservation.\textsuperscript{3} The procedure itself should be a simple injection of insulin-producing tissue at the appropriate site with minimal discomfort to the patient. The ability to immunomodulate and encapsulate islets could possibly allow transplantation using minimal immunosuppres-

Recently, successful allotransplants of human islets have been reported, using islets retrieved from several donors for each recipient.\textsuperscript{4} These reports have shown that islet transplantation is feasible in man but they have not been followed by a regularly successful transplantation protocol for a variety of reasons including: inadequate quantity and quality of transplanted islet tissue; the cellular graft was contaminated by exocrine tissue or lymph nodes; rejection; diabetogenicity of immunosuppressants; transplantation of islets to inappropriate sites; and sub-optimal storage techniques. There may also be destruction of the transplanted islets due to recurrence of the autoimmune process.

Pancreatic islet transplantation continues to arouse considerable interest in patients who suffer from diabetes. Pancreatic transplantation was considered an experimental procedure as there had been no prospective and controlled studies of vascularized pancreatic transplantation in patients at early and advanced stages of diabetes to answer the question of whether normoglycaemia can prevent, arrest, or reverse secondary complications of diabetes. It had been estimated that a trial incorporating very large numbers of treated and control patients and a long period of observation would be needed to produce a clear answer to whether vascularized pancreas transplantation is truly beneficial – about 1,000 transplant patients and 1,000 controls studied over at least 10 years,\textsuperscript{5} a study which was certainly not realistic.

The same issues would require attention for islet transplantation. However, in the case of islet transplantation, because of the simplicity of the procedure and the minimal hazard to the patient, benefit from the procedure may be easier to evaluate.

The separation and purification of large numbers of intact human pancreatic islets from one donor pancreas is the crucial limiting factor. Although hand-picking can provide pure islets, this method is obviously unsuitable for the large numbers required for human transplantation. Important causes of islet loss during human islet preparation include the processes of chopping, teasing and aspiration through needles that are common to most isolation techniques. In addition, the action of collagenase shows batch variations in effectiveness. A variety of alternative techniques of islet isolation have been developed,\textsuperscript{6} but from a possible 1–2 million islets in the human pancreas, about 250,000 islets are generally isolated, which is well below the threshold for insulin independence.\textsuperscript{7}

However, some recent advances in the field of islet transplantation have led to renewed optimism about the ultimate success of clinical islet transplantation. Previous trials of human islet transplantation have used cyclosporine A, FK506 or prednisone as immunosuppressants. These drugs have significant diabetogenic properties.\textsuperscript{8,9} The unfavourable environment created by these immunosuppressants may have prevented islet implantation. Deoxyspergualin (DSG), an experimental drug, has a different mechanism of immunosuppressive action but, more importantly, DSG may have minimal or no diabetogenic effect.\textsuperscript{10}Furthermore, DSG has also exhibited anti-diabetic activity in chemically induced diabetic mice.\textsuperscript{11} The introduction of DSG for induction of immunosuppression in islet transplantation may be an advance as this drug has been shown to be less diabetogenic.\textsuperscript{12}

Recently Gores et al.\textsuperscript{13} have shown that using DSG, transplantation of unpurified pancreatic tissue into the portal vein of human type I diabetes was successful, at least in the short term. They have challenged the previously held belief that pure islets were necessary for successful engraftment. Exocrine tissue, lymph nodes and ductal tissue have larger numbers of dendritic cells than are present in islets. Contaminated islets were therefore more immunogenic and failed to implant.\textsuperscript{13} It was also shown that contamination by lymph nodes could hasten the rejection of the implanted islets by providing a ready target for T-cell attack.\textsuperscript{14} Purification of pancreatic digest prior to human transplantation was also thought to be critical as previous clinical trials showed that transplantation of crude pancreatic digest resulted in serious complications.\textsuperscript{15}

Enormous interest has been aroused by the work of researchers,\textsuperscript{16} who transplanted islet allografts into thymus of rats treated with a single dose of anti-lymphocyte serum. The islets survived indefinitely and tests suggested that a state of donor-specific tolerance was induced. Thus it was shown that thymus may be an immuno-privileged organ for purposes of transplantation. Transplantation of islets in the thymus may therefore obviate the need for immunosuppressants.

Physical isolation of the transplanted insulin tissue from the host immune system by means of a semi-permeable membrane offers a promising solution to overcoming the immunological barrier. Earlier reports of successful transplantation using encapsulated islets were not properly documented, however, recent progress has been made with the micro-encapsulation technology. The major problem was fibrous overgrowth leading to destruction of the encapsulated islets but recently reported techniques using capsules with high glucoronic acid, could successfully reverse spontaneous diabetes in dogs for about 63–172 days.\textsuperscript{17} Recent advances in the encap-
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sulation techniques using smaller capsules and newer chemicals will greatly facilitate comparison of data among centres. Intense interest has been aroused by the work of Sullivan et al. who showed that a biohybrid artificial pancreatic device in the form of a vascular implant containing bovine islets and implanted into pancreatectomized dogs could function for 80 days. Further improvements in the membrane technology of these devices are necessary for long-term reversal of diabetes but these landmark developments are highly encouraging, especially as these devices obviate the need for immunosuppressants.

Despite recent advances, the goal of one to one human pancreatic islet transplantation remains elusive. Even if this were to be possible, there would be an acute shortage of cadaver pancreata. Therefore, the possibility of xenotransplantation and human fetal islet transplantation looks increasingly attractive.

Rahul M. Jindal
Indiana University Medical Center,
Division of Transplantation,
550-N. University Blvd,
Indianapolis, IN 46202, USA.

References


Accidental hypothermia possibly caused by antecedent heat stroke

Sir,

Accidental hypothermia in adults classically follows an exposure to cold environment, during a situation in which a person is unable to protect himself, usually due to coma, exhaustion or injury. Heat stroke, an illness in which insufficient heat dissipation causes a rise of body temperature to a noxious level and leads to an altered mental status, may theoretically precede hypothermia. In the following, we present a patient who probably had such a sequence of events during a strenuous march he performed in cold weather.

In November 1991, a young recruit, previously healthy, suddenly collapsed in the 22nd kilometre of a strenuous march, performed in the Negev desert, in cold and dry weather (ambient temperature +12°C, humidity 60% and wind velocity 15 km/hour). A night prior to the march he was on duty, and therefore unable to sleep or rest properly. Before collapsing he was confused and exhausted, but continued to walk. Two hours later he was brought to a military clinic in an open command car, covered with only one blanket. On examination he was comatose, had cool wet skin and clothing (due to profuse sweating), and his rectal temperature was 34.8°C. His physical examination was otherwise unremarkable. He was warmed up with blankets and warm intravenous saline, and transferred to a regional hospital. Laboratory studies, performed on admission to the hospital revealed elevated creatine phosphokinase (CK) 1,640 U/l (normal: 40 U/l) and transaminase (SGOT) 60 U/l (normal: 40 U/ l) and normal glucose, electrolytes, creatinine, bilirubin, prothrombin, partial thromboplastin time, platelet count and electrocardiogram. The patient recovered within a few hours and was discharged the next day with a CK of 800 U/l and a diagnosis of mild accidental hypothermia.

This patient had accidental hypothermia which developed while he was confused and comatose. Although his body temperature was not recorded at the time he collapsed, the fact that he was engaged in a vigorous physical effort prior to the event, the evolution of his illness through confusion to coma and exclusion of other diagnoses, in this young and healthy soldier, raise the possibility that the hypothermia was preceded by a heat stroke.
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R. M. Jindal

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