

Islet xenotransplantation: how sweet it is.

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Editorial

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In 1889 Mering and Minkowski discovered that surgical removal of the pancreas caused dogs to become diabetic, thus implicating the pancreas in the regulation of blood sugar. Various investigators subsequently tried to use extracts of the pancreas for the treatment of diabetes. For example, Murlin and Kramer (1913) prepared from bovine pancreas an extract which would lower the blood sugar in a diabetic dog; however, the beneficial effect of the extract was attributed in part to the presence of lactate. Kleiner (1919) used neutral saline to prepare an extract from canine pancreas which clearly exhibited a beneficial effect in experimental diabetes; however, this extract was potentially quite toxic and the results were difficult to reproduce. In 1922, Banting and Best, at the University of Toronto discovered a method for preparing a pancreatic extract that would rapidly and reproducibly lower the blood sugar of diabetic animals (1). Within a very few years, the intermittent injection of the active factor in this extract, insulin, became the mainstay of therapy for type I diabetes.

If the use of insulin provided dramatic relief from the acute, life-threatening complications of diabetes, it also brought to light the chronic complications of diabetes — nephropathy, retinopathy, neuropathy and premature atherosclerosis — due at least in part to inability of parenteral insulin administration to control subtle changes in blood glucose (2). The complications now constitute the major challenge in the treatment of diabetes. As one approach to improving the control of glucose metabolism in patients with insulin-dependent diabetes and potentially to preventing or treating the chronic manifestations of the disease, surgeons and diabetologists have endeavored to make transplantation of the whole pancreas or of isolated islets of Langerhans a therapeutic option as it is for chronic failure of the major organs.

The application of transplantation for the treatment of diabetes has proven difficult and controversial. Under the best of conditions, pancreas transplantation is plagued by a 10% incidence of technical complications, related in part to the need to divert the exocrine secretions (3). Added are the complications of immunosuppressive therapy and the limited availability of human pancreas donors. Thus, whole pancreas transplantation has not gained widespread use as a primary therapy for diabetes and is principally used in conjunction with kidney transplantation where immunosuppression is mandatory. Since the era of pancreas transplantation was begun in the late 1960's there has been interest in developing techniques for the isolation of pancreatic islets which might be transplanted as free-tissue grafts, thus avoiding the transfer of exocrine tissue and the hazards of major surgery (4). Unfortunately, clinical application of islet transplantation has proven more difficult than might have been expected. Although, islet transplants readily cure diabetes in rodent models, they succeed only rarely in large animals and humans, except as autografts. One problem has been the difficulty in obtaining sufficient numbers of islets from the limited number of human donors. If this

problem could be solved there is still the susceptibility to rejection which necessitates use of immunosuppressive therapy. Because of these problems it is widely held that islet and pancreas transplantation cannot become the treatment of choice for insulin-dependant diabetes until the requirement for immunosuppressive therapy can be eliminated and until a plentiful source of islets can be identified. To address the immunological issues, most investigators have pursued one of two approaches — induction of immunological tolerance and the sequestering of islets with a capsule which would exclude the cellular elements of the host's immune system but allow the flux of glucose and insulin. To overcome the shortage of donor tissues interest has focused increasingly on the use of animals in lieu of humans as a source of pancreas tissue, that is xenotransplantation. Unfortunately, none of the approaches has yielded unqualified success. The induction of tolerance has been accomplished in mice and rats but it has not proven so easy in large, outbred animals. The implantation of encapsulated islets has reversed diabetes in some experimental models; however, the continuing function of the implants has usually required immunosuppression and has often generated fibrotic reactions that limited the duration of graft function. Although islet xenotransplantation has been accomplished in rodents, there is evidence that the humoral immune reactions which in human and primates would cause devastating injury to organ xenografts may, under some conditions, arise in response to and potentially limit the function of islet xenografts (5).

Finally, in this issue of *The Journal* Sun and co-workers report studies which suggest that some of the daunting hurdles to the use of transplantation for the treatment of diabetes have been overcome (6). Porcine islets, sequestered in "capsules" consisting of sodium alginate and injected in the peritoneum of spontaneously diabetic monkeys were shown to restore euglycemia for periods of months to greater than a year without immunosuppressive therapy. When encapsulated islets failed, the injection of newly encapsulated porcine islets restored glucose control.

Although, as discussed below, some salient questions remain to be addressed, the results of Sun and co-workers may well prove to be a landmark in the development of islet transplantation for the treatment of diabetes. First, the results provide important evidence that islets can be isolated, encapsulated, and transplanted in such a way that destruction by the host's immune system is avoided and that transplantation of pancreatic tissue without immunosuppression may indeed be feasible. Second, that the islets were isolated from the pig raises the prospect that the shortage of human pancreatic tissue need not limit the application of this treatment. Of particular note in this regard is the evidence which this report provides by implication, that "microencapsulation" may effectively avert destruction of the islets by the humoral and cellular immune responses which ordinarily would destroy a porcine tissue transplanted into a primate (7).

Of course the results also raise some questions. The most immediate question is why the method of Sun et al. succeeded where other methods have failed. It will be important to ascertain whether success is owed to the purity of the islets and the structure of the capsule as the authors suggest or whether

some other combination of factors is critical. Of interest to the immunologist will be the question of whether islet encapsulation prevents the eliciting of an immune response or impedes the effector systems, especially humoral, associated with such a response. One question which must be addressed before widespread application can be undertaken is whether the xenogeneic islet implants will fully restore the normal regulation of blood sugar. Should microencapsulated islets fail in this regard then their use in most patients could only be justified on the basis of convenience. Still, even if this method proves unsuitable for the treatment of diabetes there is the possibility that the method might be applied to other cells for the treatment of metabolic disease and the possibility that with genetic engineering of islets (or other cells) might be used as a vehicle for delivering other proteins under tightly regulated conditions.

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