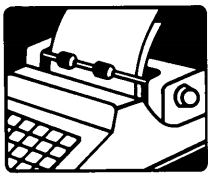
Editorials



Toward Successful Transplantation of the Endocrine Pancreas

Recently, as a supplement to DIABETES, there appeared the Proceedings of the Kroc Foundation Conference on Pancreas Transplantation.[1] The Conference dealt both with the progress that has been made in transplantation of the endocrine pancreas and with the problems that remain. Three major areas addressed are (1) the immunogenetic disparities between the donor and the recipient (i.e., the allograft reaction), which remains a major barrier to successful transplantation; (2) the utilization of islets of Langerhans, isolated from whole pancreas, as a transplantation resource, by dealing with the puzzle of tissue-specific antigens on the islet and the need to improve techniques of islet isolation and purification (by culturing, cryopreservation, and/or use of fetal pancreatic tissue) to provide adequate yields for successful transplantation; and (3) the progress being made with vascularized organ transplants (i.e., segmental transplants that have immediate function but require that exocrine secretions be dealt with). To summarize the results of work in all these areas is growing more difficult, due to the rapid proliferation of progress in each.

Insight into the immunogenicity barriers to islet transplantation is provided in the excellent review by Barker et al.[2] Although that review deals with rat and mouse species, the studies described provide a template for other species, including man. A number of conclusions emerge from the studies described, which have used islet and whole organ pancreas allografts in rodents with defined histocompatibility. In addition to allospecificity, islet tissue appears to have tissue-specific antigens, which may create additional barriers to transplantation and may preclude the use of conventional histocompatibility testing as the sole means of donor selection. A number of approaches are being used to contend with this problem, including the use of fetal pancreatic tissue, which may be less immunogenic than adult tissue;[3] the use of tissue culture explants of donor tissue in an attempt to lessen immunogenicity;[4] donor pretreatment with drugs cytotoxic to passenger lymphocytes, which are known to increase immunogenicity in other types of grafts.[5,6]

Interestingly, Barker et al. also note that the whole organ transplanted in the rat appears to be more easily accepted than comparable amounts of isolated islet tissue, in the presence of similar modes of specific or nonspecific immunosuppression.[2] Enhancement protocols in adult rodents, utilizing passive transfer and active induction of blocking antibody, have not protected islets against rejection. On the other hand, immunologic tolerance produced in neonatal animals by donor lymphopoietic cells has permitted the later engraftment of isolated donor islets or whole pancreas. These forms of specific immunoregulation—enhancement and tolerance—provide fertile areas for future investigation. It would appear, however, that with these types of protocols, islet tissue in isolated form has had less success than whole organs (kidney and heart) in achieving graft survival. It is tempting to speculate that if an autoimmune component is involved in the genesis of diabetes, newly transplanted isolated islets might indeed be more susceptible to tissue-specific immune damage than those included in the integrity of a vascularized gland in which a more "privileged site" might be present with less susceptibility to immune attack. Indeed, in our own work there appears to be in vitro evidence of lymphocyte proliferation against tissue-specific antigens on islet cells in the dog, rat, and human.[7] Others have recently demonstrated, in several experimental protocols, that indefinite acceptance of both islet and whole organ transplants is possible across major histocompatibility differences in rats, something that had been extremely difficult to achieve up to two years ago.

Although in the adult human it has been logistically difficult to obtain high yields of islets from the larger, more fibrous bulky glands, the human fetal pancreas is proving to be more favorable. Isolated reports of function of fetal islet tissue implanted into diabetic recipients[3,8] have appeared. Fetal tissue thus offers the promise of both less immunogenicity and greater yields of islets than adult tissue.

Newer adjuncts to nonspecific immunosuppression are also on the clinical horizon. The exciting technique of total lym-

phoid irradiation (TLI) has been highly successful in experimental animals[9,10] and is currently being used in several clinical trials.[11] Thoracic duct fistula and drainage (TDF), a subject of renewed interest, is being successfully used with immunologically recalcitrant recipients of kidney transplants in whom multiple previous rejections have occurred.[12] Finally, a very potent new immunosuppressive agent, cyclosporin-A, is now under extensive evaluation.[13,14] It appears to have greater effectiveness than conventional immunosuppressive agents in the suppression of stem cells in the T cell line, although its precise mechanism of action and side effects remain to be clearly delineated.

A subject of intense recent interest is the use of tissue culture of fetal or adult pancreatic islets as a means of depleting alloimmunogenic passenger lymphocytes. Stimulated by the work of Lafferty and others,[15–17] using other tissues, Lacy et al.[18,19] and Talmadge and colleagues[20,21] have demonstrated prolongation of graft survival in several species under various islet culture conditions, particularly variation in culture temperature and oxygen concentration. Although other investigators have been unable to confirm these observations, there are sufficient vagaries (both known and unknown) in standard conditions of culture to adequately account for differences between laboratories.

The most reasonable approach today for experimental pancreas transplantation in human subjects appears to be engraftment of segmental pancreas using vascular anastomosis, with free drainage of the pancreatic duct into the peritoneal cavity. Utilizing pigs and dogs, we have had extensive experience with this approach.[22–28] The concomitant use of intravenous administration of inhibitors of pancreatic secretion in conjunction with the absorption of pancreatic proenzymes secreted into the peritoneal cavity appears to be a viable approach. Indeed, in recent experiments in beagle dogs, allotransplantation of pancreases treated in this manner has been observed for 8–9 mo.[28] Interestingly, after such a period of observation, there is virtual total atrophy of the exocrine gland with residual coalescence of islets around the vascularized stalk. It would appear that further meddling by the injection of neoprine[29] or duct anastomosis[30] is unnecessary and can be avoided.

The clinical results of the University of Minnesota described by Sutherland et al. seem to pointedly bear out this approach.[31] Using this method, one recipient (the first tried) has now had a pancreas transplant function for over 23 mo, in the absence of insulin administration, but with the use of standard immunosuppression. Such immunosuppression has included glucocorticoids, indicating that their use in immunosuppression does not obviate pancreas transplantation. In fact, in both long-term canine and human studies, serial glucose tolerance testing has demonstrated retention of function in the pancreatic grafts.

These thoughts come two years after previous considerations about pancreatic transplantation expressed editorially on these pages. It is gratifying to see the developments in pancreas transplantation during this interval, as we witness the emergence of a new era of experimentation in clinical pancreatic transplantation.

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Glycosylated Hemoglobin: A Tool in Identifying Psychological Problems?

Glycosylated hemoglobins are found in increased amounts in the blood of diabetic individuals. The level of glycosylated hemoglobin varies with the degree of glycemic control achieved, and is correlated with other control parameters over a 6–12-wk period.[1–5] Thus, there has been growing use of glycosylated hemoglobin determinations as a useful objective measure of chronic degree of metabolic control of diabetes, reflecting integrated blood glucose over 2–3 mo, and perhaps being indicative of the impact of hyperglycemia on overall metabolism.

Although a powerful research tool for quantitating control, the potential clinical utility of glycosylated hemoglobin determinations is still emerging. The most useful clinical application of glycosylated hemoglobin probably is its serial determination in a given patient in whom some intervention strategy is proposed and tested. The results permit assessing the impact of that strategy, provided a reliable, reproducible assay is used.

This issue of DIABETES CARE contains two additional papers that explore the interrelationships between glycosylated hemoglobin and various control parameters[6] and endogenous insulin secretion.[7]

In addition to facilitating metabolic studies, however, glycosylated hemoglobin determinations have permitted the identification of a new category of patients: those in whom there is marked discrepancy between control as determined by glycosylated hemoglobin and control as reflected in urine glucose records.[8] Assuming that vagaries in glycosylated hemoglobin measurement, erroneous urine testing techniques, and altered renal threshold for glucose excretion are excluded, the discrepancy may be accounted for on the basis of several mechanisms. We have developed a diagnostic/therapeutic paradigm for patients with glycosylated hemoglobin-urine record discrepancy based on the presumed underlying psychological reason for discrepant results. There are at least 10 such reasons in our classification (Table 1). (In theory, this scheme may also be applied to patients monitoring blood glucose rather than urine glucose. In practice, patients monitoring their own blood glucose seem less likely to have discrepant results. This may be due to self-selection, since blood glucose monitoring is generally done only by motivated patients.) In this scheme, the diabetic individual may be responding to personal expectations or to those of family, peers, or medical professionals. Thus, seeking of perfection may be innate within the individual or may be a family characteristic. Resentment may be one's own resentment against the disease, or resentment of parents or medical professionals who impose demands relative to diabetes management. To understand the origin of discrepant results and to choose appropriate action, we must often deal with the family unit; health professionals may need greater sensitivity to these important issues and may need to alter their own behavior.

Identification of the underlying mechanism responsible for discrepant results (Table 1) involves a carefully conducted interview. The interviewer has a nonjudgmental attitude and solicits patient self-interpretation of the "meaning" of the glycosylated hemoglobin report in the face of the urine glucose results. Role playing or role reversal may be used in the assessment process. An honest exchange must be promoted, but from the standpoint of self-understanding rather than confession. Often, face-saving gestures may be used, e.g., reviewing urine testing procedures, using new Clinitest tablets, and agreeing to careful testing practices for one week. This allows the patient time to reflect on the circumstances and may permit a more fruitful interchange at the subsequent encounter.

The underlying mechanism defines the patient's needs and concerns and dictates much of the corrective action necessary. The goals for change should be set by the patient, with