TRANSPLANTATION OF THE PANCREAS

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INTERNATIONAL HUMAN PANCREAS AND ISLET TRANSPLANT REGISTRY

Introduction

BEFORE 1977, 47 pancreatic transplants were carried out. In the last 3 years more than 60 have been performed. This renewed interest is due to a new pancreatic transplant preparation technique that suppresses the exocrine function of the organ by the injection of neoprene into the pancreatic duct. This technique has allowed surgeons to obtain a vascularized pancreatic segment with purely endocrine functions that is immediately suitable for transplantation and can be used with a far greater degree of safety.

Now a new era has dawned for pancreatic transplantation in insulin-dependent diabetic patients. At this stage, we are still at the beginning, just as we were 20 years ago with kidney transplants, the ultimate goal being to ensure a total and possibly permanent substitution of the deficient pancreas so as to prevent degenerative complications or at least to stabilize them if they are present.

Even though the functional duration of the pancreatic transplant remains limited, great hopes have thus been born, and the low surgical risk associated with the implantation of a segmental pancreatic graft encourages surgeons to practice this type of intervention each time a kidney transplant is performed on a diabetic patient.

It may well be, in the years to come, that the numerous insulin-dependent diabetic patients will be confronted with the dilemma presently facing uremic patients: whether to choose pancreatic transplantation or dependency on blood sugar equilibration systems, such as, among others, the interesting "open loop" system, which is the first ambulatory system available.

Obviously, we have not yet reached this stage of development, and numerous problems remain to be solved. This is why we took the decision to organize a symposium on segmental pancreatic transplantation, the first of its kind. Many technical problems are still to be tackled. How may we best ensure the suppression of the exocrine function of the pancreas and transform a mixed function organ with external and internal secretions into one with purely endocrine functions? Which are the best implantation techniques? Which method is best for the immunologic preparation of the recipient? How may we detect pancreatic graft rejection at an early stage? How should we study the interesting immunologic phenomenon of nonsimultaneous rejection of a kidney and a pancreas taken from the same donor? How immunogenic is the pancreatic tissue, especially that of the fetal pancreatic islets?

Recent encouraging results obtained from the utilization of fetal tissue in pancreatic transplants prompted us to organize an additional session on this topic.

The aim of this symposium was above all to bring together the leading groups in this field and to make them aware of the importance of discussion and an exchange of ideas, especially as they held a leading position in a new era of organ transplantation: where manipulation and transformation of an organ for a specific function took place before its use as a transplant.

A crystallization of ideas took place during the symposium, with the important result that all groups present decided to participate in the International Pancreas Transplant Registry project. As was the case formerly for the International Kidney Registry, this organization will certainly be of immense benefit to those who are involved in the field of pancreatic transplantation.

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SEGMENTAL ORGAN TRANSPLANTATION: CLINICAL ASPECTS

Selection of the Diabetic Patient for Segmental Pancreatic Transplantation

J. Traeger, J. M. Dubernard, J. L. Touraine, and M. C. Malik

THE immediate prognosis of pancreatic transplantation has been favorably modified by the description of a new technique using a segment of the pancreas in which the external secretion has been suppressed by an injection of neoprene into the Wirsung's duct.[1]

The problem regarding selection of patients for such a treatment is thus a new one, and it is interesting to analyze it in the light of the first results obtained.

One should bear in mind that pancreatic transplantation aims at the long-term replacement of the endocrine pancreas of the insulin-dependent diabetic, so as to ensure a regular and adjusted secretion of insulin for a better regulation of the level of blood sugar, as well as to improve, or at least stabilize, the degenerative complications resulting from this kind of diabetes, complications that for the most part end dramatically for the patient.

MATERIALS AND METHODS

Fourteen patients suffering from insulin-dependent diabetes were given 15 segmental pancreatic transplants prepared by an injection of neoprene into the Wirsung's duct. The transplantation technique is reported in another article in this volume.

The patients were given immunosuppressive therapy consisting of steroids: prednisone, 1 mg/kg/day, then decreasing doses; azathioprine 2–3 mg/kg/day according to the number of polymorphonuclear cells (PMN); antilymphocyte globulin (ALG) 6 vials/day for 28 days by the i.v. route.

The characteristics of the pancreatic graft functions are reported in another article in this volume.

Of the 14 transplanted patients, 9 had reached the final stage of diabetes, with advanced renal failure treated by hemodialysis. Five patients, with a less pronounced form of chronic renal failure, had a nephrotic syndrome and had not undergone dialysis at that time. All the patients also had degenerative complications: vascular and ocular complications, hypertension, arteritis in the lower limbs, and in a few cases, coronaritis; all had diabetic retinopathy and some were blind.

The age of the patients ranged from 19 to 51 years. The average duration of the diabetes since its diagnosis was 21 years. All the cases were very unstable diabetes.

RESULTS

The general results that are useful for discussing the problem of selection are described in Table 1, which analyzes the duration of the pancreatic graft function, taking into account surgical complications and the clinical condition of the patients.

Graft Survival

The survival of the graft ranged from 0 to 650 days (the graft in the latter case remaining functional). According to indirect arguments and by the exclusion of other causes, the functional termination of the graft in most cases was considered to be caused by rejection. One patient whose graft was still functional died of infection on the 435th day.

In 4 cases, the graft ceased to function at a very early stage (from 0 to 3 days). This was due to thrombosis of the arteries or veins. It should be pointed out that 3 of the 4 patients were not suffering from renal failure, nor were they being treated by hemodialysis; in addition, they still had a nephrotic syndrome.

The best results and the longest survival rate of the graft were obtained in patients who had chronic renal failure (treated by hemodialysis) but no nephrotic syndrome.

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Table 1. Fifteen Neoprene-Injected Pancreatic Allograft Transplantations

Patient	Age	Onset of Diabetes	Diabetes Instability	Nephrotic Syndrome	CRI Hemodialysis	Kidney Graft Simultaneous or Sequential	Pancreatic Graft Duration of Function (Days)	Cause of Cessation of Function	Delay (Days) Between Cessation of Function of the Graft and Death of Patients	Cause of Death
JMC	22	16	+++	+	–	–	0	Arterial thrombosis		
PT	28	20	++	+	–	–	1	Venous thr		
MG	39	14	+++	+	–	–	1	Venous thr		
AG1	41	32	+++	0	+	–	3	Venous thr		
AG2	42	33	+++	0	+	–	28	Rejection	0	Cardiac insufficiency
MD	33	16	+++	+	–	–	30	Rejection		
GC	25	13	+++	+	–	–	40	Rejection		
IM	19	7	++	0	+	–	44	Rejection	550	Hyper K
JR	28	25	+	0	+	–	45	Rejection	100	Vascular
AB	42	17	++	0	+	–	75	Rejection	75	Vascular
AC	51	29	+++	0	+	+	110	Rejection		
NA	26	18	++	0	+	+	>150			
LV	33	19	+++	0	+	+	259	Rejection		
LF	41	21	++++	0	+	+	435		435	Infection
SG	36	32	++	0	+	+	>650			

Patient Survival

Five deaths occurred in this series. The dates at which these deaths occurred should be closely analyzed. One patient (AG2) died of heart failure on the 28th day after the transplant. This was in fact a second pancreatic transplant carried out at the insistence of the patient whose degenerative complications were persistently deteriorating.

Three patients (IM, JR, AB) died well after the pancreatic graft had been rejected and for reasons unrelated to the surgical operation.

One patient (LF) died on the 435th day from infectious meningitis linked to immunosuppression and to the persistence of a local infection.

DISCUSSION

Risk for the Patient

The new technique of pancreatic transplantation, in which a segment of the pancreas injected with neoprene is used, is relatively harmless and represents a quite modest surgical operation. Only one patient died in the days that followed the operation (AG2, deceased due to cardiac failure). The causes of death among the other patients, after rejection of the graft, were due to the development of complications connected with their diabetes, and not to surgery itself.

The immediate prognosis of a kidney transplant does not seem to deteriorate if it is linked with a pancreatic transplant carried out according to this new method.

Pancreatic Graft Survival

The survival of the pancreatic graft seems to be longest if the following three conditions are present. (1) Absence of a nephrotic syndrome. It is now known that the vascularization of the pancreatic graft is characterized by a modest blood flow and that the risk of thrombosis in these vessels is high. The presence of a nephrotic syndrome together with a reduced blood volume and a tendency towards thrombosis probably represents a risk factor.

(2) Presence of renal insufficiency and thus treatment by hemodialysis. It is known that immunodeficiency accompanies renal failure, and this factor is probably favorable for a transplant seemingly susceptible to rapid rejections difficult to treat.

(3) The longest survivals of transplants were obtained when both kidney and pancreas were transplanted simultaneously or successively. The pancreatic graft seems to be protected by a renal graft, most probably because the kidney is rejected earlier or shows warning signs that are easier to detect; the immediate administration of immunosuppressive treatment undoubtedly prevents to a certain extent rejection of the pancreas.

Transplant Recipients

The patients who received transplants all suffered from severe diabetes. Their degenerative complications consisted of ocular deterioration in particular. Diabetic instability was pronounced and many daily injections of insulin were needed.

It seems difficult, taking into account the present state of pancreatic transplantation and the as yet modest survival rate of the transplants, to treat patients who are at an early stage of degenerative complications, when the medical treatment for such cases is still relatively effective.

Life Expectancy

It must be borne in mind that the life expectancy of diabetic patients who have reached an advanced stage in their degenerative complications is extremely low. Each year, 25% of patients with advanced diabetes who are undergoing hemodialysis treatment die, whereas the death rate for those without diabetes is only 5%–10% per year. It is not certain whether CAPD (continuous ambulatory peritoneal dialysis) changes this prognosis, even though it is thereby improved. The progression of the degenerative complications will probably not be arrested by this method.

At the present time, it is accepted that kidney transplants give better results (60% of patients survive for 4 years) and that it is the best choice for diabetics with an end-stage renal failure.[2,3]

CONCLUSION

Taking into account the present state of development of the pancreatic transplant, as well as the results so far obtained, the selection of a segmental pancreatic transplant prepared by an injection of neoprene would appear to have to be recommended each time kidney transplants are performed on insulin-dependent diabetic patients who have reached an advanced stage in their illness, particularly those in whom the deficiency necessitates treatment by hemodialysis and a kidney transplant.

Owing to the fact that pancreatic transplantation has now become a modest surgical operation, the best method appears to be the simultaneous transplantation of a kidney and a pancreas.

Of course, the general conditions governing a kidney transplant should also be applied in the case of a pancreatic transplant. In our group, transplants are usually not performed on patients above the age of 50, and the cardiac and hepatic conditions have to be favorable.

We may therefore conclude that, in this very early phase of pancreatic transplantation, the combination of a kidney transplant with a segmental pancreatic transplant can offer insulin-dependent diabetic patients who have reached an advanced stage in their illness an additional chance of stabilizing their degenerative lesions, without exposing them to additional risks of a surgical nature.

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Preoperative Evaluation of Pancreatic Transplant Recipients

R. M. Dickerman, P. Raskin, W. J. Fry, and B. A. Elick

THE reversal of hyperglycemia following pancreatic transplantation may correct the complications of coma and ketoacidosis in diabetic patients, but further investigation must be undertaken to evaluate the long-term metabolic effects of this surgery. In the interest of determining whether or not pancreatic transplantation can prevent or reverse the microvascular changes occurring with routine insulin therapy, we have defined certain preoperative criteria to serve as a comparison for postoperative evaluation.

Routine glucose tolerance tests are performed using a dose of 100 g of glucose. Blood sugars are evaluated for 40 min before the dose of glucose is administered to 180 min following, at varying intervals. Insulin, glucagon, triglycerides, and cholesterol levels are also drawn serially. An additional parameter used for evaluation is the diabetic's response to an intravenous arginine infusion. This portion of our protocol is based on the role of glucagon in diabetes mellitus and has shown that these patients not only have hyperglucagonemia, but also a decreased sensitivity to hyperglycemia, so that the glucagon suppression normally seen in nondiabetics is absent in diabetics.[1,2] Finally, there is an exaggerated response of glucagon to aminogenic stimuli.[3,4] In Fig. 1, one can easily see the interrelationships of glucose, insulin, and glucagon during the typical arginine infusion. The arginine dosage used is 20 g of L-arginine monochloride (R-gene, Cutter Laboratories, Berkley, Calif.) infused over a 40-min period. Analyses of triglycerides and cholesterol are documented, as well as insulin, glucose, and glucagon at 20 min before the infusion to sometimes 180 min following, at varying time intervals. The effect on glucose, both in insulin-dependent diabetics and non-insulin-dependent diabetics, as well as in normal subjects, is minimal. The difference in the two classifications of diabetics is seen by the dramatic response of insulin to arginine infusion in adult-onset diabetics as compared to controls. The exaggerated response of glucagon that both juvenile and adult diabetics

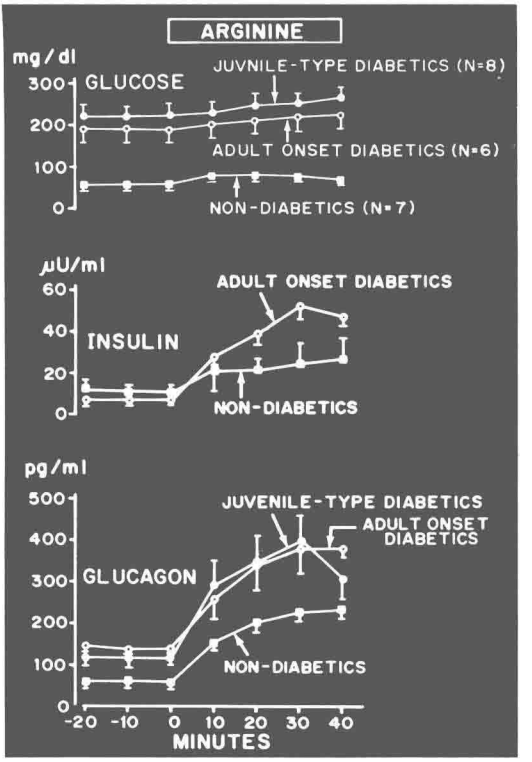

Fig. 1. Effect of i.v. arginine administration on plasma glucose, glucagon, and insulin concentrations in adult-onset and juvenile-type diabetics and nondiabetics.

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