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Comparison of whole pancreas and pancreatic islet transplantation in controlling nephropathy and metabolic disorders of diabetes.

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Abstract

To compare the long-term effectiveness of whole pancreas transplantation and pancreatic islet transplantation in controlling the metabolic disorders and preventing the kidney lesions of alloxan diabetes, metabolic and morphologic studies were performed in four groups of rats: (1) NC-116 nondiabetic controls; (2) DC-273 untreated alloxan-diabetic controls; (3) PDT-182 rats that received syngeneic pancreaticoduodenal transplants not long after induction of diabetes with alloxan; and (4) IT-92 rats that received an intraportal injection of at least 1500 and usually 2000 syngeneic pancreatic islets soon after induction of diabetes with alloxan. Each month for 24 months after diabetes was well established, body weight and plasma concentrations of glucose and insulin were measured, and five lesions were scored by light microscopy in 50 glomeruli and related tubules in each kidney by a "blind" protocol: glomerular basement membrane thickening, mesangial enlargement, Bowman's capsule thickening, Armanni-Ebstein lesions of the tubules, and tubular protein casts. There were progressive and highly significant increases in the incidence and severity of all five kidney lesions in the diabetic control rats compared with the nondiabetic control rats. No significant differences were found between the kidneys of Group PDT and those of Group NC, demonstrating that whole pancreas transplantation prevented all of the diabetic kidney lesions throughout the 2-year study period. In contrast, within 3-9 months after pancreatic islet transplantation and thereafter, the incidence and severity of the five diabetic kidney lesions were similar in Group IT and Group DC. Whole pancreas transplantation produced precise metabolic control of diabetes throughout the 24 months of study, whereas pancreatic islet transplantation did not accomplish complete metabolic control, particularly beyond the first several months after transplantation. The difference in the completeness of metabolic control achieved by the two types of transplants is the most likely explanation for their sharp difference in effectiveness in preventing diabetic nephropathy.

Full text

catecholamines, and growth hormone, but it has not accomplished long-term normoglycemia.[64,65] A number of recent studies have reported progression of nephropathy[21–23] and retinopathy,[24–32] and failure to improve neuropathy[32] during insulin pump therapy, perhaps because metabolic control has not been sufficiently precise to reverse the diabetic lesions.

The development and progression of diabetic nephropathy have not been prevented by conventional treatment with insulin injections and diet.[8–10] Nephropathy often develops in normal kidneys transplanted into diabetic recipients for end-stage renal failure, despite concerted efforts at metabolic control with conventional therapy.[66–69] Our previous findings that whole pancreas transplantation is capable of preventing GBMT and ME, and our current demonstration that pancreaticoduodenal transplants are effective in preventing all renal lesions of experimental DM, suggest that whole pancreas transplantation may be indicated in patients with end-stage diabetic nephropathy who require kidney transplantation and, therefore, must be given immunosuppression therapy for life. The outlook for the usefulness of pancreatic islet transplantation appears less promising.

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Discussion

DR. JOHN S. NAJARIAN (Minneapolis, Minnesota): I want to congratulate the author on a very nice presentation of studies that we have followed with interest over the years.

I am, at one point, however, concerned about the conclusions that Dr. Orloff has reached. Therefore, I would like to state a few facts and ask a couple of questions.

In 1974, in the journal *Diabetes,* we showed that syngeneic islets, when transplanted to rats, can prevent, as well as reverse, the lesions of experimental diabetes in the kidney. This finding was reported in a syngeneic rat system in which the recipient rat was made diabetic with streptozotocin, a different form of beta cell poison than alloxan. This reversal was complete for diabetic lesions, which occurred within 3 months of streptozotocin treatment. However, if we waited 6–9 months, we could not reverse the lesions, which now became collagen-filled and irreversible. In its early and proliferative stages, however, the mesangial matrix material, which is the *sine qua non* of this lesion, could be reversed.

In 1975, armed with this information, we progressed to treating 20 patients who were Type I diabetics with allogeneic islets. We transplanted them with what we believed were enough islets, and yet, in each instance, we were only able to reduce their insulin requirements but never cure a single patient (insulin independence).

We temporarily gave up on this technique and went back into the clinical arena to perform segmental organ transplantation of the pancreas, as we had done initially in 1966 with whole organ pancreaticoduodenal transplants. Since 1978, we have performed 185 segmental or whole organ pancreas transplants.

At the same time we were puzzled with what happened to the transplanted islets in the previous clinical series. Was it a fact that we did not technically transplant viable islets, or was the lack of success due to immunologic rejection?

To determine which phenomenon was responsible for this failure, we investigated a series of patients with chronic small duct pancreatitis. We removed their pancreases, isolated the islets, and gave them back their own (autologous) islets, so there could be no immunologic consequences.

Under those circumstances, even though the number of islets was limited, half of these patients did not require further insulin, and currently, we have seven patients on isolated autogenous islets transplanted to the liver who do not require insulin and have excellent metabolic control. Our technique, therefore, was good; therefore, there must be immunologic problems that need to be solved to make islet allotransplantation successful.

Dr. Sutherland and I then went on and did 185 pancreatic organ transplants, whose results we presented to this Association, and clinically 60% of these transplants have worked very well. With pancreas transplants, we have seen partial reversal of triopathy; the renal lesions, the retinal lesions, and the neurologic lesions.

It is tempting to hope that the islets would work because, in fact, it would involve less surgery. In addition, you have enough islets so that you could treat more than one patient with the islets obtained from a single cadaveric donor.

It has been shown by various groups that you can transplant islets and achieve a completely normal glucose tolerance curve. This has been shown by David Sharp in St. Louis, Gus Nossal's group in Australia, Conrad Federle in Germany, and John Paul Squifflet in Brussels. All of these investigators have shown that with islets they can get normal glucose tolerance curves and can prevent the lesions that Dr. Orloff observes with animals that receive pancreatic transplants.

Thus, what has happened in the Orloff experiment with islet transplantation? We have found that when you put islets into the liver you lose about half of them. Therefore, we increased the number of islets transplanted sufficiently enough to get equivalent numbers of islets to those that we transplanted with whole organ pancreas transplants.

When we did that, there was no difference between the results of pancreatic organ transplants and islet transplants.

My question to Dr. Orloff is: how did you measure the amount of islets or insulin content that you had in the liver? In addition, even the slightest bit of species difference with islets would show the kind of erosion that he reported with the loss of islets with time. What species did you use and what combinations?

DR. KEITH REEMTSMA (New York, New York): The question posed by Dr. Orloff is of central importance, and in his studies, islet transplants do not work well. However, other investigators have found that islet transplants can, in the long run, produce normal metabolism and reversal of the vascular diabetic changes, as measured by renal function and morphology.

The important question here is why, under the circumstances of this study, islet transplants do not function well. I would agree with Dr. Orloff that the most likely explanation for the vascular changes is the incomplete reversal of the metabolic state. But why? The pattern of failure suggests an inhospitable environment for the transplanted islets. Perhaps Dr. Orloff could comment on the liver pathology, as alloxan produces periportal fibrosis, and this might interfere with islet function.

These studies confirm that whole pancreas grafting is effective, and it results in hyperinsulinemia. The eventual role of islet transplants, however, remains unanswered.

DR. ROBERT J. CORRY (Iowa City, Iowa): I compliment Dr. Orloff on an excellent paper regarding an important issue; that is whether or not successful pancreatic transplantation can prevent or stabilize the devastating secondary complications of Type I diabetes. In his study, rats who received islets did not achieve normal glucose control, suggesting either that an insufficient supply of islets was administered or something happened to them in the first few months, such that normal glucose control could not be achieved. On the other hand, whole organ pancreatic transplantation resulted in normal glucose metabolism and prevented complications.

With regard to whole organ grafting we have reasons to be optimistic as a result of evidence emerging from a few U.S. and European pancreas transplant programs. In Stockholm, Carl Groth has shown prevention of the mesangial thickening in the glomeruli in patients who received combined kidney and pancreas grafts compared with another group of patients transplanted at the same time, namely diabetic recipients who received kidneys only. All patients who received kidneys and were followed after 3 years had microscopic changes of diabetes in the glomerulus, whereas none of the patients who received combined kidneys and pancreases had any degree of mesangial thickening.

In addition, Walter Land in Munich has shown some evidence of reversal of neuropathy as well as vasculopathy. Donald Dafoe in Michigan has presented some interesting data showing that blood lipids are significantly lowered in patients who have received successful pancreas grafts.

I would like to show a few slides indicating that whole organ transplantation of the pancreas does not necessarily preclude successful liver donation. This illustration shows the blood supply of both organs dissected. Essentially the gastroduodenal artery is ligated and the splenic artery is divided a few millimeters from its origin on the hepatic artery. The superior mesenteric artery is divided near the pancreas. The portal vein is divided as it exits the pancreas. In this way the blood supply for the donated liver will be normal, namely the aortic patch and entire portal vein go with the liver. Extension grafts are placed on the pancreas under ice by taking a segment of donor iliac artery with both branches. The internal iliac artery is then joined to the superior mesenteric artery and the external iliac artery is joined to the splenic artery. Donor iliac vein is then used to extend the portal vein. These extension grafts are placed under iced solution so the ischemic time is not extended very much.

DR. THOMAS E. STARZL (Pittsburgh, Pennsylvania): This is a grand organization that we belong to and the prestige of the organization is so great that a paper presented here is apt to be construed as the last word. If we really accept this paper on absolutely face value, this could be the death knell of islet cell transplantation. It is in that context that I want to make a few comments and this is where I am inclined to be in agreement with Dr. Najarian.

Solid pancreas transplantation in principle as practiced successfully by Dr. Orloff and by others at Minnesota and elsewhere, is different than almost anything else we do. If we transplant the kidney, there is no carrier tissue that comes along with the graft. It is a simple, straightforward intellectual exercise. If there is any carrier function that comes with the kidney, it might be the production of erythropoietin. The heart is a simple pump, and with the liver, practically every cell does something that is essential for the survival and health of the recipient. In the case of the pancreas we are transplanting an organ in which if we transplant 100 g, almost all of that is tissue, which, first of all, is not needed, and second, is a nuisance. That extra tissue accounts for almost all the morbidity and mortality of whole organ pancreas transplantation, which is considerable.

What are the options? One of the options is the procedure that fared so poorly in Dr. Orloff's comparison. I do not doubt for a moment his conclusions, but I must say that I still have hopes for islet cell transplantation. I hope that this paper, as fine as it is, will not cause funding to be precluded for islet cell research or efforts to be stopped by some of those groups that are still making those efforts such as Scharp in St. Louis, Lafferty and Weil from Colorado, Mintz and Miller from Miami, and possibly others including Sutherland of Minnesota and Barker et al. from Pennsylvania.

Other options have to be carefully explored because of the deficiencies not only of whole organ transplantation, but also of islet cell transplantation. One possibility might well be gene splicing, in which cells are endowed with the ability to produce insulin. Anything that could move us in that direction would be valuable and certainly would be worth pursuing.

The annals of history, as my friend, Mark Ravitch, has reminded me often, are replete with missed opportunities. I could recount many but these would reveal my age. We do not have to go much farther back than last month's *New England Journal of Medicine* in which there was a report from Mexico about successful transplantation of adrenal tissue into the brain for the treatment of neuropsychiatric disorders. This was a procedure that had been thoroughly discredited in previous Scandi-

navian trials, but that now holds great promise instead. I hope that islet transplantation or some analogue or derivative of that procedure is not actually dead.

DR. MARSHALL J. ORLOFF (Closing discussion): I am honored to have this work discussed by some of the giants in this field, and there is no doubt that they are the giants. Keith Reemtsma was working on pancreas transplantation when I was just a boy, and he reminded me of that before he got up to discuss my paper. He has made enormous contributions to this field. As to John Najarian, whenever I present a paper, he always gets up and says: "It is a very nice piece of work, but we did that back in 1970." And he is sometimes right. His experimental and clinical work and that of his group, David Sutherland and the others, has been monumental in the field of pancreas transplantation. I guess you would have to call the Minnesota group the leading pancreas transplantation group in the world. Of course, I cannot even begin to describe what Tom Starzl has done for everything in transplantation. It is awesome. I hate to think about it because I feel so inferior after thinking about all the things that he has done. Rob Corry is a relative newcomer, the new kid on the block, but the results that they are having in Iowa with clinical transplantation of the pancreas are extremely promising and they have developed very rapidly. They certainly have my respect.

The main issue I believe, and it is a critical issue, is what degree of metabolic control is required to prevent and/or reverse the lesions of diabetes, not just in the short term, but in the long term. Our experimental data suggest, and in fact the clinical data including the data on insulin pump therapy suggest, that the control must be very precise and must be of long duration. Brief periods of control for a few months do not really mean a lot. It has to be very precise and prolonged.

As far as we can tell, at least to this point, the most precise metabolic control comes from transplanting the whole pancreas. It is the only form of endocrine pancreas replacement therapy that has produced complete and prolonged metabolic control.

Regarding the comments of John Najarian, I have the following response: (1) The 1974 report of his group in *The Journal of Experimental Medicine*, in which kidneys from 11 diabetic rats were transplanted into normal rats, did not show statistically significant reversal of mesangial matrix thickening. Furthermore, this was a very short-term, nonquantitative study in which the kidneys were transplanted after only 6 months of diabetes and then were studied only 2 months later. I do not believe any conclusions from this study, positive or negative, are possible. (2) As to his six patients who have received autologous islets, the problem with all of these case reports is that the patients have not had long-term, well-established diabetes before islet transplantation, and there is always the question of whether the patients would have had diabetes without the autologous islet transplantation. The hard facts are that there is not a single case of successful, prolonged relief of diabetes mellitus among the more than 100 diabetic patients who have received islet transplants. (3) Regarding John's statement that many have shown completely normal GTT's following islet transplantation, the facts are that if one examines the literature carefully, one will be hard-pressed to find *long-term*, clearly documented normalization of the GTT. For example, Renold's group and Barker's group both found that the GTT remained abnormal, and numerous studies, including those from Dr. Najarian's own institution (Steffes et al., Vialettes et al.) have shown failure of plasma glucose and insulin levels to normalize both initially and in the long term. (4) John asked: Is it possible that our islets were being rejected? We used highly inbred Lewis rats. We have shown that these rats accept transplants of skin, whole pancreas, liver, intestine, stomach, spleen, and heart without developing clinical or histologic evidence of rejection. There was no histologic evidence whatsoever of immunologic rejection of our islet transplants. (5) Finally, Dr. Najarian asked how we measured the volume of islets transplanted. We counted the number of islets microscopically in an aliquot of the islet suspension. We transplanted approximately 2000 islets, which is more than the number used by the vast majority of workers. For example, in intraportal transplants, Kipnis, Lacy et al. used 350–1000 islets, Barker et al. used 400–500 islets, and Federlin et al. used 500–800. There is no question that our transplants were successful, since they produced normal plasma glucose and insulin levels for the first several months. Measurement of insulin output from the liver is not a good way of quantitating the adequacy of the transplant, unless repeated measurements over a long period are made, and no one has done that.

Keith Reemtsma raised the possibility that alloxan might cause periportal fibrosis that interferes with the viability of the islets. We have studied several thousand rats with alloxan diabetes and have never seen any evidence of periportal fibrosis or hepatic changes. Moreover, our islet transplants were very viable for the first several months. However, as others such as Barker et al. have observed in streptozotocin diabetes, there is a progressive loss of islets after initial metabolic control, I believe because they do not bring their own supply of blood vessels and have a very tenuous existence. As time goes by, the islets are easily lost, perhaps as a result of even transient reductions in hepatic blood flow and oxygen supply.

Tom Starzl made an inspirational statement about continued funding for research in islet transplantation. I do not believe there is anything to fear. Having worked in the field of portal hypertension for many years, I have often observed that nothing dies except the patients.

Although I have considerable doubt about the ultimate success of islet transplantation, there is no question that continuing research is warranted along all avenues that could conceivably help the millions of patients who suffer from diabetes. Moreover, islet transplants have provided and will continue to provide important information about many aspects of diabetes and its treatment. An understanding of islet physiology, islet immunology, and prevention of islet rejection are but a few of the potential and actual benefits of islet transplant research.