

DeGruyl and his colleagues found that ligation of the pancreatic duct in the dog was followed by normal serum insulin levels and glucose tolerance curves for two years.⁴ Moreover, DeGruyl reported that autotransplantation of the duct-ligated whole pancreas in the dog, although associated with a high rate of technical failure, resulted in a few survivors that had normal endocrine function for up to three years.

By all criteria used in this study, the duct-ligated pancreas transplants were as effective as pancreaticoduodenal grafts in controlling diabetes. Moreover, the operative mortality rate associated with transplantation of the duct-ligated pancreas was lower than that of pancreaticoduodenal transplantation, and there was no clinical evidence of pancreatitis or toxicity. The characteristic morphologic features of the duct-ligated pancreas were dilatation of the ducts and atrophy of the acini, not pancreatitis, and the islet tissue, although fragmented, remained viable with abundant beta cell granules.

There have been conflicting reports regarding the necessity of providing venous drainage of pancreas transplants into the portal system. Some investigators have suggested that systemic venous drainage results in high serum insulin levels and hypoglycemia because of bypass of hepatic insulin metabolism.^{1,16,18} Other workers have failed to observe any difference between portal and systemic venous drainage of the transplant.^{6,9} The results of this study indicate that venous drainage of the pancreas graft into the inferior vena cava was associated with normal endocrine function so that portal venous drainage appears unnecessary.

The use of syngeneic grafts in inbred animals provided an ideal experimental model for these studies of the physiological function of the transplanted pancreas. Whether or not similar results can be achieved with pancreas allografts beset by the familiar problems of immunologic rejection remains to be determined. To date, 45 pancreas allografts have been transplanted in human subjects.^{2,3} Only two patients are currently alive with functioning grafts. The longest survivor of a pancreas allograft is living 2.8 years after transplantation. While control of hyperglycemia clearly has been accomplished, reversal or stabilization of the vascular complications of

diabetes has not yet been established. The results of the present study provide hope that such may be possible.

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DISCUSSION

DR. KEITH REEMTSMA (New York City): This excellent study by Dr. Orloff and his colleagues emphasizes the importance of long term studies in experimental diabetes.

He has asked several important questions related to whole organ transplantation. This technic introduces certain problems, and for this reason we have asked the question of whether one can achieve the same metabolic results by transplanting islets. The answer is yes.

Dr. Collin Weber in our laboratory at Columbia has shown reversal of

the diabetic state in animals for one year following transplant of the isolated islets in isologous strains.

Our control animals, as in Dr. Orloff's study, remained diabetic, while those receiving islet isografts had normal fasting glucose levels 10–12 months following transplantation. They also have normal glucose tolerance curves.

However, the reason I rise to discuss this is to mention the insulin and glucagon levels in animals that received isolated islet transplants. These levels were determined 10–12 months following transplantation.

The interesting observation is that, in comparison with findings in

normals and control diabetic animals, the insulin and glucagon levels are all elevated in these islet recipients twelve months following transplantation.

These findings emphasize the importance of studies such as Dr. Orloff's which give us comprehensive, long term results.

DR. WALTER F. BALLINGER, II (St. Louis): As some of you know, we too prefer the use of isolated islets of Langerhans as a sub-organ form of transplantation for several reasons. First, it's a smaller volume of a transplanted tissue. Secondly, it relieves the animal of the exocrine secretion which Dr. Orloff now suggests may be well controlled by ductal ligation. And, thirdly, and I think most importantly, avoids the very complex vascular anastomosis that are required.

Dr. Orloff and his group are to be complimented on the simply marvelous microvascular technique that they have developed.

As we see it, there are four major problems that still remain. First, in all of our experiments—and I hope Dr. Orloff might comment on this—in spite of the fact that normoglycemia is consistently maintained throughout or up to two years, whenever the animals have glucose tolerance curves performed, they are not identical to normal animals and, in fact, when the rats, or now monkeys, are stressed by a variety of means, the glucose tolerance curves tend to return toward the diabetic state. This is an unanswered question, however, but I think an important one.

Furthermore, other similar metabolic studies such as insulin stimulatory tests, tolbutamide stimulation studies, reveal the animals to be not completely normal.

Secondly, there are problems with isolation of islets. Certainly as Dr. Reemtsma knows, isolation of the islets in the rat is relatively simple, but in the monkey and in man the pancreas is a compound organ and somewhat different from the rat. And, isolation problems are still severe.

Thirdly, the problems of tissue preservation will always be with us until we develop some other technique not yet in sight.

Fourthly, the problem of immunosuppression in the severely ill diabetic, I think, is a problem we have not yet adequately addressed ourselves to.

Now, the goal of transplantation in diabetes is not normoglycemia. We can do that with exogenous insulin today. The goal is to restore some sort of glucagon insulin islet balance in order to prevent the long range complications of diabetes. We have not yet seen the complications that Dr. Orloff has described in his animals. We have seen a non-specific protein deposition in the basement membrane in the renal vasculature, but have not seen many cataracts. We have seen no clear-cut diabetic nephropathies or any vascular lesions.

So I'm fascinated by the return to normal in these diabetic animals

and I hope as he cut short his talk he might dwell on this somewhat further. I might ask whether he tested these animals to see if their metabolic studies do remain normal or whether they revert to the diabetic state.

DR. MARSHALL J. ORLOFF (Closing discussion): The two competing hopeful forms of therapy in dealing with transplantation for diabetes are, of course, transplantation of the whole organ, as described in our presentation, and the transplantation of the isolated islets.

I think several questions remain about both forms of transplantation in the allograft situation. The key to answering these questions, of course, is that by starting with the isograft situation without immunosuppression and immunologic rejection is carrying out the studies for a very long period of time, but there is a considerable question about whether the diabetes that is observed for both islets and whole organ will persist.

I think our studies have demonstrated that during the full lifespan of a diabetic rat, which might be comparable to some 60 or 70 years in the human being, the diabetes was relieved by the whole organ. I'm sure that the same would be true with isolated islets.

We did perform some glucose tolerance tests and some thalbutamide tolerance tests in these animals and we have observed perfectly normal glucose tolerance tests with the whole organ which is different from the findings Dr. Ballinger and his group have reported previously with the isolated islets. Perhaps that's simply a matter of the amount of insulin secretion and the degree of control of the diabetic state.

The pathologic changes are very interesting because they are not impressive for the first nine months or year of the studies. Most of the work in this field has been confined to that relatively short term period.

But at or about nine or ten months, changes in the kidney begin to appear and consist of xangio-hyperplasia and thickening of the basement membrane and the glomeruli, some vacuolization of the tubules, infiltration of the interstitium with plasma cells, and beginning hyalinization of blood vessels and there are very minimal changes at that period.

As one goes into the second year, they become more prominent so that they achieve a kidney pathology which, in many respects, is similar to that seen in Kimmelstiel-Wilson's Disease in man.

The ocular changes are absolutely spectacular. There is formation of neovascular membrane on the cornea and retina. There is practically complete destruction of the retina and progressive disappearance of all the cells and, again, findings similar to the retinopathy that is found in man. But these can only be demonstrated, and in fact, the relief can only be demonstrated by the long term studies.

I think the issue is not yet settled about whether islet cell transplantation or transplantation of the whole organ will be the best approach to this problem. Certainly, both avenues must be approached and continued further.