Long Term Studies of Pancreas Transplantation in Experimental Diabetes Mellitus

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Alloxan diabetes was induced in inbred rats that then were divided into four groups consisting of unoperated diabetic controls, sham-operated diabetic controls, rats given pancreaticoduodenal isografts, and rats given duct-ligated pancreas isografts. The animals were studied for from 18 months (controls) to two years (transplants) and the following important results were obtained: 1) In striking contrast to the diabetic controls, pancreas transplants of both types produced immediate and permanent relief of hyperglycemia, immediate and lasting elevation of serum insulin levels, a normal weight and growth curve, and good health for two years. Removal of the graft was followed by recurrence of severe diabetes. 2) Pancreas transplants of both types prevented the widespread and severe renal, ophthalmic and neural lesions of diabetes that were found in the diabetic controls. 3) The duct-ligated pancreas graft and pancreaticoduodenal transplant were equally effective in controlling diabetes. Ligation of the pancreatic duct was not followed by significant morphologic or clinical evidence of pancreatitis or by loss of endocrine function. 4) Portal venous drainage of the pancreas transplant was unnecessary for good endocrine function.

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DIABETES MELLITUS is a very common disease that is responsible for substantial morbidity and mortality. It is estimated that more than 4.5 million people in the United States have diabetes, approximately one million of whom require insulin therapy for control of hyperglycemia.[17] Currently, diabetes is the seventh ranking primary cause of death in this country, and it is a major contributor to deaths attributed to heart disease and stroke. Approximately one-quarter million individuals in the United States have juvenile-onset diabetes, the most severe form of the disease, and most of these develop nephropathy and retinopathy by the fourth decade of life regardless of how well their blood sugar levels have been controlled by available medical means. Substantial evidence indicates that current treatment of diabetes with insulin and diet has had little influence on the development of the widespread vascular lesions that complicate this condition. Although the etiology of diabetes mellitus is still not known, the weight of opinion favors the view that insufficiency of the islets of Langerhans is the primary abnormality, so that provision of physiological islet function might prevent the crippling and often lethal effects of the disease. Therefore, the clinical stimulus to research in pancreas transplantation is apparent.

If pancreas transplantation is to be useful in the treatment of diabetes mellitus, four important questions must be answered. These are:

1) Is *long-term* control of diabetes possible? Will the pancreas transplant remain viable with good endocrine function for prolonged periods of time?

2) Will the pancreas transplant prevent or relieve the widespread vascular, renal, ophthalmic and neural manifestations of diabetes?

3) Is transplantation of the pancreas alone, with its ducts ligated, followed by autodigestion of the gland and resultant toxicity from pancreatitis, and by loss of endocrine function?

4) Is portal venous drainage of the pancreas transplant unnecessary for good endocrine function?

In 1970, a microvascular surgical technique of heterotopic transplantation of the pancreas in rats was developed in our laboratory by Dr. Sun Lee.[5,10,11] Use of this technique for transplantation of isografts between inbred rats has provided the opportunity to study the function of the transplanted pancreas without the complications of immunologic rejection or immunosuppres-
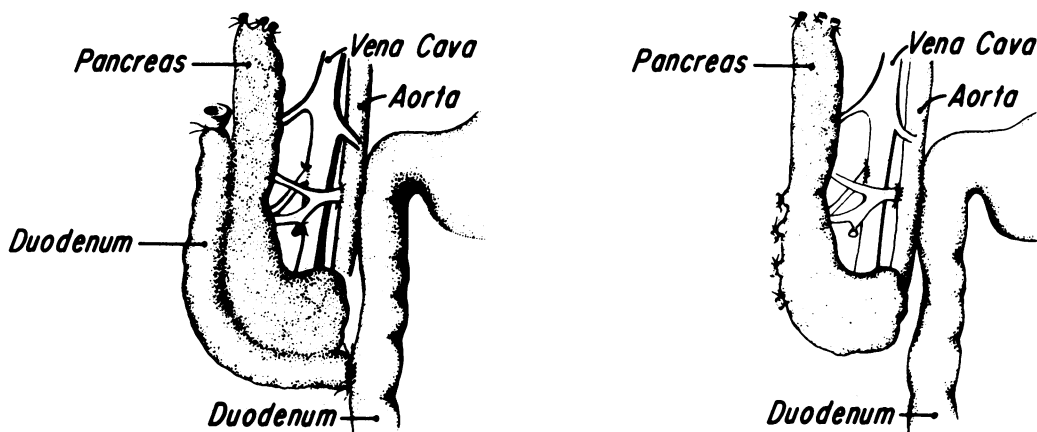
FIG. 1. Microvascular surgical technique of heterotopic pancreaticoduodenal transplantation and of duct-ligated pancreas transplantation showing the operations in the recipient.

Pancreaticoduodenal Transplant

Duct Ligated Pancreas Transplant

sive therapy. The study reported herein was designed to answer the four critical questions by means of experiments involving transplantation of the pancreas in rats with alloxan-induced diabetes.

Materials and Methods

Experimental Groups

Male Lewis strain rats approximately six months of age and weighing approximately 350 gm were used in these studies. Diabetes mellitus was induced by intravenous administration of alloxan in a dose of 42–44 mg/kg. Only those rats that had blood glucose levels above 200 mg % on two successive determinations during the first week after alloxan injection were continued in the experiments. One week after diabetes was established, the rats were randomly assigned to four experimental groups as follows:

Group I consisted of 65 unoperated diabetic controls.

Group II contained 43 sham-operated diabetic controls. The sham operation involved isolation of segments of the abdominal aorta and inferior vena cava, and occlusion of the aorta and vena cava for 25 minutes.

Group III was made up of 69 diabetic recipients that received syngeneic pancreaticoduodenal transplants from normal Lewis strain donor rats of the same age, sex and weight.

Group IV consisted of 49 diabetic recipients that received syngeneic transplants of the whole pancreas with its ducts ligated from normal Lewis strain donor rats of the same age, sex and weight.

The rats with pancreas transplants in Groups III and IV were studied for a period of two years. Since the

animals entered the study at six months of age and the normal life span of the Lewis rat ranges from two to two and one-half years, the transplanted rats were observed through their entire natural life. Because of the progressively increasing mortality rate in the diabetic controls in Groups I and II, an insufficient number of animals survived to permit observations beyond 18 months.

Transplantation Techniques

We have previously reported the microvascular surgical technique of heterotopic transplantation of the pancreas in inbred rats.[5,10,11] The pancreaticoduodenal graft was harvested from the donor rat through a midline abdominal incision. The duodenum and pancreas were separated from the colon and greater omentum, the left gastric artery was divided, and the spleen was excised after ligation and division of its vascular pedicle. The duodenum was ligated just beyond the pylorus and divided, and the bile duct and hepatic artery were ligated and divided close to the liver. The aorta was isolated from above the celiac artery to below the superior mesenteric artery, and all of its branches except the celiac and superior mesenteric were ligated and divided. The portal vein was divided at the level of the duodenal-jejunal junction. The aorta was cross-clamped, the graft was perfused with 8 ml of iced 0.85% saline by injection through the aorta, and the aorta was divided to produce an aortic segment with attached celiac and superior mesenteric arteries supplying the graft. The portal vein was divided at the liver hilum, the duodenum was divided in its distal third, and the entire pancreas with attached duodenum, aortic segment and portal vein were excised and placed in iced saline.

TABLE 1. *Blood Glucose Levels in the Four Experimental Groups of Rats*

	I. Unoperated Diabetic Controls (n=65)		II. Sham-operated Diabetic Controls (n=43)		III. Pancreaticoduodenal Transplants (n=69)		IV. Duct-ligated Pancreas Transplants (n=49)	
Time After Induction of Alloxan Diabetes	Mean Blood Glucose mg%±S.E.	Per cent of Rats with Blood Glucose >200 mg%	Mean Blood Glucose mg%±S.E.	Per cent of Rats with Blood Glucose >200 mg%	Mean Blood Glucose mg%±S.E.	Per cent of Rats with Blood Glucose >200 mg%	Mean Blood Glucose mg%±S.E.	Per cent of Rats with Blood Glucose >200 mg%
1 week (Preoperative for Groups II, III, IV)	292±10	100	318±13	100	325±12	100	330±19	100
3 months	278±23	67	264±15	68	76±5	0	82±3	0
6 months	274±13	74	303±30	79	97±6	0	81±2	0
9 months	366±31	86	370±37	89	79±7	0	95±12	0
12 months	318±19	80	374±23	100	79±12	0	91±4	0
15 months	283±16	100	275±41	75	109±22	0	92±4	0
18 months	284±26	79	250±45	68	89±3	0	91±6	0
21 months	*	*	*	*	72±2	0	93±5	0
24 months	*	*	*	*	107±2	0	100±6	0

*Insufficient number of survivors
Statistical Comparisons: Group I vs Group II - No significant difference at any time
Group III vs Group IV - No significant difference at any time
Group III vs Groups I and II - P=<0.001 at all times
Group IV vs Groups I and II - P=<0.001 at all times

The pancreaticoduodenal graft was transplanted to the recipient rat through a midline abdominal incision (Fig. 1). The recipient aorta and inferior vena cava below the level of the left renal vein were cleaned and occluded with a partial occlusion clamp. End-to-side vascular anastomoses were performed using continuous 9-0 nylon sutures between the graft aortic segment and the host aorta, and between the graft portal vein and the host inferior vena cava. The open distal end of the graft duodenum was anastomosed end-to-side to the third portion of the host duodenum, using a continuous 7-0 silk suture. The graft ischemia time was 30 ± 5 minutes.

Transplantation of the duct-ligated pancreas alone, without the duodenum, was performed by a technique similar to that of pancreaticoduodenal transplantation except that in harvesting the graft the pancreas was dissected free from the duodenum and its excretory ducts were meticulously ligated and divided at their junction with the bile duct (Fig. 1).

Blood Glucose and Insulin and Clinical Observations

The concentrations of glucose and insulin in blood obtained from a tail vein, body weight, food and water consumption, and physical appearance were determined every two weeks for the first three months, and then monthly for up to two years. Plasma glucose was measured by a modification of the O-toluidine method which involves the spectrophotometric detection of N-glucosylamine formed from the reaction of glucose with O-toluidine in glacial acetic acid in the presence of heat. Serum insulin was measured by a double antibody radioimmunoassay according to the principle of Yalow and Berson,[20] using the Pharmacia Phadebos kit.

Morphologic Studies

Complete autopsies were performed in the rats at the time of death, and tissue was obtained for study by both light and electron microscopy. Particular attention was given to examination of the host pancreas, graft pancreas, kidneys, eyes, peripheral nerves, brain and blood vessels. Sections of pancreas were stained with both hematoxylin and eosin and with Gomori's aldehyde fuchsin to demonstrate the beta cells in the islets of Langerhans. In addition, at intervals throughout the study, animals were sacrificed randomly to provide optimal material for evaluating the evolution of morphologic changes.
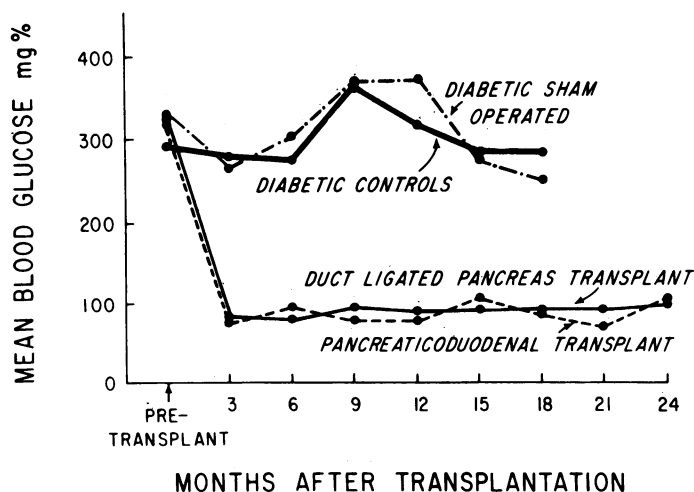

FIG. 2. Mean blood glucose levels in the four experimental groups of alloxan diabetic rats.

TABLE 2. *Serum Insulin Levels in Four Experimental Groups of Rats*

Time After Induction of Alloxan Diabetes	I. Unoperated Diabetic Controls (n=58)		II. Sham Operated Diabetic Controls (n=35)		III. Pancreaticoduodenal Transplants (n=32)		IV. Duct-ligated Pancreas Transplants (n=37)	
	Mean Serum Insulin ng/ml±S.E.	Per cent of Rats with Insulin <1.0 ng/ml	Mean Serum Insulin ng/ml±S.E.	Per cent of Rats with Insulin <1.0 ng/ml	Mean Serum Insulin ng/ml±S.E.	Per cent of Rats with Insulin <1.0 ng/ml	Mean Serum Insulin ng/ml±S.E.	Per cent of Rats with Insulin <1.0 ng/ml
1 week (Preoperative for Groups II, III, IV)	1.15±0.16	65	1.20±0.09	72	0.68±0.09	92	0.87±0.08	89
3 months	0.88±0.12	62	1.01±0.12	61	2.23±0.19	17	1.47±0.06	8
6 months	0.84±0.12	77	0.73±0.12	84	1.80±0.13	21	1.53±0.08	17
9 months	0.62±0.05	96	0.67±0.09	81	1.63±0.19	22	1.35±0.10	26
12 months	0.48±0.04	100	0.46±0.09	100	1.61±0.09	20	1.33±0.07	3
15 months	0.59±0.07	90	0.55±0.07	100	1.23±0.13	33	1.16±0.04	46
18 months	0.65±0.09	89	0.56±0.06	100	1.14±0.18	33	1.18±0.06	30
21 months	*	*	*	*	1.85±0.16	67	0.90±0.13	50
24 months	*	*	*	*	1.10±0.03	50	1.15±0.06	50

*Insufficient number of survivors
Statistical Comparisons: Group I vs Group II - No significant difference at any time
Group III vs Group IV - P=<0.001 at 3 months, no significant difference at any other time
Group III vs Groups I and II - P=<0.001 at all times
Group IV vs Groups I and II - P=<0.001 at all times

Removal of the Transplant

To assess further the effectiveness of pancreas transplants in controlling diabetes, the grafts were removed from 19 animals that had been relieved of diabetes, and the studies of blood glucose, serum insulin, body weight and physical appearance were continued to determine if diabetes would recur. Twelve pancreaticoduodenal transplants were removed, 11 at one year and one at two years postoperatively. Seven duct-ligated pancreas grafts were removed, one at 18 months, two at 20 months, three at 22 months and one at 25 months postoperatively. The excised grafts were examined microscopically. In addition, complete morphologic examinations were performed when these animals ultimately died.

Results

Blood Glucose

The mean blood glucose levels and the per cent of animals with blood glucose levels above 200 mg % in the four experimental groups are shown in Table 1 and Fig. 2. All of the animals had blood glucose concentrations greater than 200 mg % at the time of operation, one week after administration of alloxan. The hyperglycemia persisted in both the unoperated and sham-operated controls, and the diabetes was associated with a progressively increasing mortality rate so that few animals survived beyond 18 months. The blood glucose levels in the two control groups were not significantly different at any time (P>0.10). In contrast, every animal with a pancreas transplant had an immediate and permanent reduction of the blood glucose level to normal for the two-year study period. The differences in blood glucose concentrations between the two groups with transplants and the two control groups were highly significant at all times (P<0.001). Control of hyperglycemia was equally effective in the two transplant groups, and there were no significant differences between them at any time (P=>0.10).

Serum Insulin

The mean serum insulin levels and the per cent of animals with serum insulin levels below 1.0 ng/ml in the four experimental groups are shown in Table 2 and Fig. 3. Following induction of alloxan diabetes, all of the rats developed a significant fall in serum insulin concentration. In the unoperated and sham-operated diabetic control rats, the decline in serum insulin levels progressed so that by one year every animal had a serum insulin con-
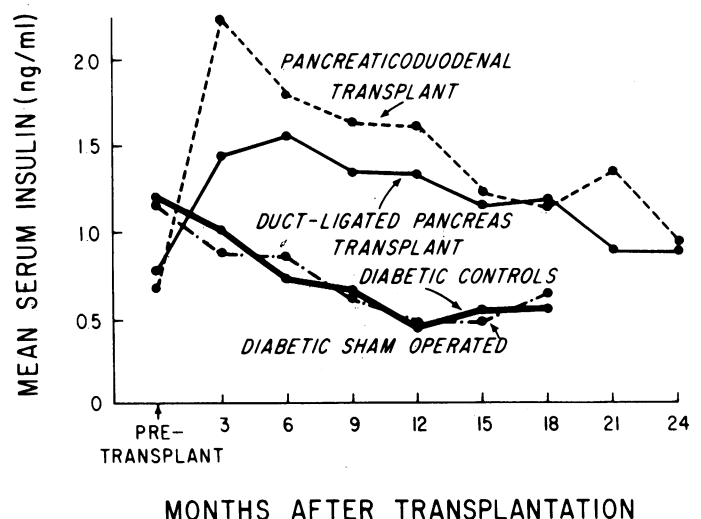

MONTHS AFTER TRANSPLANTATION

FIG. 3. Mean serum insulin levels in the four experimental groups of alloxan diabetic rats.

TABLE 3. *Mean Body Weight in Four Experimental Groups of Rats (gm±S.E.)*

Time After Induction of Alloxan Diabetics	I. Unoperated Diabetic Controls (n=65)	II. Sham-operated Diabetic Controls (n=43)	III. Pancreaticoduodenal Transplants (n=69)	IV. Duct-ligated Pancreas Transplants (n=49)
1 week (Preoperative for Groups II, III, IV)	307±2	301±5	294±10	304±6
3 months	332±11	331±6	396±12	394±15
6 months	355±30	354±11	455±20	457±6
9 months	358±10	361±10	404±22	482±6
12 months	349±10	366±10	474±11	488±8
15 months	371±11	362±14	542±15	499±10
18 months	384±21	386±11	556±24	473±30
21 months	*	*	517±44	489±15
24 months	*	*	577±22	516±21

*Insufficient number of survivors
Statistical Comparisons: Group I vs Group II - No significant difference at any time
                         Group III vs Group IV-P=<0.001 at 9 months, no significant difference at any other time
                         Group III vs Groups I and II-P=<0.05 at 9 months, P=<0.001 at all other times
                         Group IV vs Groups I and II-P=<0.02 at 18 months, P=<0.001 at all other times

centration below 1.0 ng/ml. The serum insulin levels in the two control groups were not significantly different from each other at any time. In contrast, transplantation of the pancreas, with or without the duodenum, produced an immediate and persistent rise in serum insulin to levels that were significantly higher than those in the control groups at all times during the study (P=<0.001). The absolute levels of serum insulin in the transplanted animals gradually declined over the two-year study period, similar to what has been observed in the normal Lewis rat as it ages. Comparison of the serum insulin levels in the two transplant groups showed a significantly higher mean insulin concentration three months postoperatively in the rats with pancreaticoudodenal grafts, but no significant differences thereafter (P=>0.10). There was no evidence that the duct-ligated pancreas transplant secreted less insulin than the pancreaticoduodenal graft up to two years after transplantation.

FIG. 4. Mean body weights in the four experimental groups of alloxan diabetic rats.

Body Weight

Mean body weights of the four experimental groups are shown in Table 3 and Fig. 4. All of the animals lost 40–50 gm of weight during the week following the injection of alloxan. The unoperated and sham-operated diabetic controls did not regain their pre-injection weights until 6 months later, and then gained weight at a rate far slower than that of normal Lewis rats. By 18 months, the mean weight of the two control groups was only 10% above their mean pre-alloxan weight. In contrast, the rats with pancreas transplants of either type regained their pre-injection weight within one month postoperatively, and subsequently gained weight at a normal rate. The differences between the control and transplant groups were highly significant at all times. Except for measurements made at 9 months after operation, when the rats with duct-ligated pancreas transplants were significantly heavier than those with pancreaticoduodenal transplants, there were no significant weight differences between the two transplant groups.
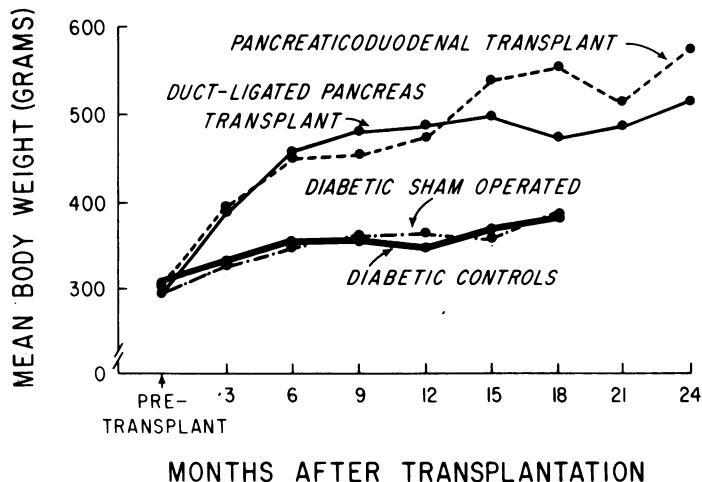
Clinical Observations

The texture of fur in the diabetic control groups was poor and they were less active than normal rats. The animals with pancreas transplants were not distinguishable from normal rats with regard to fur and activity. The diabetic control rats suffered from chronic polydipsia, polyuria and polyphagia. None of these manifestations of diabetes were observed in the transplant groups. The incidence of cataracts of the lens was 80% during a period of 18 months in the diabetic control animals, in contrast to an incidence of 12% during a two-year period in the rats with pancreas transplants.

The operative mortality rate, defined as death during the first two weeks after operation, was 32% for the pancreaticoduodenal transplant procedure and 26% for

TABLE 4. *Blood Sugar, Serum Insulin and Body Weight Following Removal of Pancreas Transplants in 19 Rats One to Two Years After Transplantation.*

	Mean Blood Glucose (mg%±S.E.)		Mean Serum Insulin (ng/ml±S.E.)		Mean Body Weight (gm±S.E.)	
	Pancreatico-duodenal Transplant † n=12	Duct-ligated Pancreas Transplant † n=7	Pancreatico-duodenal Transplant n=12	Duct-ligated Pancreas Transplant n=7	Pancreatico-duodenal Transplant n=12	Duct-ligated Pancreas Transplant n=7
Prior to graft removal	76±3	91±2	1.85±0.05	1.00±0.7	473±17	496±14
1 week after graft removal	399±65*	304±44*	0.63±0.09*	0.72±0.13	421±16*	438±9*
2 weeks after graft removal	333±49*	223±48*	0.76±0.06*	0.69±0.13	381±26*	433±8*
3 weeks after graft removal	302±2*	215±30*	0.73±0.04*	0.74±0.12*	387±43*	422±11*
4 weeks after graft removal	400*	261±46*	0.38*	0.54±0.17*	338*	391±25*

*P=<0.05 to <0.001 compared to values prior to graft removal

† In the pancreaticoduodenal transplant group, 11 grafts were removed after one year and 1 was removed after two years

In the duct-ligated pancreas transplant group, 1 graft was removed after 18 months, 2 were removed after 20 months, 3 were removed after 22 months and 1 was removed after 25 months.

transplantation of the duct-ligated pancreas. The animals with duct-ligated pancreas transplants showed no signs of pancreatitis or systemic toxicity at any time during the study, and they were clinically indistinguishable from the rats with pancreaticoduodenal transplants.

Removal of the Transplant

Table 4 and Figs. 5 and 6 show the effects of removal of pancreas transplants on blood sugar, serum insulin and body weight in 19 rats that had been relieved of diabetes by transplantation. Eleven of the 12 pancreaticoduodenal grafts were removed one year postoperatively, while all seven duct-ligated pancreas transplants were removed between 18 and 25 months after operation. Every animal had an immediate and sustained rise in blood glucose, an immediate and sustained fall in serum insulin, and a progressive loss of body weight following removal of the graft. In 17 of the 19 rats the blood glucose level exceeded 200 mg % and in eight it rose above 400 mg %. Recurrence of diabetes was accompanied by a progressive decline in health, and death of most of the rats within one month. As previous studies have demonstrated, these results indicate that alloxan diabetes is permanent, unlike diabetes induced with streptozotocin which frequently disappears with time.

Pancreas Pathology

Examination of the host pancreas at monthly intervals up to two years after exposure to alloxan showed collapse of the islets of Langerhans and permanent disappearance of almost all of the beta cells. There was no evidence of repair with time, and specimens examined two years after induction of diabetes were indistinguishable from those removed after one or two months.

Pancreaticoduodenal grafts examined serially up to two years after transplantation had all of the features of the normal pancreas of similar age. The acini, ducts and

islets of Langerhans were well-preserved and beta cell granules were abundant.

The morphologic changes in the duct-ligated pancreas transplant were of particular interest. During the first two months after transplantation there was mild to moderate chronic inflammation consisting mainly of plasma cells and some lymphocytes. Subsequently, evidence of inflammation was absent or mild. The most striking features during the first several months were dilatation and proliferation of the pancreatic ducts accompanied by marked atrophy of the acini, moderate fibrosis and replacement of the parenchyma by fat. By one year, the parenchyma of the pancreas had undergone almost complete atrophy and consisted mainly of fat, some fibrous tissue and some dilated ducts. This picture underwent little change during
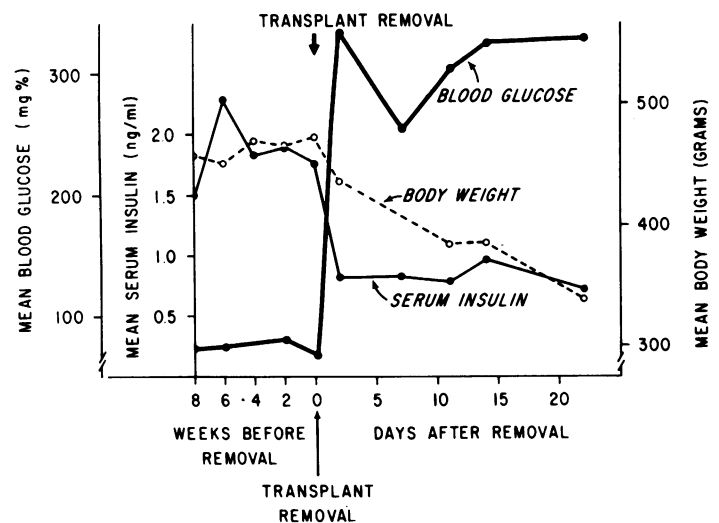

FIG. 5. Blood glucose, serum insulin and body weight following removal of pancreaticoduodenal transplants after 12–24 months in 12 rats. Eleven grafts were removed after one year and one graft was removed after two years.
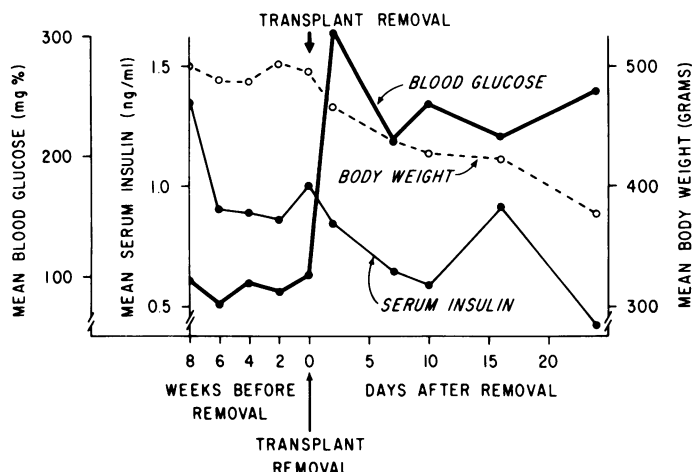
Fig. 6. Blood glucose, serum insulin and body weight following removal of duct-ligated pancreas transplants after 18–25 months in 7 rats. One graft was removed after 18 months, two after 20 months, three after 22 months and one after 25 months.

the second postoperative year. The islets of Langerhans remained intact during the first several months after transplantation. However, at about six months after transplantation fragmentation of the islets was observed, and appeared to result from invasion by dilated ducts, Despite the fragmentation, abundant islet tissue was found in every specimen up to two years postoperatively, and plentiful beta cell granules were demonstrated by the Gomori aldehyde fuchsin stain.

Systemic Pathology

A detailed description of the pathologic changes in the kidney, eye, peripheral nerves, brain and blood vessels will be the subject of a separate communication. Pathologic abnormalities in the kidneys of diabetic control rats were first observed in specimens examined nine months after induction of diabetes. These changes progressed during the second year of the disease. The glomeruli showed mesangial hyperplasia, thickening of the basement membrane and fibrosis of Bowman's capsule. The tubules contained large quantities of protein in the lumen, and there was thickening of the basement membrane that progressed to focal fibrosis of the tubules. The interstitium was infiltrated by lymphocytes and plasma cells and underwent focal fibrosis. Finally, there was progressive hyalinization of the blood vessels.

The eyes of diabetic control rats developed severe abnormalities. In addition to the previously mentioned cataracts, there was neovascularization of the corneal stroma, edema of the corneal epithelium, vacuolization of the corneal endothelium and formation of a neovascular membrane behind the cornea. Hemorrhage into the anterior chamber was not uncommon. In the retina, there was progressive loss of all cellular components and

neovascularization on the surface with some vessels extending into the vitreous.

Examination of peripheral nerves showed severe vascular sclerosis, progressive demyelination and heavy deposits of interstitial crystals in the diabetic control animals.

The pathologic findings in the animals with both pancreaticoduodenal transplants and duct-ligated pancreas grafts were strikingly fewer and less severe than those seen in the diabetic controls. In large measure, transplantation of the pancreas prevented the systemic pathologic abnormalities associated with alloxan diabetes for the life span of the rat.

Discussion

The results of this study indicate clearly that pancreas transplants were consistently capable of good endocrine function and control of alloxan-induced diabetes throughout the normal two-year life span of the rat. The permanent nature of alloxan diabetes and its cure by transplantation of the pancreas were confirmed by the prompt recurrence of the disease following removal of the grafts at intervals ranging from one to two years postoperatively.

Of potentially more far-reaching consequence, the results of this study show that pancreas transplantation prevented the widespread systemic manifestations of diabetes mellitus. The diabetic control rats developed severe pathologic abnormalities in the kidneys, eyes and nerves, many of which were similar to those that have been observed in the human disease. The prevention of the progressive renal lesions by pancreas transplantation confirms the observations made by Weil and his colleagues and by Mauer and his associates in shorter-term studies with transplants of both whole pancreas and isolated islets of Langerhans.[12,19] Whether or not transplantation of the pancreas will stabilize or reverse already established systemic abnormalities remains to be established.

The results obtained with the duct-ligated pancreas transplants are noteworthy. There has been a general impression, unsubstantiated by detailed long-term studies, that ligation of the pancreatic ducts causes autodigestion of the gland and severe pancreatitis, and ultimately leads to destruction of the islets of Langerhans and diabetes. This impression has arisen from experiments involving autotransplantation of segments of the pancreas, a procedure beset with technical difficulties related to transection of the pancreas and inadequate blood supply to the graft because of small vessel size and segmental vascular anatomy.[7,8,13–15] The applicability of the results of these studies to transplantation of the whole pancreas as an auxilliary graft is highly questionable. In the only reported study involving the whole pancreas,

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 glucogon 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