Pancreatico-Duodenal Allotransplantation:

Experimental and Clinical Experience

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The origin of an original work is always the pursuit of a fact which does not fit into accepted ideas—CLAUDE BERNARD

IN 1922 Banting and Best reported on the use of pancreatic extracts to treat diabetes mellitus in man [3] (Fig. 1). This advance seemed to herald the end of this scourge of man for all time. In the nearly half century since this discovery, diabetic acidosis nearly disappeared as a cause of death. Moreover, the juvenile-onset diabetic for the first time was able to look forward to reaching maturity, marrying and having children. Yet, at the same time, doubts have steadily increased that diabetes mellitus could be cured by giving insulin. For, despite careful control with insulin and diet, the premature deterioration of small arteries which characterizes diabetes seemed to proceed inexorably in many patients. This arterial disease, which occurs all over the body is characterized initially by thickening of the basement membrane and has a predilection for the kidney and retina. As a result over three quarters of juvenile-onset diabetics have significant retinopathy or nephropathy by age 30 no matter how carefully they have been managed. These problems are becoming more common as more diabetics reach maturity and the absolute number of diabetics increases. This problem is less severe in adult-onset diabetes mellitus. Nevertheless, the principal cause of death in adult-onset diabetics is also associated with premature onset of vascular disease.

Diabetes mellitus is a genetically based disease, probably associated with a recessive gene of variable penetrance. This gene may occur in up to 20% of the population. Presently about 2.5–3%, or five million of the population in the United States have the disease in varying degrees of severity. At the present growth rates in the United States our population may reach 275,000,000 in the year 2,000. It is probable by this date that about 8% of the population may be diabetic or over 20 million.[16] Similar projections are true for almost every country in the western world. Thus, diabetes mellitus is now a public health problem which is nearing epidemic proportions.

The failure of insulin to prevent these vascular complications of diabetes mellitus indicates that this disease is far more complex than originally believed (Fig. 2).

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PANCREATIC EXTRACTS IN THE TREATMENT OF DIABETES MELLITUS

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SINCE the year 1889, when von Mering and Minkowski (1) produced severe and fatal diabetes by total removal of the pancreas in dogs, many investigators have endeavoured to obtain some beneficial effect in diabetes mellitus, either by feeding pancreas, or by administration of pancreatic extracts.

Minkowski, Sandmeyer (2), Pfluger (3) and others found that feeding pancreas was followed by negative or even harmful results. More recently, Murlin (4), Kleiner (5) and Paulesco (6) have tried the effects of aqueous extracts of the pancreas intravenously, on depancreatized animals and have found transitory reduction in the percentage of blood sugar and in the sugar excreted in the urine.

In 1907, Rennie and Fraser (7), recognizing the possibility that pancreatic enzymes might have harmful effects on the internal secretions, secured islet tissue from teleosteal fishes, where it exists separately from the rest of the pancreas, and fed it to human diabetics. Their studies demonstrated no beneficial influence on the condition of the patient. E. L. Scott (8) in 1912 sought to eliminate the influence of proteolytic enzymes by using alcoholic extracts of the pancreas. He did not find, however, that such extracts caused as marked a reduction in the urinary sugar or in the G-N. ratio as when extracts were made with acidulated water. The whole question has been reviewed recently by Allen: (9), by him, and, indeed, by the majority of recent writers, it is usually stated that pancreatic extracts have no clinical value whatsoever. During the past ten months, two of us (F. G. B. and C. H. B.), working in the Department of Physiology of the University of Toronto, have reinvestigated the problem. Certain of the results obtained have already been published, (10) others are now in press. These may be briefly reviewed here.

Believing that extracts of the pancreas, as usually prepared, did not satisfactorily demonstrate the presence of an internal secretion acting on carbohydrate metabolism, because the active principle was destroyed by the digestive enzymes also present in such extracts, attempts were made to eliminate these enzymes. In the first experiments, this was done by taking advantage of the fact that the acinous tissue (from which the digestive enzymes are derived) but not the insular tissue of the pancreas degenerates in seven to ten weeks after ligation of the pancreatic ducts. Extracts were therefore made with ice-cold Ringer's solution, of degenerated pancreatic tissue removed ten weeks after the ligation of the ducts. The extract obtained by this procedure, when injected intravenously or subcutaneously into diabetic dogs, invariably caused a marked reduction in blood sugar and in the amount of sugar excreted in the urine. It also enabled a diabetic dog to retain a much higher percentage of injected sugar than it otherwise would. Extracts of liver or spleen, prepared in the same manner as the extracts of degenerated pancreas, were found to have neither of these effects. The active principle of the extract of degenerated pancreas was destroyed by boiling in neutral or acid solution or by incubating for two hours at body temperature with pancreatic juice.

In later experiments, it was found that the pancreas of foetal calves of under five months development did not contain proteolytic enzymes, thus confirming the observations of Ibrahim (11). By extracting such foetal pancreatic tissue, a highly potent and readily procurable preparation was obtained. Besides affording a much more practicable method for securing larger quantities of extracts, this result demonstrated that the active principle is essentially the same from whatever animal it is prepared. A method

FIG. 1. The title page from the original article by Banting and Best and associates on the use of pancreatic extracts to treat diabetes mellitus in man.

Unfortunately there is no experimental animal which spontaneously develops diabetes mellitus and the characteristic vascular changes seen in man. Hence, man himself has been the "experimental animal" for many of the studies on this disease. In general, diabetologists may be divided into two camps. One group believes that diabetes mellitus is associated with islet cell dysfunction and the vascular complications are directly related to this disturbance; the other group believes that diabetes mellitus is a systemic vascular disease and the islet cell dysfunction is merely one of the early manifestations of the disease.

The background of experience in experimental and clinical transplantation of other organs in the past decade, suggests that this debate over diabetes mellitus could be resolved by answering the following questions. Will a normally func-

tioning pancreas in the form of an allograft influence the vascular disease of diabetes mellitus? Could such a transplant stop further damage from occurring or cause existing lesions to regress or even prevent new ones from appearing? Or will it have no effect at all? If we knew the answers to these questions we could then determine whether the complications of diabetes mellitus are associated exclusively with endocrine dysfunction of the pancreas or whether dysfunction of the pancreas is only a manifestation of the systemic vascular disease we have labeled, diabetes mellitus. A key point in answering such questions is to develop a procedure of pancreatic allotransplantation in the experimental animal which could form the basis for a similar procedure in man.

While interest in experimental transplantation of the pancreas has been strong, the efforts regularly ended in failure until Largiader [32] and Idezuki [23] of our own laboratory described the first successful short-term and then long-term survival of pancreatectomized dogs with pancreaticoduodenal allografts. But this is getting ahead of our story and the background prior to the successful work of these investigators needs to be presented.

Although early investigators felt that pancreatic transplantation would eventually become feasible,[18-52] results with experimental pancreatic transplantation were discouraging.[8] The principal problem was the almost constant occurrence of pancreatic self-digestion. Even a few minutes of pancreatic ischemia was thought to trigger this dreaded autodigestion of the gland. Initial attempts to "dry up" the pancreatic external secretion by duct ligation or by irradiation were futile, and survival of a pancreatic allograft in the new host was limited to a few hours or days. Efforts to prolong survival with immunosuppression were also initially unsuccessful.[46, 47]

Yet the knowledge from these early unsuccessful experiences have formed a basis

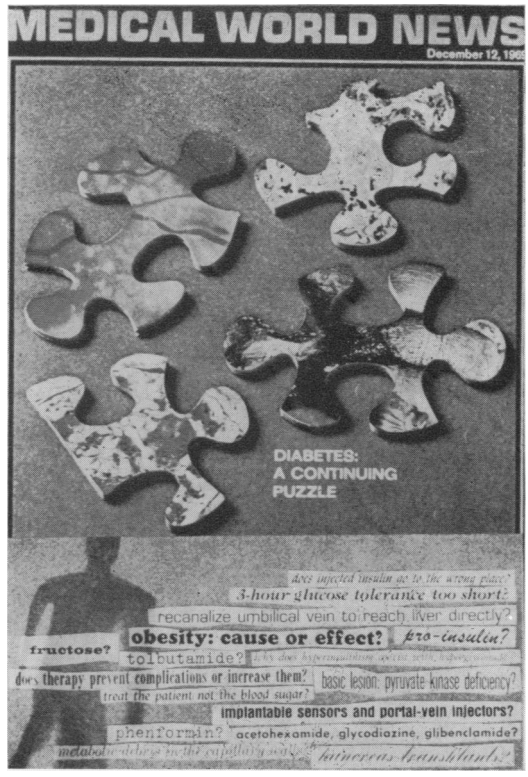

FIG. 2. The use of insulin has not prevented vascular deterioration characteristic of diabetes mellitus from occurring. This has lead to many theories for the etiology of diabetes in addition to a deficiency in insulin.

for more recent successful studies. New technics, and materials for small vessel anastomosis have also aided in finally solving the problem of pancreatic transplantation in the laboratory. Now, our own results and those of others have clearly shown that allotransplantation of the pancreas can be performed in the dog with success comparable to that attainable with the kidney, liver, heart, or lung.

Technics of Pancreatic Transplantation

Implantation of Pancreatic Tissue

It is well established that the sliced or minced fragments of endocrine tissue in lower animals can be implanted without the need for revascularization by vascular suture.[15, 34] Hence, implantation of pancreatic tissue was attempted by many investi-

gators in the past using various species of animals.

Selle [51] cultured canine pancreatic fragments taken from a canine fetus or from duct ligated adult glands and allotransplanted them to a subcutaneous pouch in the groin or axilla of pancreatectomized dogs. Unfortunately, no evidence of active function of the graft was ever obtained and the grafts completely disappeared within three weeks.

Browning and Resnick [9] allo-implanted embryonic pancreatic tissue taken from mice subcutaneously or into the anterior chamber of the eye of other alloxan-diabetic mice. They reported reduction of glycosuria in some of the mice after implantation of the pancreatic tissue but no long-term survival of implanted tissue.

DuBois and Gonet [14] injected pancreatic fragments taken from fetal rats into the testes of the alloxanated albino rats. Hyperglycemia in the recipient disappeared within 48 hours. In a further step they injected a preparation of the testes of these rats into normal rats and this resulted in hypoglycemic coma and death of the previously normal rats within 2 hours.

House and associates [19] described allotransplantation of hamster neonatal pancreatic tissue into the cheek pouch of adult hamsters made diabetic with alloxan. But, they did not give any data on long-term function of the graft.

Hultquist and Thorell [21] transplanted islet tissue isolated from the duct ligated rat pancreas into the anterior chamber of the eye either as an auto or an allograft. Ninety per cent of autografts and 50% of such allografts survived histologically for a period of 1 month.

Attempts to implant larger pieces of pancreatic tissue were described by Ivy and Farrell.[29] They developed a technic for autotransplantation of the uncinate portion of the canine pancreas in the following manner. First, the uncinate lobe of the pancreas was shifted to the abdominal subcutaneous tissue without interruption of blood supply. Three to 4 weeks later the vascular pedicle to the uncinate lobe was ligated and divided. All grafts survived and maintained their function through a new blood supply from surrounding tissues.

This two-staged technic of autotransplantation of the pancreas was more recently used by Brooks and Gifford.[8] In their experiment the uncinate lobe of the canine pancreas was first transferred to the rectus muscle. Its vascular pedicle was then ligated 2 to 3 weeks later. By this time, vascularization from the rectus muscle has developed sufficiently to maintain the graft's survival and function.

Brooks and Gifford also investigated the possibility of allotransplantation of large pancreatic fragments using the staged technic. Rectus auto-implants were cross-exchanged between two dogs as allografts, again using the rectus muscle. These implants were quickly absorbed without showing any significant function in the new hosts. Other attempts to alloimplant canine embryonic or neonatal pancreatic tissue into the thigh muscles of adult dogs were also without success.[34]

Similar staged auto-implantation of the canine pancreas into the rectus muscle was done by Rundles and Swan.[48, 53] In their experiments, rectus auto-implants were then transferred a second time to a new location of the abdominal wall of the same dog. They showed evidence of active function of these auto-implants even after the second move, but they did not carry the study to implantation of the successfully shifted pancreatic tissue as an allograft.

Reemtsma and associates [46] also implanted homologous canine pancreatic tissue (body and tail) into the subcutaneous tissue of the groin of the pancreatectomized recipients, but the hyperglycemia of the recipients was not altered by this procedure.

Implantation of pancreatic tissue as allografts has also been tried in humans.

Brooks and Gifford [8] used fragments of pancreatic tissue taken from stillborn neonates and placed these allografts in the quadriceps muscles of the diabetic mothers of the dead neonate. Specific immunosuppressive drugs were not used but 15 mg. per day of cortisone was used. They also utilized the diffusion chamber technic to implant minced insulinoma tissue into the subcutaneous tissue of the two diabetic patients. Some of the patients showed brief reduction of insulin requirements but no prolonged evidence of graft function was ever obtained in these patients.

Gaillard recorded temporary success in one patient who received an allo-implant of insulinoma tissue along the axillary artery after the fragments of tissue had been cultured in the recipient's serum.

These studies by various investigators clearly indicate that auto- or allo-implantation of small fragments of pancreatic tissue is possible, but clinical results are disappointing. Although it is still conceivable that implantation of the islet cells in man might eventually become successful and could be a preferable method of islet cell transplantation, it is likely that success in the near future will come only with transplantation of the whole pancreas or large segments of it which are immediately revascularized.

Pancreatic Transplantation by Vascular Anastomosis

Based on studies with lung, heart, liver, kidney, and intestine, it appears that pancreatic transplantation using vascular suture is the best method to obtain immediate function of the graft. Several technics of pancreatic transplantation using direct vascular reconstruction have been tried.

Gayet and Guillamie [17] and Houssay [20] were first to successfully employ vascular anastomoses over cannulas for pancreatic transplantation. They showed that the allotransplanted pancreas could lower the blood sugar level in diabetic dogs for periods up to 12 hours. Bottin [6] also described similar studies and reported survival of a pancreatic graft for seven days but did not mention if the transplant functioned.

Lichtenstein and Barshack [33] described a method to transplant of the uncinate lobe of the pancreas by direct vascular suture in the dog. Vascular anastomoses were made end-to-end between the iliac vessels of the host and superior mesenteric artery and the portal vein of the graft. They reported that transplantation was technically successful but since no effort was made to suppress the recipient's own pancreatic function, it was not possible to assess graft function. Moreover, histological evidence of graft survival could not be found at re-exploration 6 to 8 weeks afterwards.

Brooks and Gifford [8] also used a vascular suture technic to allotransplant the entire pancreas into the abdomen of a normal dog. They used the host's aorta and iliac vein for attachments to the graft. However, they were unable to obtain functioning grafts in the new host because of thrombosis and/or hemorrhagic pancreatitis in the allograft soon after transplantation. They attributed this to the self-digestion of the pancreatic tissue from tying off the pancreatic duct. Yet, attempts to drain the external secretion by cannulating the pancreatic duct of the graft or irradiation of the graft to destroy exocrine function did not reduce the universal occurrence of graft necrosis.

Lucus and associates [37] transplanted the tail of the pancreas to the groin of the pancreatectomized dog by anastomosing the portal vein and the celiac artery of the graft end-to-side to the femoral vessels of the host.

Reemtsma and associates [46] using this same technic, showed immediate endocrine function of a pancreatic allograft in a pancreatectomized host and also succeeded in obtaining graft survival for over 2 weeks. They observed that the suppression of the ascinar or exocrine function by

prior duct ligation of the donor's pancreas resulted in better immediate endocrine function of the graft, but this preliminary procedure of duct ligation did not improve the long-term survival of the allograft. They used immunosuppressives to prolong survival but this also was without effect in increasing survival beyond a week or two.

DeJode and Howard [11] described a method of heterotopic pancreaticoduodenal allotransplantation which successfully preserved both exocrine and endocrine function of the graft. They removed the body of the pancreas along with the attached duodenum from a donor dog and placed this pancreaticoduodenal graft into the groin of the recipient dog anastomosing the portal vein and celiac artery of the graft to the host's femoral vessels. The distal end of the attached duodenum was brought out as a duodenostomy and served as an external conduit for exocrine secretion. Average allograft survival in these experiments was 6 days.

Bergan and associates [4] described a method for total pancreatic transplantation in the dog. They allotransplanted the pancreas heterotopically into the abdomen of the pancreatectomized recipient by end-to-side aorto (host)—celiac (graft), and porto (graft)—inferior vena cava (host) anastomoses. These allografts functioned for a week after transplantation.

Largardier of our group [32] was the first to report successful orthotopic allotransplantation of the pancreas in the dog. The whole pancreas and attached duodenum from the donor was revascularized in a pancreaticoduodenectomized recipient using end-to-side anastomoses between the suprarenal abdominal aorta (host) and celiac artery (graft) and suprarenal inferior vena cava (host) and the portal vein (graft). Gastrointestinal continuity and biliary drainage were restored in a Roux-en-Y fashion using the duodenal segment of the graft. External and internal function of the allograft was observed up to 9 days after transplantation but long-term survival was not obtained. Modifying this original technic, Idezuki [23, 26] described an orthotopic interposition, and an intraabdominal heterotopic method for pancreaticoduodenal allotransplantation. One pancreatectomized dog survived for 169 days supported by a heterotopic pancreaticoduodenal allograft. Idezuki also used a method in which the portal vein of the graft was anastomosed end-to-side to the superior mesenteric vein of the recipient so that the pathway of venous return from the pancreatic graft was into the portal venous system in the normal fashion.

Pancreatic auto- or allotransplantation using these various technics has also been used by Chaya and associates,[10] Dreiling and Ashikari,[13] Ota and associates,[43] Mitchell and Davidson,[42] Merkel and associates,[40, 41] Parra and associates,[44] and Joisen.[30]

While each technic of pancreatic transplantation varies considerably in details, they may be classified in two categories according to whether the exocrine function of the pancreatic allograft is retained or not.

In total or segmental pancreatic transplantation without the attached duodenum, the pancreatic duct is usually ligated. Consequently, ascinar tissue atrophies and fibrosis occurs. In contrast, in pancreaticoduodenal transplantation, the pancreatic duct remains patent and the attached duodenum serves as a conduit for the external secretion of the pancreas. Hence, both exocrine and endocrine function of the pancreatic graft are preserved.

If a pancreatic allograft is to be used as an endocrine graft for treatment of diabetes mellitus, the exocrine function of the pancreas and the attached duodenum would not appear necessary. Moreover, total or segmental pancreatic allotransplantation without a duodenum is less complicated than pancreaticoduodenal transplan-

tation. Yet, autodigestion of the pancreas by its own enzymes has been the major hurdle in pancreatic transplantation. Occlusion of the pancreatic duct and subsequent congestion of pancreatic juice in the total or segmental pancreatic graft causes edema and inflammatory reaction in the tissues. This might be avoided by "drying up" the external secretion of the ascinar tissue of the pancreas by irradiation or by tying the duct several weeks prior to transplantation. Brooks and Gifford [8] tried irradiating the pancreas of the donor before transplantation into the recipient, but they were still unable to prevent necrosis of the graft. More recently, Merkel [41] used a similar technic for segmental pancreatic transplantation and obtained graft survival up to 42 days in alloxinated dogs.

Reemtsma [47] ligated the pancreatic duct of the donor dog 6 weeks prior to transplantation and then transplanted the atrophied gland into the recipient, but was unable to prolong the survival of the graft in the recipient.

Similar attempts by Bergan [4] also failed to affect the graft survival in the recipient.

Seddon and Howard [49, 50] also attempted to ablate exocrine function by tying the duct of the pancreas several weeks prior to transplantation but they thought there was a higher incidence of thrombosis at the site of the venous anastomosis of the graft when they used atrophied glands. Duct ligation prior to transplantation is an interesting experimental procedure, but clinical application is impractical since the only possible donors of pancreatic grafts for humans are cadavers. Yet the advent of better means to prevent rejection so that xeno-grafts are used could change all this. The best means presently available to prevent autodigestion of the pancreas is to drain the external secretions by making an external or internal fistula. In pancreaticoduodenal transplantation, the attached duodenum serves as an ideal external or internal conduit of pancreatic secretion. Autodigestion of the pancreatic graft using this technic is rare.

Attempts to drain the external secretion by direct cannulation of the duct have been used by various investigators,[8, 13, 50] but preservation of the patency of the cannulated duct is difficult and adds another technical problem for clinical use. Besides problems with the pancreatic duct, venous congestion within the pancreas may also be an important factor in post transplantation pancreatitis and fistula formation.[1, 2, 55]

In addition to preventing self-digestion, drainage of the external secretion and preservation of exocrine function is also important in preserving the integrity of the endocrine function of the pancreas. Banting and Best [3] originally used pancreatic duct ligation in the dog to obtain pure extracts of endocrine tissue of the pancreas. This apparently has led to the belief that endocrine function of the duct ligated pancreas is not altered by this. To be sure endocrine function is unaffected by duct ligation initially but there is increasing evidence that fibrotic degeneration of the exocrine tissue secondary to the duct occlusion ultimately leads to deterioration of islet tissue as well. Dragstedt in 1943 [12] reported that extensive fibrotic degeneration of the pancreas after occlusion of the pancreatic duct could lead to diabetes in the dog. More recently, Idezuki [28] proved by direct measurement of plasma insulin, that latent diabetes is common in duct ligated dogs, although manifest diabetes is unusual. Most dogs with pancreatic duct ligation have a deficient insulin response to a glucose overload. Diminished blood flow through the atrophied fibrotic pancreas has been suggested as the contributing factor to this endocrine deficiency after duct ligation. Mitchell and Davidson [42] and Rappaport and associates [45] also reported a high incidence of hyperglycemia associated with fibrosis of the acini after segmental autotransplantation of the canine

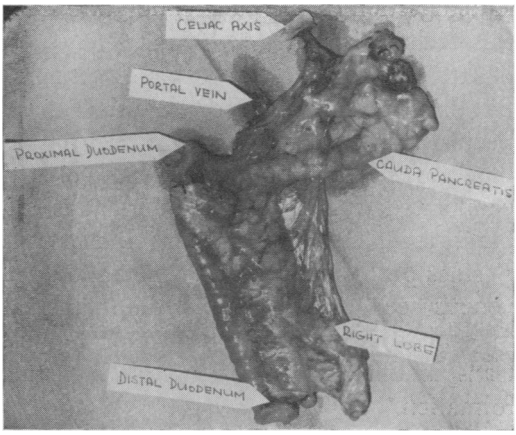

FIG. 3. Preparation of the pancreatico-duodenal graft in the dog. The entire pancreas and attached duodenum are removed together with the celiac axis and portal vein.

pancreas. Clinically, many have noted that latent or overt diabetes mellitus is common in patients with chronic pancreatitis.

These findings indicate that duct ligation is not an innocuous procedure and we believe that pancreaticoduodenal transplantation is, at this time, the procedure of choice for clinical use. This does not mean that new technics and knowledge may not change this belief.

Intra-Abdominal Heterotopic Allotransplantation of the Pancreas

Among the several technics developed in our laboratory, intraabdominal heterotopic replacement is the most successful. The procedure is as follows:

Preparation of the Graft

The abdomen is entered by a long midline incision. The pylorus dissected free, and the right gastric and right gastroepiploic vessels ligated and divided. After division of the duodenum just distal to the pylorus, the tail of the pancreas is freed from the dorsal surface of the omentum. The splenic artery and vein distal to the tail of the pancreas, left gastroepiploic vessels, left gastric artery and coronary vein are then ligated and divided. The lesser omentum is divided down to the aorta and the third portion of the duodenum transected. The branches of the caudal pancreaticoduodenal vessels to the pancreas are ligated and divided. If circulation to the uncinate lobe of the pancreas appears impaired after this step, this lobe is resected. Finally, the celiac axis and adjacent aorta are mobilized, the hepatic artery and common bile duct are ligated and divided and the portal vein is isolated. The pancreaticoduodenal graft is removed by ligating and dividing the superior mesenteric vein, excising the aortic wall around the celiac artery and dividing the portal vein (Fig. 3).

The graft is immediately immersed in cold Ringer's solution and perfused through the celiac axis with a cold (4° C.) balanced salt solution containing 5% low molecular weight dextran (pH adjusted to 7.4 with sodium bicarbonate). This perfusion is continued until the effluent from the portal vein is clear indicating that the graft is free of blood. Usually 400 to 800 ml. of perfusate solution is necessary. Heparin was originally added to the perfusate but it seems to increase edema and so is no longer used. The pancreaticoduodenal graft is now ready for allotransplantation in the recipient.

Preparation of the Recipient Dog

To evaluate accurately the function of the allograft in the recipient, complete removal of the recipient's own pancreatic tissue is mandatory. Moreover, regeneration of the pancreatic tissue along the duodenal wall after pancreatectomy using Markowitz's technic [39] often occurs, so it is also necessary to remove the recipient's duodenum to prevent this from occurring. The abdomen is opened with a long mid-line incision and the stomach is divided proximally to the pylorus followed by mobilization of the tail of the pancreas and division

of the vascular connection to the omentum and splenic vessels. After freeing the duodenum by dividing the ligament of Treitz, the caudal portion of the duodenum is transected as high as the vascular supply permits and the pancreatic branches of the inferior pancreaticoduodenal vessels are ligated. Division of the caudal pancreatic vein, the gastroduodenal artery, and the common bile duct then follows and the pancreaticoduodenal segment is removed after division of the pancreatic veins.

Reconstruction of the gastrointestinal and biliary tract continuity in the recipient for heterotopic allograft replacement is accomplished by anastomosing the distal gastric stump end-to-end to the distal duodenum and the gallbladder end-to-side to the duodenum.

Heterotopic Placement of the Allograft

The pancreaticoduodenal allograft is now put in place in the recipient by joining the celiac axis of the graft together with a small cuff of aortic wall end-to-side to the infrarenal aorta of the recipient. The portal vein of the graft is similarly joined to the host's infrarenal vena cava and circulation to the pancreaticoduodenal allograft is now restored. To complete the procedure the proximal end of the graft duodenum is closed and, finally, the distal end of the graft's duodenum joined end-to-side to the proximal jejunum of the recipient. In this manner, the duodenum serves as an internal conduit for the exocrine secretion of the pancreatic allograft (Fig. 4). It is also important to fix the duodenum of the graft to the right side of the abdominal wall in order to avoid torsion of the graft vessels by motion of the dog.

During the procedure the recipient dog usually receives 500 to 1,000 ml. of Ringer's solution and antibiotics. The technic described here is a modification of the method originally described by DeJode and Howard [11]; but internal rather than external drainage of pancreatic secretion from the allograft in our method greatly simplifies the postoperative care of the dog.

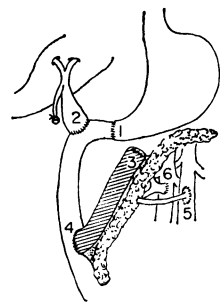

FIG. 4. Intra-abdominal heterotopic allotransplantation of the pancreas. The exocrine secretions of the pancreatic allograft drain into the proximal jejunum of the recipient dog.

1. Gastroduodenostomy, end to end
2. Cholecystoduodenostomy, end to side
3. Closure of proximal end of duodenum
4. Duodenojejunostomy, end to side

Vessel Anastomosis

5. Artery Aorta → Celiac A., side to end, patch
6. Vein Portal V. → IVC end to side

Results of Experimental Pancreatic Transplantation

Survival

Until the method of Idezuki was used, survival of pancreatic allografts in the recipient was limited to only a few weeks, although an 18-month survivor and a 6-month survivor with partial autografts were reported by Dreiling and Ashikari,[13] and Mitchell and Davidson.[42]

The two hurdles responsible for this poor result with allografts have been technical and immunological. Early attempts to prolong graft survival with 6 MP, azathioprine, steroids, or thoracic duct lymph drainage were futile.[6, 47] Yet, more recently, using a combination of azathioprine and steroids and the heterotopic pancreaticoduodenal allograft, we have succeeded in prolonging the survival of dogs for periods up to 6 months, results equal to that achieved with renal allografts in dogs (Fig. 5). Others

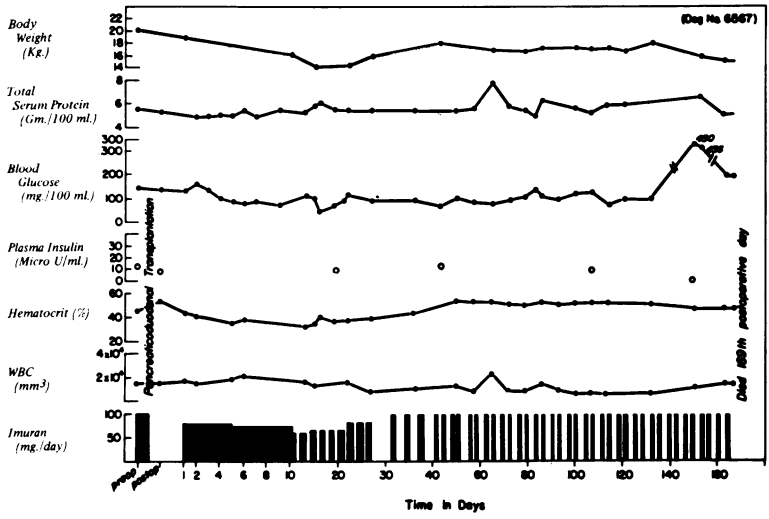

FIG. 5. Postoperative course of a dog with a pancreatico-duodenal allograft. Rejection of the graft after nearly 6 months was associated with a rapid increase in blood sugar and decrease in plasma insulin.

have tried the azathioprine-steroid combination but without getting the same results. We have also used horse anti-dog lymphocyte serum (HADLS) in addition to Imuran as a means of immunosuppression and Merkel and associates [41] also have used HADLS as an additional potential means of controlling pancreatic allograft rejection. We have not been sure if HADLS has added any benefit in the dog over using azathioprine and steroids.

Endocrine Function of the Graft

It is well established that pancreatic allograft functions immediately in the recipient if the procedure is technically successful. Lowering of the high blood sugar of the pancreatectomized, or alloxan treated dog is the most commonly used criterion of endocrine function. Gradual increase of blood sugar often indicates the onset of graft rejection whereas sudden increase of blood sugar is usually due to graft failure due to vascular thrombosis or acute pancreatitis.[23, 26]

Oral or intravenous glucose tolerance tests are also used to test the active function of the pancreatic graft and to detect latent graft rejection while fasting blood sugar is still normal. Glucose tolerance curves immediately after allotransplantation are usually elevated, but within 24 hours after operation the glucose tolerance curve and insulin response to the glucose stimulation are usually normal and remain so until rejection occurs. This indicates that a humoral factor rather than nervous control is responsible for a normal blood sugar.

More recently, direct measurements of plasma insulin have also been used to assess endocrine function of the pancreatic allografts.[23, 26, 41, 55] Circulating plasma insulin remains within a normal range while the graft is functioning, but decreases or completely disappears when rejection of the graft occurs.

Bergan and Teixeira [4, 55] noted an initial low blood sugar and elevated plasma insulin levels in dogs with pancreatic allografts and explained this by the presence of insulin antagonists in the liver which were bypassed by directing venous return from the graft into the systemic rather than the portal venous circulation. In contrast, other investigators [10, 11, 13, 26, 46] have not seen this initial hypoglycemia and hyperinsulinemia. Idezuki [23] compared technics of pancreatic allotransplantation using systemic or portal venous return (Fig. 6) and could find no significant difference in blood sugar or plasma insulin in the two

groups of dogs (Fig. 7). Idezuki[24, 25] did note an initial release of a large amount of insulin from the graft into the pancreatic venous blood immediately after re-establishment of circulation to the allografts. This he believed was due to transient or reversible ischemia of the islet cells suffered during the transfer of the gland from donor to host. This is confirmed by preservation studies which are detailed below.

Exocrine Function of the Graft

Compared to the large literature on endocrine function of pancreatic transplants the number of studies of the pancreatic exocrine function is rather small. Still, the volume of pancreatic and duodenal secretion and the concentration of amylase, lipase, pH, protein, bicarbonate, sodium, and chloride in the secrete have been studied.[11, 49, 31] The volume of pancreatic secretion declines sharply during the 24 to 48 hours prior to rejection.[32] Seddon and Howard[49] also noted that pancreatic allografts responded less to food and hormonal stimulation than normally innervated glands and suggested that vagal denervation of the graft might be responsible for this finding.

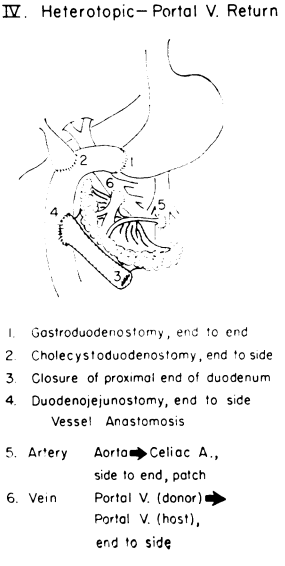

FIG. 6. Technic for intra-abdominal heterotopic allotransplantation of the pancreas-duodenum with portal venous return from the graft.

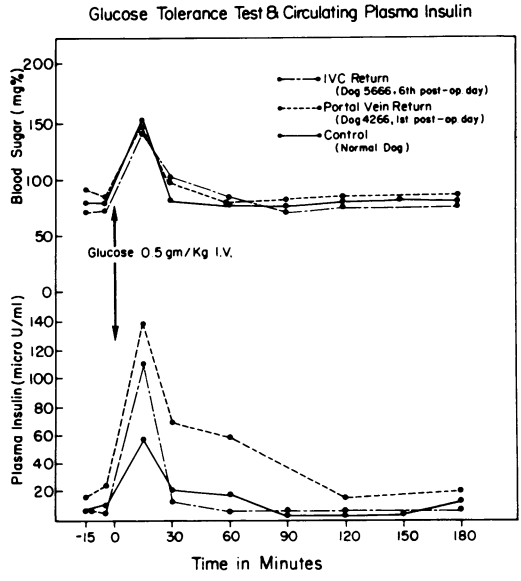

FIG. 7. Glucose tolerance curve and plasma insulin levels in dogs with pancreatico-duodenal allografts with systemic or portal venous return from the graft. There is no significant difference between the two technics.

An increase in serum lipase (Seddon and Howard)[49] and amylase (Teixeira)[54] have also been used as possible signs of impending allograft rejection.

Fat content in the feces and gross and microscopic findings of undigested food in the stool are also used as an indication of exocrine function.[26]

It appears also that when rejection occurs exocrine function declines before endocrine function, but the reason for this is obscure.

Histology

In the early stage of rejection, the pancreas becomes grossly edematous, indurated and shows interstitial hemorrhages. The duodenum turns a reddish purple in color and thickening of all layers. Microscopically, round cell infiltration is seen predominantly in the interlobular connective tissue (Fig. 8). Focal round cell infiltrations are observed as early as on the fourth postoperative day and are most prominent around the small arterioles. In

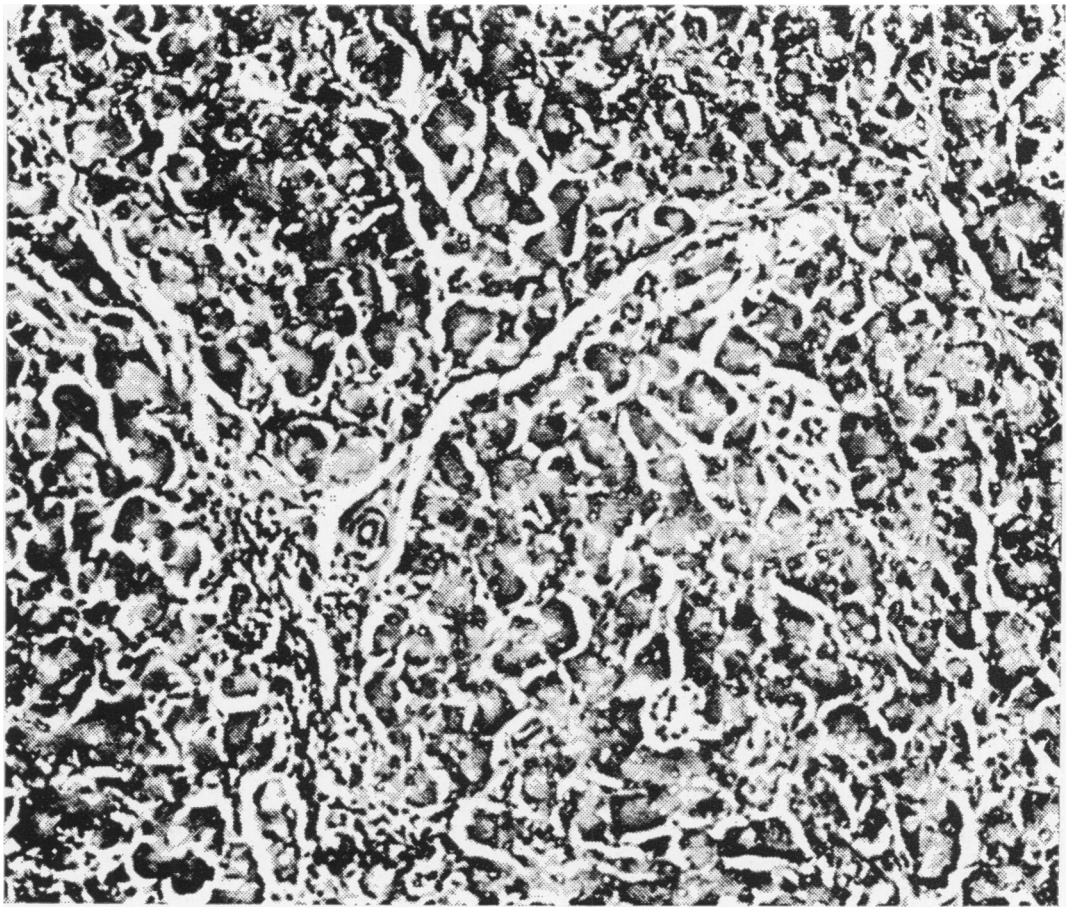

FIG. 8. Photomicrography of canine pancreatic allograft 43 days after transplantation. There is round cell infiltration seen predominantly in the interlobular connective tissue (H-E stain, 40×).

the duodenum, round cell infiltration is concentrated in the submucosa (Fig. 9).

With more advanced rejection, the pancreas becomes hemorrhagic and swollen with nodular induration (Fig. 10). Microscopically, the rejected pancreas shows hemorrhagic necrosis with complete destruction of both exocrine and endocrine tissues.

In mild and/or chronic rejection, the pancreas has a normal gross appearance and consistency and microscopically shows normal ascinar and islet structures. Round cell infiltration is present predominantly around the small arterioles in interlobular spaces. In the final stage of chronic rejection, the pancreatic allograft atrophies and feels fibrotic. Microscopically, the ascinar tissue is almost completely replaced with fibrous tissue but islet tissue can still be distinguished although beta granulation is reduced and round cell infiltration is present within the islets of Langerhans (Fig. 11).

Atrophy and fibrosis of the exocrine tissue is probably a result of the exocrine rejection but vagal denervation of the allograft may also contribute to ascinar atrophy.

Storage of the Pancreatic Graft

The need for succesful means to preserve organs is most urgent for transplan-

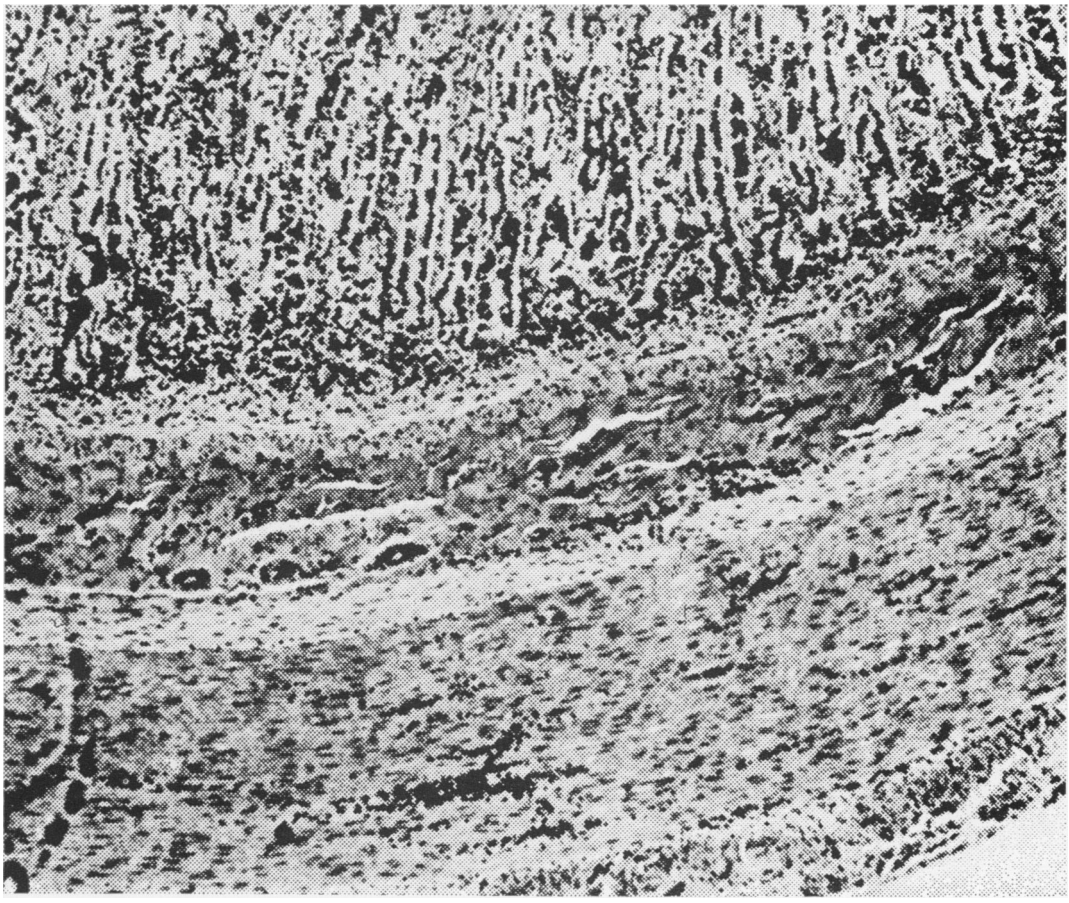

FIG. 9. Photomicrography of duodenum of canine pancreatico-duodenal allograft 43 days after transplantation. In the duodenum the round cell infiltration is concentrated in the submucosa. (H-E, 40×).

tation of unpaired organs such as the heart, liver, or pancreas, which can only be obtained from cadavers. The future of pancreatic transplantation in man if it is to be done in any numbers will have to depend on development of successful methods for preservation of pancreatic tissue.

Although many investigators have described methods to preserve the kidney, heart, liver, lung, spleen, or intestine, none have worked with the pancreas because of the supposed extreme sensitivity to ischemia of the pancreas.

In previous studies in our laboratory,[35, 38] we found that hypothermia, hyperbaric oxygen, metabolic inhibitors and hypothermic perfusion when used in various combinations could preserve the viability *in vitro* of kidney, heart, lung, spleen, and intestine for periods up to 48 hours. The liver also has been preserved by these same means but for shorter periods.[7]

Recently, we have succeeded in preserving a pancreaticoduodenal graft for 24 hours using combinations of hypothermia and hyperbaric oxygen.[24, 26, 27] The success of preservation is established by the ability of such a preserved pancreaticoduodenal graft to secrete insulin *in vitro* when perfused with a blood-glucose solution

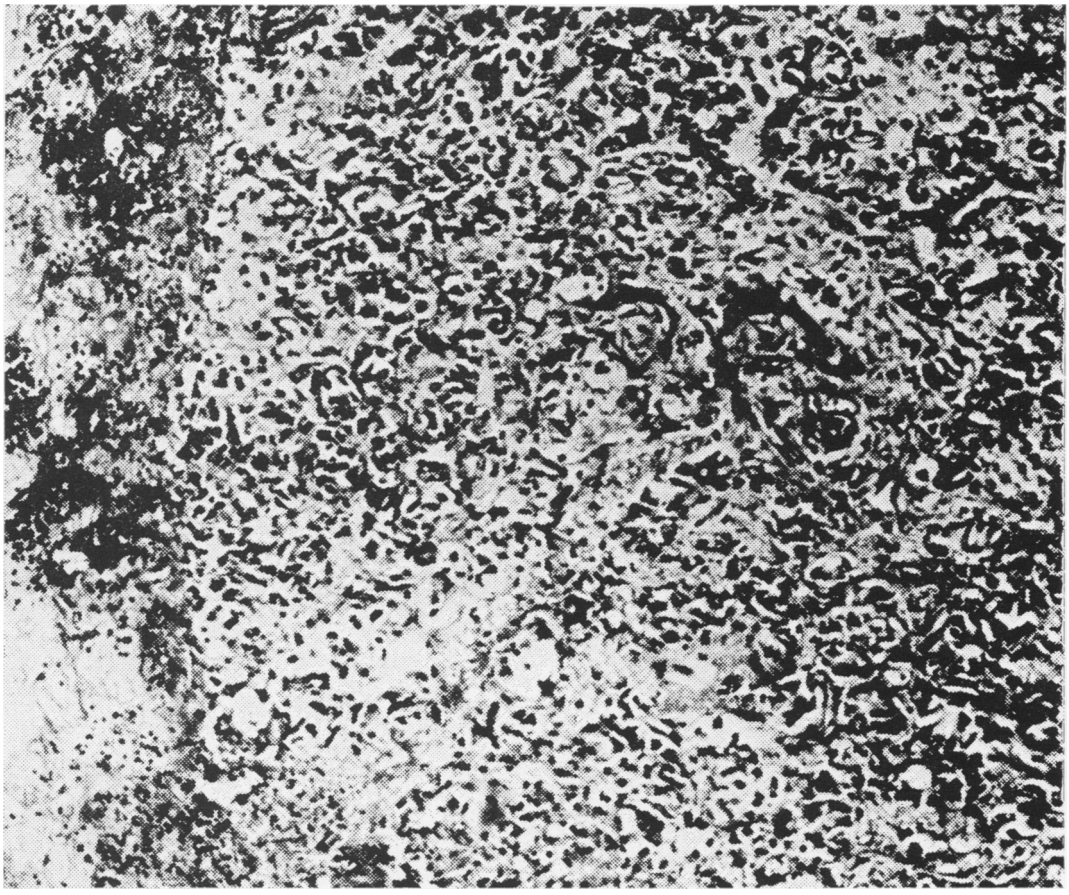

FIG. 10. Photomicrograph of acutely rejected pancreas in the dog. The normal ascinar and endocrine tissue is completely destroyed. (H-E, 40×).

and by allotransplantation into pancreatectomized recipients after preservation.

Preservation of Pancreatic Grafts with Hypothermia and Hyperbaric Oxygen

The pancreas and attached duodenum is removed from a donor dog in the manner described above. The pancreaticoduodenal graft is immediately immersed in the iced Ringer's solution and perfusion started through the celiac artery using a cold (4° C.) Ringer's solution or balanced salt solution containing 5% low molecular weight dextran with a pH of 7.4.

Perfusion is stopped when the graft is blanched and the perfusate clear. More effort is made to ensure the complete washout of the blood from the tissue to be preserved than when immediate transplantation from the donor to the recipient is planned. The pancreaticoduodenal graft is next immersed in Ringer's solution (2 to 4° C.) in a hyperbaric chamber. The chamber is pressurized to 4 atmospheres absolute of oxygen and the graft is left in the chamber for up to 48 hours (Fig. 12). It is then tested for viability using an *in vitro* perfusion system specifically developed for this purpose or allografted into a pancreaticoduodenectomized recipient using the heterotopic method described.

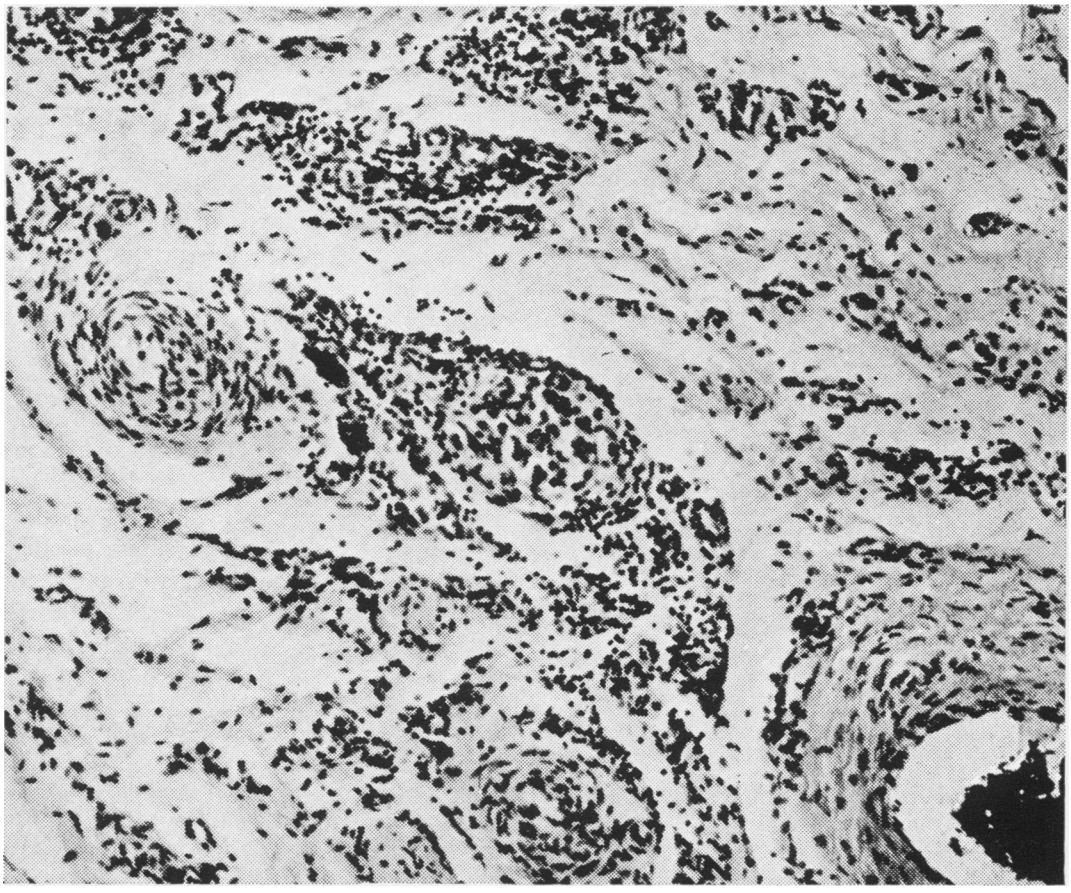

FIG. 11. Photomicrograph of canine pancreas undergoing chronic rejection nearly 6 months after allotransplantation. The ascinar tissue of the pancreas is completely replaced with fibrous scar tissue but the islets of Langerhans can still be distinguished (H-E, 40×).

In Vitro Test to Assess Viability of Pancreatic Graft

After removal from the hyperbaric chamber the pancreaticoduodenal graft is placed in an isolated organ perfusion system and perfused through the celiac axis with oxygenated diluted blood at 38° C. for 50 minutes (Fig. 13). The venous effluent from the portal vein is collected at intervals for insulin determination and other studies. The principal criteria for determining viability of the graft are flow rate, oxygen consumption, inulin output, weight gain, and duodenal peristalsis during perfusion. Probably the best measure of viability is the *vitro* insulin productivity in response to glucose stimulation during perfusion. Moreover, the magnitude of insulin response can be accurately used to predict graft survival. The preserved pancreaticoduodenal graft has a good insulin response when storage is less than 24 hours. The 48-hour preserved pancreas showed no response to the glucose stimulation indicating that none of the islet tissue was viable (Fig. 14). Oxygen consumption of the graft, duodenal contraction, and gross appearance of the graft during *in vitro* perfusion are also used to predict graft survival.[27]

Although this test is not yet applicable to patients, the potential use of such an *in*

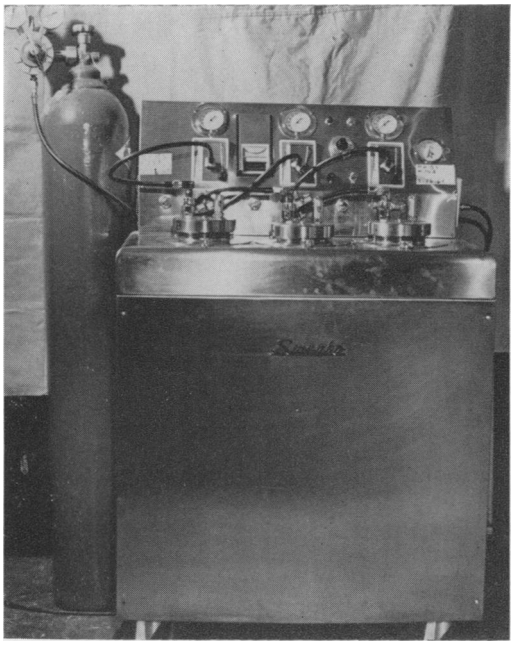

FIG. 12. Preservation apparatus used for hypothermic-hyperbaric preservation of the pancreas-duodenum (supplied by Swenko Incorporated, Minneapolis).

vitro functional test of cadaver organs could prevent the use of a non-viable or severely damaged pancreas.

Allotransplantation of Preserved Pancreas

Survival of a pancreatectomized recipient with a preserved pancreaticoduodenal graft is the ultimate test to show that the preservation method is successful.

Most of the grafts stored less than 24 hours pinked up immediately after re-establishment of circulation in the recipient and the attached duodenum also contracted promptly after blood flow was restored. The course of a recipient of preserved pancreaticoduodenal allograft is essentially the same as when fresh tissue is used although we did note a higher incidence of pancreatitis and peritonitis in dogs with preserved tissue.

Studies of fasting blood sugar, circulating plasma insulin, glucose tolerance, and serum amylase of recipients indicates varying degrees of ischemic damage to the transplanted pancreatic tissue, but the damage is usually reversible within 2 weeks (Fig. 15).

These data indicate that the pancreas can be preserved *in vitro* with hypothermia and hyperbaric oxygen for periods up to 24

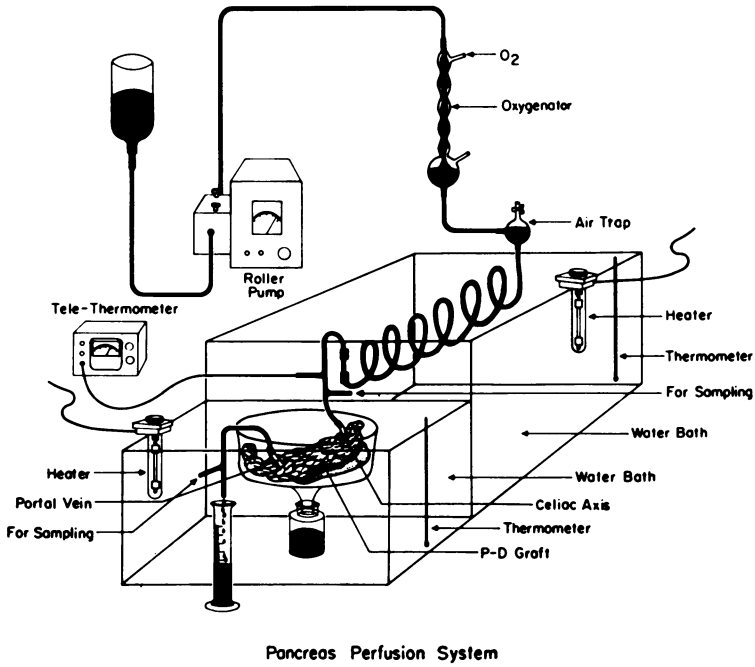

FIG. 13. Diagram of *in vitro* organ perfusion system for testing the viability of a preserved pancreatico-duodenal graft.

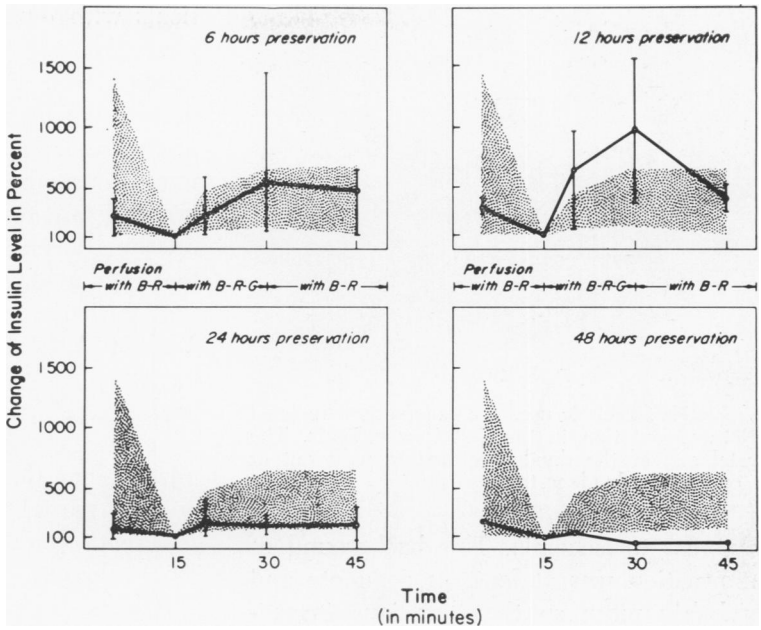

FIG. 14. Changes in plasma insulin in venous effluent of *in vitro* perfused, previously preserved, pancreatico-duodenal grafts. The insulin concentrations in the venous effluent are expressed as a percentage of change during each 15 minutes of perfusion. B-R equals Blood-Ringer's perfusion, B-R-G equals Blood-Ringer's Glucose perfusion. Only the 48-hour preserved pancreas failed to secrete any insulin at all.

hours, but 48-hour preservation leads to extensive ischemic damage even though there is some islet function.

Bergan [5] has recently described a technic for *ex vivo* perfusion of the pancreas in the dog and has preserved the functional viability of the pancreas for several hours. The use of *ex vivo* perfusion is an interesting model to study pancreatic physiology and may also eventually be a method of testing organ compatibility in a recipient.

The Human Experience

With this laboratory experience we reached a point a few years ago where pancreatic allotransplantation in man could be considered. That is, we now had a successful technic for the procedure; we could prevent rejection of the pancreatico-duodenal allograft at least as well as we could for other organs that are transplanted in the laboratory; and, finally, we had dispelled the myth of the sensitivity of the

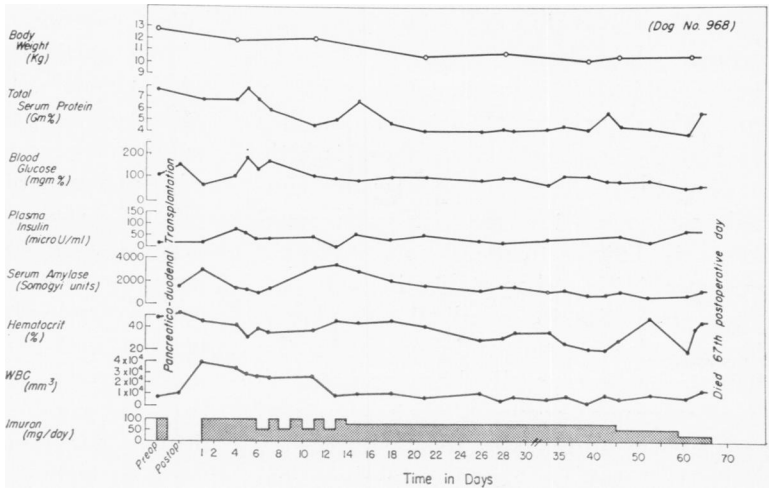

FIG. 15. Postoperative course of pancreatectomized dog receiving pancreatico-duodenal allograft preserved for 22 hours before grafting took place.

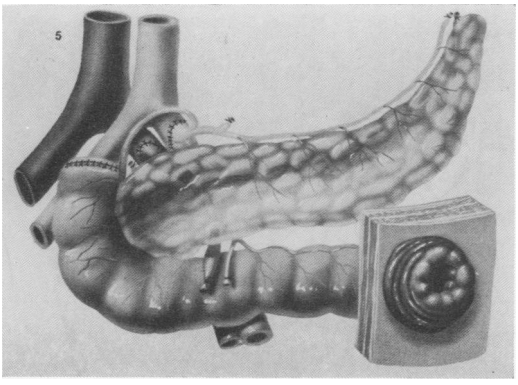

FIG. 16. Technic used for pancreatico-duodenal allotransplantation in the first four patients. The distal end of the duodenum was brought out as a cutaneous duodenostomy.

pancreas to ischemia. This background of information was at least as complete and probably more so than previous investigators possessed before renal, hepatic, pulmonary or cardiac allotransplantation was started in man.

Yet, it is not enough to have this requisite information from the laboratory to begin pancreatic transplantation in man. The patients on whom such a procedure is done must be suffering a risk greater than that entailed by such an experiment. They must have reached a point where conventional therapy had nothing to offer them.

Are there such patients with diabetes mellitus? Certainly the juvenile-onset diabetic with terminal renal nephropathy comes close to such a definition. These unfortunates have been the pariahs of medicine even in this transplantation oriented age. When their renal deterioration has reached the terminal stages, there is little to offer them. Dialysis facilities are limited; moreover, the diabetic with renal failure is difficult to dialyse and suffers a high morbidity and mortality in such programs. Facilities for renal allotransplantation are also limited and here again the diabetic has not usually been accepted in these programs because of their associated problems in addition to renal failure.

We believed we could help these patients with renal and pancreatic allotransplantation and our program began in December 1966. Patients with juvenile-onset diabetes mellitus with terminal renal failure were seen from time to time in our renal transplantation unit. We explained in great detail to these patients and their relatives a possible avenue of treatment that they might follow. Surgery on the first such patient was carried out on December 17, 1966. A detailed report of this procedure has previously appeared.[31] In light of the problems of partial allotransplants of the pancreas in experimental animals, it may puzzle some that this first patient received only a partial pancreatic rather than a pancreaticoduodenal graft along with a renal allograft.

It was typical of the "Wangensteen" approach that more than one group often worked independently on a research problem within our Department of Surgery and pancreatic transplantation was no exception to this. Kelly[41] had taken a different approach than ours, believing that the simpler technical aspects of a partial pancreatic graft dictated that this procedure should be used. His approach was backed by experimental work indicating that a partial pancreas transplant could support the life of dogs made diabetic by Alloxan for 1–2 months.

Dr. Kelly being senior in the transplantation program, our initial human trial was with a partial pancreatic graft combined with a renal allograft. Unfortunately, the patient developed the complications which so often occur in the laboratory, pancreatitis and pancreatic fistula. These complications destroyed the islet function of the pancreas and necessitated its removal. Since that initial experience we have done pancreaticoduodenal allografts in 10 other patients and 9 of these patients have simultaneously received a renal allograft from the same cadaver. Neither pancreatic fistulas nor pancreatitis has occurred in these patients.

TABLE 1. *Combined Pancreatico-Duodenal (P-D) and Renal (R) Allotransplantation for Juvenile Onset Diabetes Mellitus with Terminal Nephropathy*

Patient	Sex	Age	Tissue Type	Drainage of P-D	Survival (months)	Graft Function (+ to +++)* R	Graft Function (+ to +++)* P-D	Cause of Death	Comment and/or Autopsy
R. R.	F	32	—	Duodenostomy	4½	1+	3+	Sepsis	Chronic R rejection; P-D normal
J. R.	M	37	—	Duodenostomy	1	0	0	Sepsis	Probable lethal ischemia of R and P-D in donor
A. Z.	F	44	—	Duodenostomy	1	— (only P-D)	4+	Sepsis	P-D normal septicemia from hemodialysis
D. O.	F	31	D	Duodenostomy	5½	1+	4+	Acute hyperkalemia	Chronic R rejection; P-D normal; ALG
G. M.	M	34	B	Roux-y	12	3+	4+	Living (out of hospital)	Repair of renal a. stenosis of R 1 month postoperative; ALG
C. B.	M	34	B	Roux-y	7	2–3+	4+	Acute perforation graft duodenum with sepsis	Minor bouts of R rejection; ALG
N. T.**	F	28	B	Roux-y	1 week	0	4+	Sepsis secondary to ATN – ?? rejection	Thrombus in portal V of P-D; no histological signs of rejection in R
M. P.	F	34	C	Roux-y	1	4+	4+	Acute necrosis R and duodenum P-D	Contaminated ALG immediately preceded death
R. K.	M	30	D	Roux-y	5	0–2+	4+	Living (in hospital)	Leak ureteroneocystostomy ATN following repair, due to sepsis ?? rejection ?? recovering—ALG
I. O.	M	26	C	Roux-y	1	0–3+	4+	Sepsis	ATN—due to urinary tract infection and/or rejection; ALG

* P-D 4+ = No insulin post-transplant.
** Previous R graft only from husband with rejection.

Technic

The procedure used for removing the pancreas and duodenum from the cadaver donor is similar to that developed in the laboratory. The entire pancreas with attached duodenum is removed from the cadaver along with its vascular connections. This includes a cuff of donor aorta containing the celiac axis and superior mesenteric artery and the donor portal vein. The pancreaticoduodenal allograft is placed in the iliac fossa of the host and the blood supply restored by anastomosing the aortic cuff containing the celiac axis and superior mesenteric artery of the graft to the side of the host's common or external iliac artery. The end of the donor portal vein is similarly joined to side of the host's common iliac vein. The proximal end of the graft duodenum is closed. In the first four patients the distal end of the duodenum was brought out through the skin as a duodenostomy so that the external secretions of the pancreas and duodenum drained externally (Fig. 16).[36]

We initially choose external rather than internal drainage of the exocrine secretions in contrast to our experimental work where we drained these secretions internally, for two principal reasons: (1) early detection of allograft rejection might be facilitated by direct observation of the duodenal mucosa and by measurements of the volume of exocrine secretion; these in addition to following blood sugar and amylase. (2) to avoid danger of anastomotic leak as a result of rejection if the duodenal graft was initially anastomosed to the recipients bowel. It was our plan

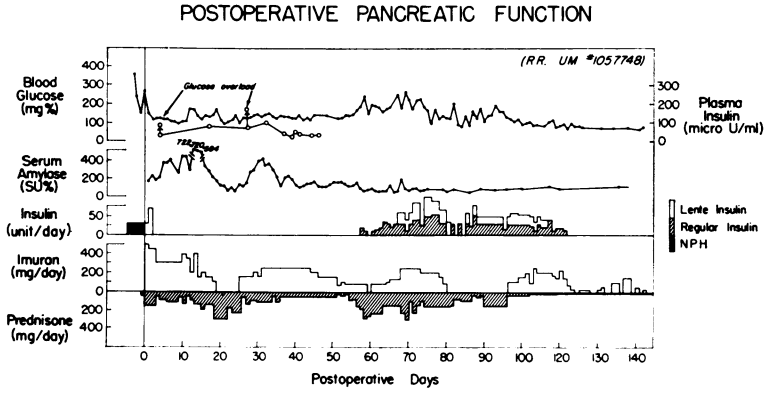

FIG. 17. Postoperative course of patient R. R.

after stabilization to take down the duodenostomy and join it to the host's small bowel to allow internal drainage of the exocrine secretions of the pancreas and duodenum.

In nine of the ten patients a kidney, taken from the same cadaver, was transplanted simultaneously in the host's opposite iliac fossa. The one exception, patient A. Z. had only a pancreaticoduodenal allotransplant and her renal failure was managed by hemodialysis (see below). The host's own functionless kidneys were either removed prior to transplantation, or at the same time, or, on one occasion, left in-place. The pancreas of the host was left intact. A summary of results with these ten patients is shown in Table 1 and short resumes are included below.

Case Reports

Patient Potocols

Case 1. R. R., a 32-year-old woman, had diabetes mellitus since age 11. She was admitted to the University of Minnesota Hospitals initially for evaluation of terminal diabetic nephrosclerosis and retinopathy in September 1966. She was maintained on hemodialysis until 12/31/66 when she received cadaver renal and pancreaticoduodenal allografts. A duodenostomy was formed from the distal end of the graft duodenum.

The course of this patient is charted in Figure 17. She had continuing problems with chronic renal rejection but few if any problems with the

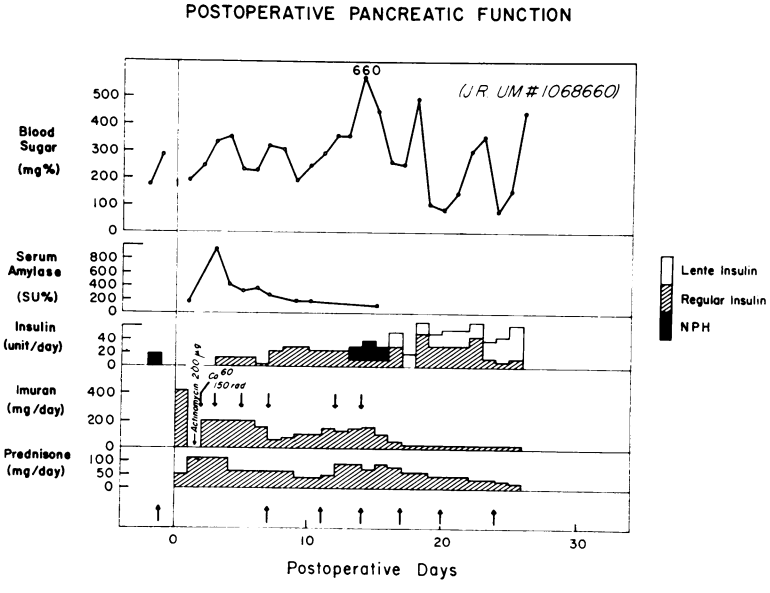

FIG. 18. Postoperative course of patient J. R.

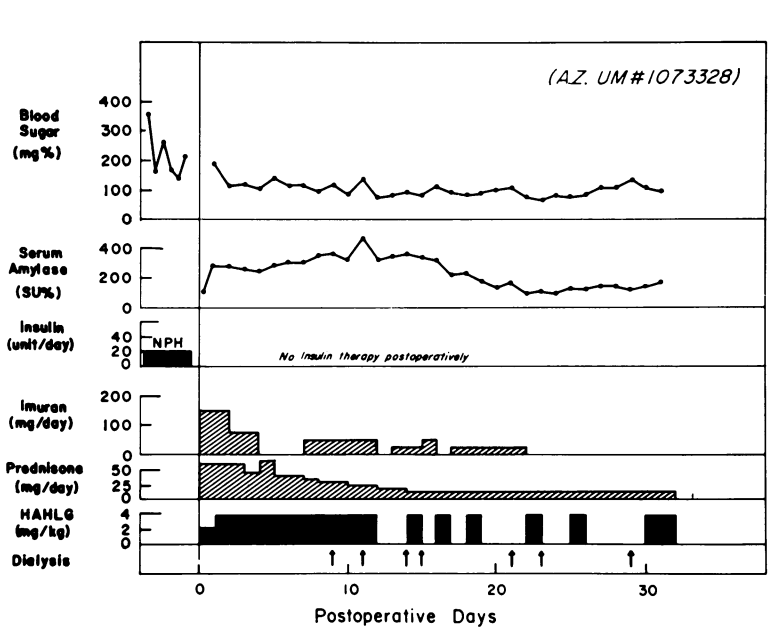

FIG. 19. Postoperative course of patient A. Z.

pancreas. The duodenal mucosa on occasion appeared to change color indicative of some change in vascularity but otherwise no evidence of severe rejection occurred. Insulin was not required except on two occasions during her 4½-month survival and these needs coincided with high prednisone dosages used to reverse renal rejection. Eventually she died from gram-negative septicemia secondary to pneumonia. The continuing need for large doses of immunosuppressives no doubt contributed to the development of the pneumonia. At autopsy her renal allograft showed chronic rejection while the graft pancreas and duodenum appeared normal. Neither tissue typing technics nor anti-lymphocyte globulin were available at this time.

Case 2. J. R., a 37-year-old man, had suffered diabetes mellitus for 20 years. In June 1967 he was admitted in terminal renal failure to the University Hospitals. He was placed on hemodialysis until 8/25/67 when he received renal and pancreaticoduodenal allografts. The cadaver donor was a patient who had been operated upon for valvular heart disease but then could not be removed from cardiopulmonary bypass after several attempts.

By the time consent from next of kin was obtained, over 8 hours of bypass had passed. Neither renal nor pancreatic allografts ever functioned and they were removed 16 days later (Fig. 18). Pathological examination of the removed organs showed infarction of kidney, duodenum and pancreas without evidence of rejection. These organs probably suffered lethal ischemic damage while still in the donor. The patient died 2 weeks later from sepsis. Tissue typing and antilymphocyte globulins were not used.

Case 3. A. Z., a 44-year-old woman, had diabetes mellitus first diagnosed at age 19. She was admitted to the University Hospitals in September 1967 with terminal renal failure, retinopathy, and peripheral neuropathy. She was placed on hemodialysis but her overall physical state improved only slightly. On 3/4/68 she received a cadaver pancreatico-duodenal allograft only, with construction of a duodenostomy. We omitted the renal allograft in hopes that a shorter operative procedure would be better tolerated, and, with improvement in her diabetic state, a renal allograft could be done at a later date. In the meantime she would be carried on hemodialysis.

Postoperatively, the patient's course was smooth, Figure 19, and no signs of rejection occurred; neither was any insulin required. One month after transplantation, and immediately following a hemodialysis, the patient spiked a high fever, became unresponsive and hypotensive and died in a few hours. Blood cultures and dialysis cultures subsequently grew Klebsiella. At autopsy the pancreatico-duodenal allograft was normal. Tissue typing was not done and antilymphocyte globulins were not used.

Case 4. D. O., a 31-year-old woman, had known diabetes mellitus for 20 years. She was evaluated for terminal nephropathy and retinopathy in February 1968 and then placed on hemodialysis. On 10/11/68 she received cadaver renal and pancreatico-duodenal allografts with drainage through a duodenostomy. In addition to the usual immunosuppressives of azathioprine and cortico-

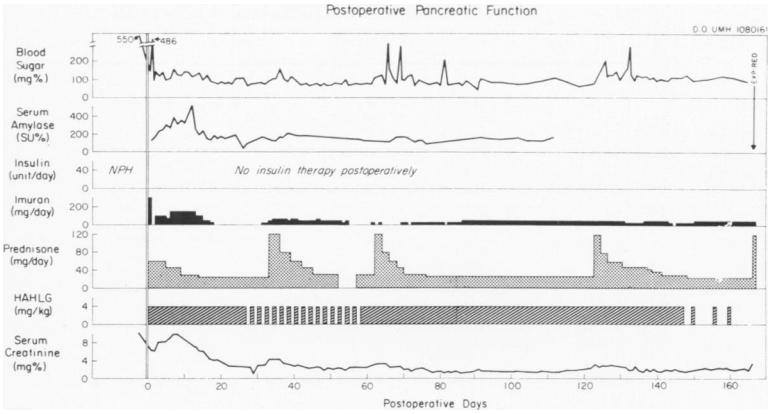

FIG. 20. Postoperative course of patient D. O.

steroids, she received antilymphocyte globulin. Her postoperative course was marred only by episodes of renal rejection but little evidence of pancreatic dysfunction (Fig. 20). No insulin was needed at anytime during her course. She died acutely at 5½ months following transplantation from a cardiac arrest secondary to hyperkalemia induced by another bout of renal rejection. At autopsy, her renal graft showed chronic rejection while the pancreas was normal (Fig. 21).

Prior to her sudden death, Dr. William Summerskill of the Mayo Clinic studied the exocine function of D. O.'s pancreatic allograft via the duodenostomy. While concentrations of enzymes were decreased from normal, a normal response to duodenal stimulation and administered secretogogues occurred.

Case 5. G. M., a 34-year-old man, had suffered diabetes mellitus since age 9 and was admitted to the University Hospitals in February 1969 with terminal renal failure, severe peripheral vascular disease, and neuropathy. He was placed on hemodialysis while awaiting a cadaver donor. During this period he suffered an acute thrombosis of the popliteal artery and ischemia in the right lower leg. The embolus was removed on 3/31/69 and he had a bilateral sympathectomy on 4/18/69.

On 6/3/69 he received renal and pancreaticoduodenal allografts from a cadaver. The graft duodenum was connected to G. M.'s small intestine via a Roux-Y loop. Following operation his course was initially smooth but he then developed what appeared to be renal rejection, but, an arteriogram showed narrowing of the anastomosis of the renal artery to the host iliac artery. This was repaired on 7/11/69 and his renal function improved markedly (Fig. 22). Throughout his course in the hospital, no insulin was required and none has been used in the 11 months since operation. Four months following discharge, G. M. had a normal glucose tolerance and tolbutamide stimulation tests (Figs. 23, 24).

After discharge, G. M. became active for the first time in several months and his right foot gradually passed from an ischemic to a gangrenous state. On 11/26/69 a below knee amputation was done and his stump healed in a normal fashion and he was soon walking with an artificial limb and returned to work.

On 4/11/70 he was found to have a blood urea nitrogen of 70 mg./100 ml. and a creatinine of 2.9 mg./100 ml. on a routine outpatient check. Blood sugar was normal. He was admitted to the hospital and responded initially to increased doses of azathioprine and corticosteroids. Because of domestic problems, he signed out against advice on 4/16/70 and headed for his home in a neighboring state. Unfortunately, he discontinued all his immunosuppressive drugs for a 4-day period and when seen again on 4/20/70, he was anuric with a blood urea nitrogen of 138 mg./100 ml. and a creatinine of 10.0 mg./100 ml. His blood sugar was 118 mg./100 ml. An arteriogram was done which showed no flow to his kidney and it was removed on 4/22/70. At operation, the kidney was necrotic so it will be difficult to tell whether the loss of the renal allograft is due completely to rejection or if a second arterial problem at the renal artery-iliac artery anastomosis contributed to the acute loss. The patient is now on hemodialysis and pancreatic function has continued normal. He now constitutes a fascinating "clinical" experiment in future management. We are looking for another cadaver kidney donor for this patient.

Case 6. N. T., a 28-year-old woman, had the onset of diabetes at age 11. She was admitted to the University Hospitals in April 1968 in renal failure. After a long wait for a cadaver donor without success, her husband who was a "B" match with her offered to donate his kidney.

On 9/23/68 she received a renal allograft from her husband but rejection occurred on the fourth post-transplant day and repeated rejections occurred after this. A chronic wound infection further complicated her course. On 2/21/69 her renal graft was removed. This lady who was very

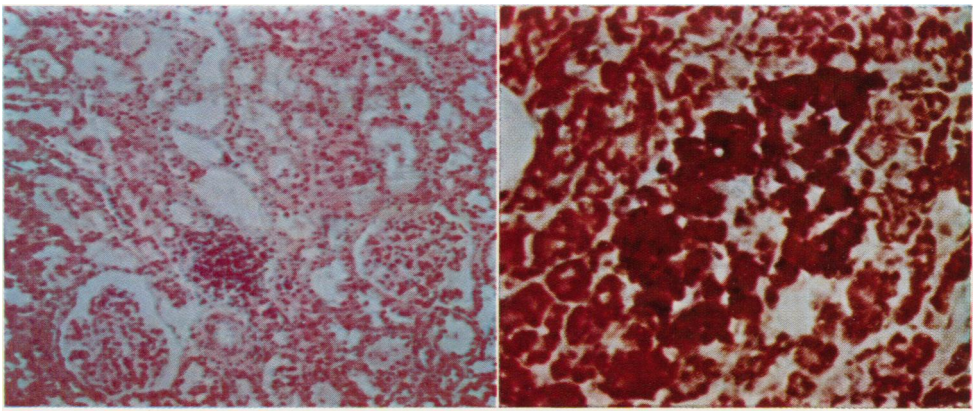

FIG. 21. Microscopic section of transplanted kidney and pancreas taken at autopsy from patient D. O. The kidney shows round cell infiltration characteristic of chronic rejection while the pancreas had no such infiltration.

small to begin with, was now down to about 40 Kg.

On 7/11/69 she received cadaver renal and pancreatico-duodenal allografts with Roux-Y reconstruction. Our principal problem at this juncture was space and we closed her abdominal incision only with great difficulty. Following this procedure, the renal graft never functioned but pancreatic function was normal (Fig. 25). One week later, N. T. suffered a stroke, respiratory arrest, and died. Pathological examinations of the kidney, duodenum and pancreas showed interstitial edema, but no signs of rejection. There was also a partially occluding thrombus in the portal vein-iliac vein anastomosis draining the pancreatico-duodenal graft. Pancreatic function, however, had remained normal until death. It is probable that the tight abdominal closure may have caused obstruction to renal and portal venous drainage from the grafts.

Case 7. C. B., a 34-year-old man, had diabetes mellitus diagnosed at age 11. He was first seen at the University Hospitals in July 1969 suffering renal failure and retinopathy and was placed on hemodialysis.

On 9/7/69 he received cadaver renal and pancreatico-duodenal allografts with a Roux-Y reconstruction. The donor-recipient match was "B". His course was uncomplicated and he was discharged 3 weeks later (Fig. 26). Two months later he returned and had normal tolbutamide and glucose tolerance tests. After this he returned home to California. He was treated there for renal rejection for the first time in November 1969 and responded nicely. On 1/12/70 he was admitted to the Orange County Medical Center in California showing signs of intestinal obstruction. Renal and pancreatic function at this time were normal. His distention gradually relented only to be followed by a recurrence of symptoms and, this time, free air was seen on his abdominal x-ray. He was explored and found to have a perforation at the proximal end of the graft duodenum and this was drained. The patient became septic and died on 3/4/70, 7 months after transplantation. At autopsy the pancreas and duodenum grossly were infarcted due to clots in the portal vein and celiac and superior mesenteric arteries, not associated with the anastomoses to the host vessels. This explained the need for insulin for the first time following transplantation 1 week prior to death. The kidney appeared normal. The microscopic findings on these organs have not yet been received from California.

Case 8. M. P., 34-year-old woman, had the onset of diabetes mellitus at 18 years. She was admitted to the University Hospitals in renal failure in November 1969. On 12/15/69 she received renal and pancreatico-duodenal allografts with a Roux-Y reconstruction. The tissue match was "C". Initial renal and pancreatic function were good. On the day following operation she spiked a fever to 106° F. after receiving intravenous antilymphocyte globulin. Other patients receiving ALG that same day showed similar pyrogenic reactions and this batch of ALG was found to be contaminated with pyrogens. Following this, her renal function deteriorated precipitously and over the next few days she developed signs of acute abdomen (Fig. 27). Pancreatic function remained normal in the face of these events. On 12/30/69 she was explored and the graft kidney and duodenum were infarcted. The pancreas was swollen but viable. Microscopic examination showed such renal and duodenal destruction that we were unable to tell whether rejection was the cause. The pancreas showed only edema without any signs of rejection. This precipitous course of events following the contaminated ALG suggests a "Shwartzman-type" reaction may have led to the renal and duodenal destruction.

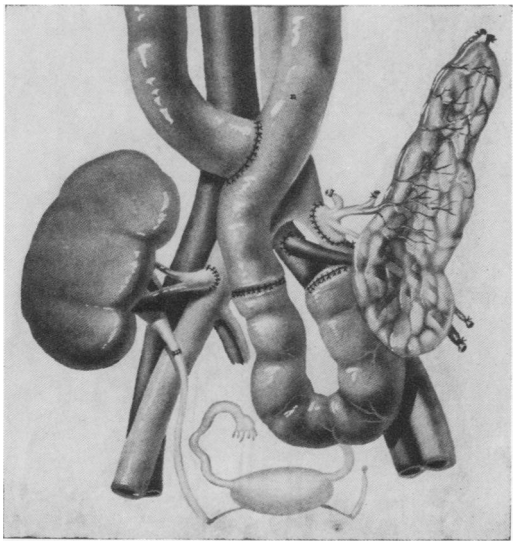

FIG. 22a. Technic used in G. M. and in all subsequent patients.

Case 9. R. K., a 30-year-old man, had diabetes mellitus first diagnosed at 12 years. He was seen at the University Hospitals in November 1969 suffering renal failure. He received a renal allograft from his brother on 12/10/69 but it never functioned because of graft renal artery thrombosis at the anastomotic site. This kidney was removed on 12/23/69 and the patient was maintained on hemodialysis until 1/27/70. On that date he received cadaver renal and pancreatico-duodenal allografts. Initial renal and pancreatic function were good but he required re-exploration on 2/2/70 because of a leak from the uretero-neocystostomy. Another re-exploration for this same problem was needed on 2/5/70. Throughout this period pancreatic function remained good (Fig. 28). He then gradually began to recover but developed repeated gram-negative septicemias seeded from the urinary tract. He also began to show increasing melena changing to bright bleeding and was re-explored on 3/16/70 with the thought he was bleeding from the graft duodenum; but this structure was normal and no other abnormal findings were seen. Since then the patient has gradually recovered with good renal and pancreatic function.

Case 10. I. O., a 20-year-old man, had diabetes mellitus diagnosed at age 1. He was admitted to the University Hospitals in December 1969 in renal failure. Soon after dialysis was begun he became paraplegic due to a transverse myelitis of unknown cause. On 3/19/70 he received renal and pancreatico-duodenal allografts with a Roux-Y loop. His initial renal function was poor and he needed dialysis a few days after operation (Fig. 29). On 3/20/70 his left flank wound over the area of the pancreatico-duodenal graft became tender and he underwent operation. We found a sterile hematoma around the graft but the pancreas and duodenum looked normal. Shortly after, he showed enterococci in the urine and soon thereafter in the blood. Despite this finding renal allograft function began to improve. On 4/8/70 he pulled his Scribner shunt apart and bled to shock levels. He was resuscitated but subsequently showed increasing systemic signs of sepsis with twitching, lethargy and low platelets. He died suddenly on 4/21/70. At autopsy there were perinephric, peri-pancreatic and pericardial abscesses. The kidney showed signs of chronic rejection while the pancreas appeared normal. The mucosa of the graft duodenum was hemorrhagic but the duodenal wall was viable.

In this patient death appeared related to a genitourinary tract infection which then led to metastatic abscesses in the pericardial sac and renal and pancreatico-duodenal graft areas.

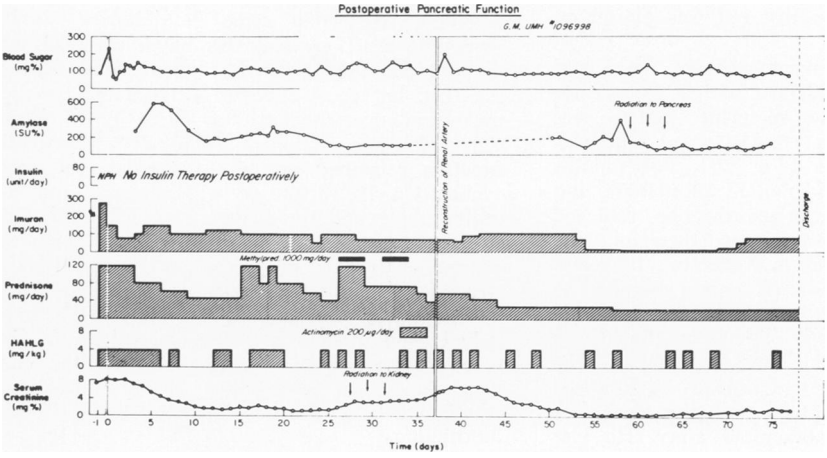

FIG. 22b. Postoperative course of patient G. M.

Conclusions

At first glance these results may create pessimism over the use of pancreatic grafts for treating diabetes mellitus. No patient has so far survived beyond 11 months and only two are currently alive; one of these without his renal allograft. Yet, a closer look will instill some optimism. Almost without exception, the pancreas has functioned normally in all patients and insulin has not been required in the postoperative period. The principle problems have been associated with the cadaver kidney. An examination of the critical points in the course of each patient will reinforce this optimism.

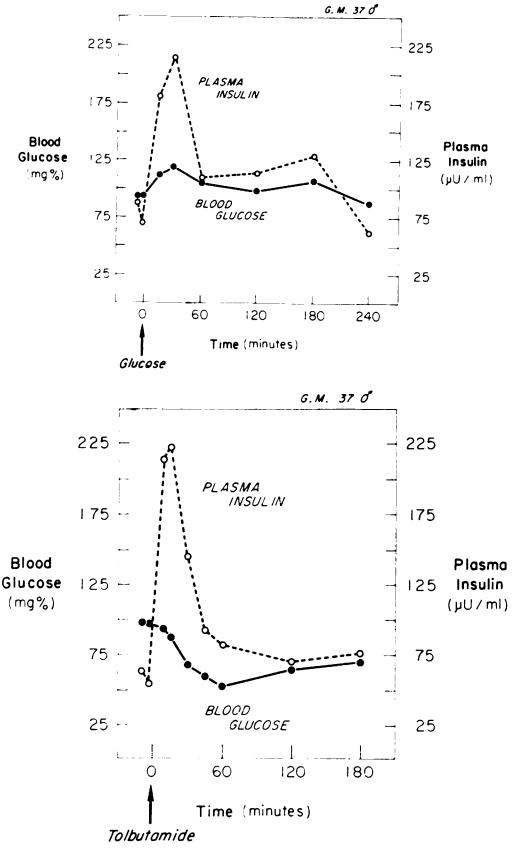

FIG. 23 (top). Glucose tolerance curve in G. M. at 4 months after transplantation. It is still normal at 1 year.

FIG. 24 (bottom). Tolbutamide stimulation test in G. M. 4 months after transplantation. It also is still normal at 1 year.

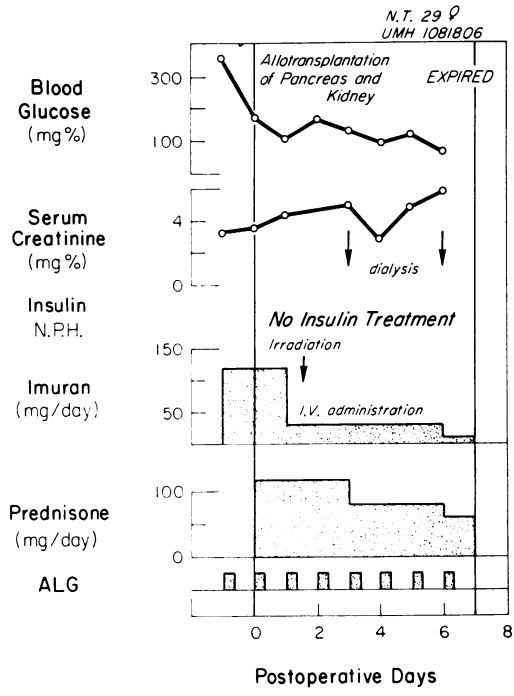

FIG. 25. Postoperative course of patient N. T.

Patient, R. R., had repeated problems with renal rejection and eventually died of septicemia secondary to a pneumonia associated with the high dosages of steroids and azathioprine used in an attempt to control renal rejection. The patient's grafted pancreas and duodenum were normal at autopsy while the renal graft showed chronic rejection.

Patient, J. R., had his pancreatico-duodenal and renal allograft taken from a cadaver which had been on cardiopulmonary bypass for over 8 hours before the organs were finally removed. Neither grafted pancreas nor kidney functioned immediately and they probably suffered lethal ischemic damage in the cadaver before removal.

Patient, A. Z., received only a pancreatico-duodenal allograft and was maintained on chronic dialysis but died as a result of septicemia contracted on the dialysis. Blood cultures from the dialysate showed the same organism as found in the blood of the patient. Her grafted pancreas

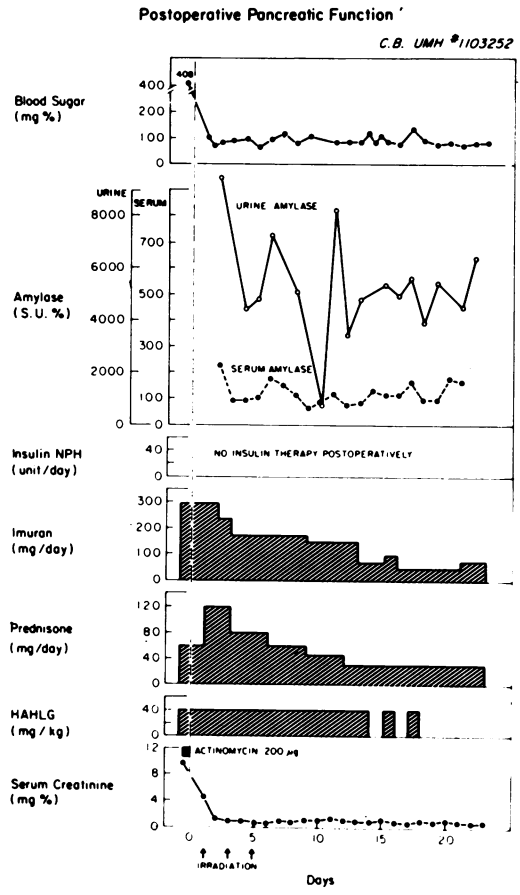

FIG. 26. Postoperative course of patient C. B.

and duodenum were normal at autopsy.

D. O.'s postoperative course was complicated by repeated bouts of chronic renal rejection. Her death was due to hyperkalemia associated with acute rejection. At autopsy gross and microscopic examination of the pancreas and duodenum showed no signs of rejection; mucosal thinning of the duodenum was the only change noted. The kidney showed chronic rejection.

Patient G. M. is still alive at 12 months. His early problems with his kidney were due to stenosis of the renal-iliac artery anastomosis and upon correction, he had no problems until he suffered acute renal rejection and/or thrombosis of the renal artery with loss of his kidney at 11 months. He is now maintained on dialysis. Throughout his course pancreatic function has been normal. In his present anephric state, with a functioning pancreatico-duodenal allograft, he presents a serendipitous opportunity to make observations on the present need for immunosuppression compared with the past experience.

C. B. had the smoothest course of all and was out of the hospital in 3 weeks. He suffered several minor bouts of renal rejection which were easily controlled. His death at 7 months was due to sepsis secondary to perforation of the graft duodenum, the only death in the series directly attributable to the pancreatico-duodenal allograft.

N. T. had a previous kidney transplant from her husband which she rejected. She then received combined cadaver renal and pancreatico-duodenal allotransplantation. The kidney never functioned while the pancreas functioned normally even though portal venous drainage was partially obstructed by clot. Autopsy findings were puzzling since the kidney, pancreas and

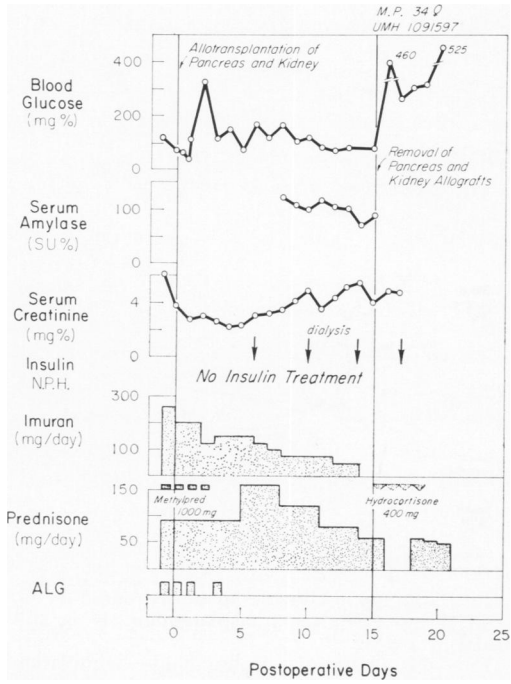

FIG. 27. Postoperative course of patient M. P.

duodenum showed only interstitial edema. Her death seemed to result from a cerebrovascular accident.

M. P. was doing well in her early postoperative period until she received a dose of contaminated antilymphocyte globulin. Immediately following this she suffered acute renal shutdown and gradually developed an acute abdomen. Re-exploration showed the grafted kidney and duodenum to be necrotic which necessitated their removal. The pancreas, while swollen, had continued to function until removed. A type of "Shwartzman-like" reaction, probably related to the pyrogens or endotoxin contaminating the antilymphocyte globulin appears to have occurred here.

R. K. is living, although he had continuing problems with his transplanted kidney, primarily due to the two additional procedures required for leak of the ureteral-neocytostomy. He is now recovering and pancreatic function has been excellent throughout the stormy course.

Finally, patient I. O., also suffered renal shutdown either due to an enterobacter infection in the urinary tract and/or acute rejection. The sepsis led ultimately to death. At autopsy the kidney showed gross and microscopic signs of rejection while the pancreas appeared normal.

The paradox of renal rejection in almost

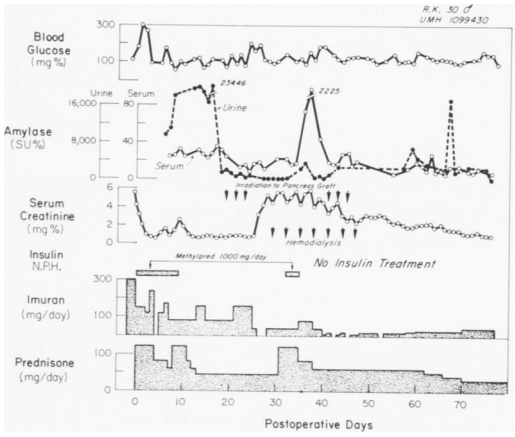

FIG. 28. Postoperative course of patient R. K.

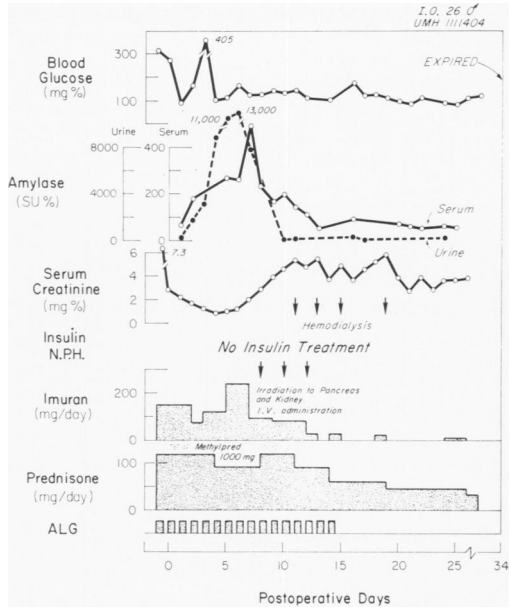

FIG. 29. Postoperative course of patient I. O.

all of these patients without evidence of pancreatic rejection is most provocative, especially if we keep in mind that both organs come from the same cadaver. It is clear from this experience that rejection is not an all or none affair and various organs apparently have varying abilities to stimulate rejection in the host. At the risk of offending many immunologists a "hierarchy" of rejection can be proposed in which the pancreas is probably the least antigenic organ so far transplanted in man, Table 2. At the same time the pancreatic allograft occupies this "privileged" position in the hierarchy does it somehow call down on the renal allograft a more severe rejection? It seems that renal rejection seen in these patients has been more frequent and severe than when cadaver renal allografts alone are done.

Probably the duodenum of the pancreatico-duodenal allograft is more sensitive than the pancreas itself and this has stimulated us to search for new ways to transplant the entire pancreas with elimination of the duodenum. This is a difficult technical problem because of the tendency of

TABLE 2. *Hierarchy of Rejection*

1. Skin	↑
2. Heart	
3. Kidney	Increasing antigenicity
4. Liver	
5. Pancreas	

the pancreas to leak from any cut surface no matter how the surface is closed or in what manner it is attached to the small intestine. These problems are magnified by the use of immunosuppressive drugs. Nonetheless, we are searching for new technics to make such transplants of the whole pancreas in the experimental animal with elimination of the duodenum.

Perhaps the emphasis on transferring the whole pancreas by one means or another is misplaced. Yet, our own studies in the laboratory show that atrophy and fibrosis of the ascinar tissue of the pancreas does lead to functional disability of the islets in contrast to those of others. Moreover, the "experiment of nature" chronic pancreatitis in man seems to confirm this emphasis. Perhaps a third or more patients with chronic pancreatitis develop diabetes mellitus.

There are theoretical reasons also for transplanting the entire pancreas. While islet and ascinar function is indeed separate, there are many intimate relations between these two functions, and as we learn more about diabetes mellitus we appreciate that insulin is not the only factor in its genesis. The rate of absorption of glucose, fats and protein also play a role in the disease.

With this experience, what of the future? With the cooperation of our medical, pediatric and biostatistical colleagues, we are planning the following program: We will continue to treat selected patients with juvenile-onset diabetes mellitus and renal failure with renal and pancreatico-duodenal allografts but we will expand the study in the following manner. Some of these patients will receive a renal allograft only from a blood related donor, if available or from a cadaver. All patients will be followed with retinal photography, needle or open biopsies of the renal allograft and muscle biopsies in an attempt to follow the course of their vascular disease and see if it afflicts the new kidney.

We will do pancreatico-duodenal allotransplantation alone in still another group of juvenile-onset diabetics who have significant but not terminal nephropathy and/or severe retinopathy. Since most of the problems with pancreatico-duodenal and renal allotransplantation are associated with the kidney, pancreatico-duodenal allografts alone should greatly reduce the morbidity and mortality of the procedure. For comparison, another group of patients with juvenile-onset diabetes mellitus and severe retinopathy and nephropathy, will be treated in a conventional manner and followed. Again, renal biopsies, muscle biopsies, and retinal photography will be used for comparison of these patients with those receiving renal and/or pancreatico-duodenal allografts.

These studies are designed to answer the question: will a normally functioning pancreas influence the course of the characteristic vascular lesions of diabetes mellitus? Even if the answer to this question is no, we will still have contributed much knowledge to understanding the nature of diabetes mellitus and opened new areas of research into the disease.

If the answer is yes, then pancreatic allografting could become the most frequent organ transplant procedure in man and we will have offered the diabetic the most important contribution to his survival since the introduction of insulin.

Summary

A procedure has been developed in the laboratory for pancreatico-duodenal allotransplantation in the pancreatectomized dog. Dogs with such grafts have survived

for many months when treated with azathioprine and prednisone to prevent rejection. Contrary to usual beliefs, the pancreas is not particularly sensitive to total ischemia since it has been possible to preserve a pancreatico-duodenal allograft *in vitro* with only hyperthermia and hyperbaria up to 24 hours. Such preserved pancreatico-duodenal grafts have then been allotransplanted into pancreatectomized dogs with survival of the dogs for long periods.

We have now done pancreatico-duodenal allotransplantation in ten patients with juvenile onset diabetes mellitus and renal failure. Nine of these patients have received a renal allograft taken from the same cadaver simultaneously. In all but one of these patients the pancreas has functioned immediately. This exception was in a patient who received a pancreatico-duodenal allograft taken from a cadaver which had suffered irreversible ischemia. While only two patients are currently living, the longest 12 months, in no case have we seen evidence of pancreatic rejection. In seven of the eight deaths, problems concerned with the cadaver renal allograft were at fault and in only one patient was the pancreatico-duodenal allograft the cause of death. This patient died 7 months after pancreatico-duodenal allografting from an acute perforation of the duodenal graft. It is clear from these studies that the pancreas is far less antigenic than the kidney and possibly less than other organs as well. Pancreatico-duodenal allotransplantation alone is now planned for juvenile-onset diabetics who have significant but not terminal renal nephropathy. If the characteristic vascular disease of diabetes mellitus can be altered by a pancreatic allograft, then this will become one of the most commonly performed transplant procedures.

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