
Conversion of Exocrine Secretions From Bladder to Enteric Drainage in Recipients of Whole Pancreaticoduodenal Transplants

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Between September 1984 and August 1991, 265 whole pancreaticoduodenal transplants were done at our institution, with bladder drainage of exocrine secretions through a duodenocystostomy. Seventeen patients subsequently underwent conversion from bladder to enteric drainage at 2 to 64 months after transplant. Eight conversion procedures were done to correct chronic intractable metabolic acidosis due to bicarbonate loss from the allograft: seven to alleviate severe dysuria, presumed secondary to the action of graft enzymes on uroepithelium; one to prevent recurrent allograft pancreatitis, presumed secondary to back pressure from the bladder; and one because of graft duodenectomy for severe cytomegalovirus duodenitis with perforation. None were done to correct technical complications from the initial transplant operation. The conversions were done by dividing the graft duodenocystostomy, then re-establishing drainage through a graft duodenal-recipient jejunal anastomosis. A simple loop of recipient jejunum was used for the duodenojejunostomy in 15 cases, and a Roux limb in two. One of those two cases had a previously created Roux limb that was available for use. The other was in the patient who underwent graft duodenectomy and subsequent mucosa-to-mucosa anastomosis of the pancreatic duct to a newly created Roux limb of jejunum. All patients experienced relief of their symptoms after operation. Two patients had surgical complications (12%), an enterotomy in one case, which was closed operatively, and an enterocutaneous fistula in the other case, which healed spontaneously with bowel rest and parenteral nutrition. The drawback to conversion is loss of urine amylase as a marker for rejection, particularly in recipients of solitary pancreas grafts ($n = 5$). In recipients of simultaneous pancreas-kidney (SPK) allografts ($n = 12$), the kidney can still be used to monitor for rejection (two with follow-up <1 year, 10 with follow-up >1 year). None of our solitary pancreas recipients, however, have lost graft function (follow-up, 10 to 36 months). The only pancreas allograft loss was in an SPK recipient who also rejected the kidney 6 months after conversion. She received a second SPK transplant with enteric drainage, and is insulin independent and normoglycemic 10 months after retransplantation. Patients converted for metabolic acidosis tended to have

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impaired renal function (mean creatinine, 2.14 ± 0.98 mg/dL at time of conversion) due to chronic rejection, progression of native kidney diabetic nephropathy, or cyclosporine toxicity, and possibly could not compensate for bicarbonate loss from the pancreas allograft. The authors conclude that cystoenteric conversion of pancreas allografts is safe and therapeutic for intractable metabolic acidosis and dysuria in patients with stable pancreas graft function, and can be done with a low risk of subsequent rejection.

SINCE ITS CLINICAL introduction in the early 1980s,¹ bladder drainage (BD) with a duodenocystostomy has become the most common method to manage exocrine secretions of cadaver whole pancreaticoduodenal transplants. According to a report from the Pancreas Transplant Registry,² during 1984 to 1985 (less than 2 years after the introduction of BD), 77 of 387 (20%) pancreas transplants worldwide used this technique. In a subsequent report on all 1986 to 1990 cases, 1566 of 2087 (75%) used this technique.³ Of U.S. cases during this time, 1224 of 1308 (94%) used BD.

In addition to being a safe procedure, duodenocystostomy offers the advantage of monitoring graft exocrine function by serial measurement of urine amylase, a decrease signalling possible early acute rejection.⁴ With other techniques, such as enteric drainage (ED)⁵ or ductal injection with a synthetic polymer,⁶ exocrine function cannot be monitored permanently, although placement of a catheter in the pancreatic duct for temporary external drainage of graft secretions during the first few weeks after transplant has been advocated.^{7,8} Monitoring exocrine function is particularly important for solitary pancreas grafts. For simultaneous pancreas-kidney grafts from the same donor, rejection episodes are signalled by an increase

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in serum creatinine; however, there are no surrogate markers for a pancreas transplant alone.⁹

In a series of pancreas transplants at our institution, BD has been associated with improved clinical outcome¹⁰ and a lower complication rate.¹¹ Two of the difficulties of this approach are the ongoing obligatory loss of bicarbonate (HCO_3) and other electrolytes secreted by the pancreas and duodenum (ordinarily absorbed in the gut) and the deleterious action of exocrine enzymes on the urinary tract mucosa.¹² Either of these complications can be resolved by dividing the duodenocystostomy, closing the bladder, and diverting exocrine secretions into the bowel. Previously, in a brief communication, we reported on our early experience with five patients who were converted from BD to ED,¹³ and expressed our reservations about the procedure regarding the decreased ability to monitor for rejection and the possible risk of infection. Our current analysis includes 12 additional conversions, bringing our total experience to 17 cases.

Materials and Methods

Between October 1984 and August 1991 at our institution, 265 patients with type I diabetes mellitus underwent pancreas transplantation with exocrine drainage into the bladder: 122 simultaneous with a kidney (SPK), 63 after a kidney, and 80 without a kidney transplant. Of the 265 grafts, 249 were whole pancreaticoduodenal allografts in which the first, second, and a portion of the third segment of the duodenum were transplanted and a duodenocystostomy was created (Fig. 1). Some duodenocystostomies were hand-sewn¹⁴; others, stapled.¹⁵ In five of the whole pancreas grafts, only a small duodenal patch was anastomosed to the bladder; 11 were segmental grafts in which mucosa-to-mucosa ductocystostomy was done by a technique previously described.¹⁶

All patients were immunosuppressed with induction antilymphocyte globulin (ALG) or OKT3 and cyclosporine, azathioprine, and prednisone according to our standard protocol.¹⁶ Because of the tendency for BD pancreas transplant recipients to develop metabolic acidosis, all were placed on oral sodium bicarbonate (NaHCO_3) replacement therapy. The dosage was adjusted to maintain serum HCO_3 levels of 20 to 30 mmol/L.

Serum electrolytes, including HCO_3 levels, were measured at least weekly on an outpatient basis. Weekly urine amylase activity also was measured; a 50% decline prompted readmission to investigate possible pancreas rejection. Patients submitted urine cultures once a month, and were admitted if they had symptoms of intractable urinary tract infections (UTI), whether cultures were positive or not.

The main indications for the conversion procedure were intractable metabolic acidosis and dysuria. Intractable

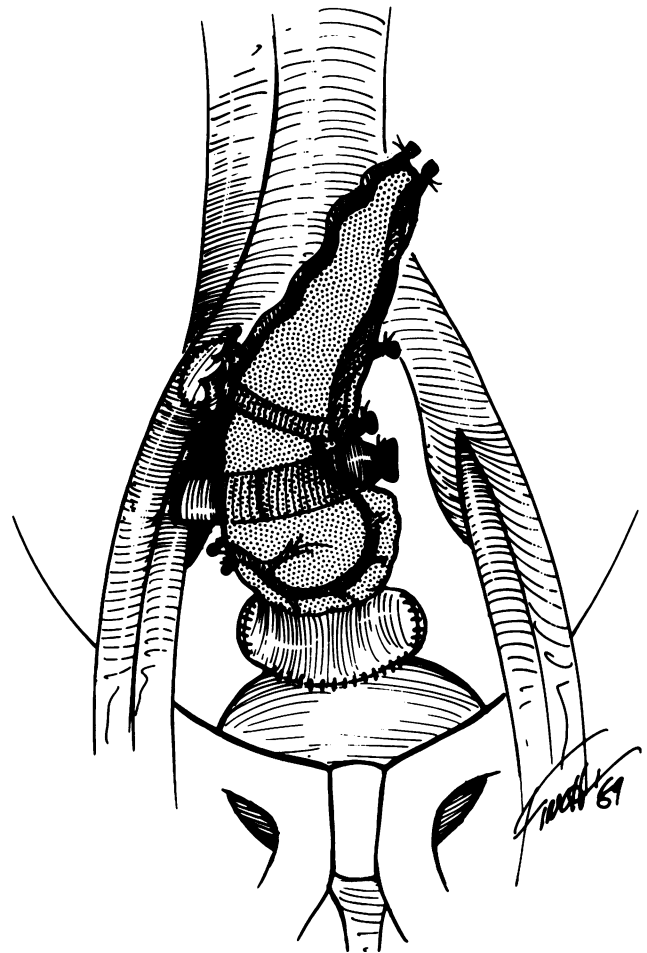


FIG. 1. Technique for whole pancreaticoduodenal transplantation with exocrine secretion drainage into the bladder via a duodenocystostomy.

acidosis usually resulted from some patients' intolerance to large amounts of oral NaHCO_3 replacement. Sodium bicarbonate was supplied in 650-mg tablets, so patients needed to ingest many tablets in one day; for example, a supplement of 20,800 mg daily corresponds to 32 tablets. There were wide differences between patients not only in the dosage of NaHCO_3 required, but also in their tolerance to the same dosage. Repeated bouts of metabolic acidosis below 15 mmol/L, despite the maximum dosage of oral NaHCO_3 physically tolerated, led to consideration for enteric conversion. Similarly, the severity of dysuria in patients with sterile urine cultures also varied widely. In some, relief could only be obtained with Foley catheter drainage.

Enteric conversion involved isolating and dividing the duodenocystostomy, closing the bladder in multiple layers. Enteric drainage then was established in 15 patients by direct anastomosis of the graft duodenum to an intact, undivided loop of recipient jejunum, using the most proximal loop that was easily accessible for simple side-to-side enteroenterostomy. In the remaining two patients,

ED was established by anastomosis of the graft duodenum to the afferent end of a Roux-en-Y limb of recipient jejunum. In one of these (patient 13), a Roux limb was available from a previous operation (rejected segmental pancreas graft). In the other (patient 12), a Roux limb was specifically created at the time of ED; this was the only case in which the graft duodenum was not available for anastomosis, having previously been removed because of cytomegalovirus (CMV) duodenitis and perforation, thus necessitating a pancreatic duct–enteric anastomosis.

Individual case histories of our 17 patients are presented below.

Case Reports

Patient 1

A woman diagnosed with diabetes in 1968 at age 13 received two silicone rubber duct-injected pancreas transplants, first in April 1981 and then in April 1982. After both transplants, she was initially normoglycemic, but lost both allografts to rejection at 2 and 7 months after transplant. Her diabetic nephropathy progressed to uremia, and in October 1986, she received a BD SPK transplant. At discharge, she was normoglycemic, with an average urine amylase of 4500 U/hour and serum creatinine of 1.3 mg/dL. She required 10,400 mg oral NaHCO₃ daily to maintain a normal serum HCO₃.

During the first 3 months after her SPK transplant, she had three acute rejection episodes that clinically involved the renal allograft alone. They resulted in serum creatinine elevation to 4.4 mg/dL. During this period, average urine amylase remained stable at 4500 U/hour, and she remained normoglycemic. The first two rejection episodes were reversed with a temporary increase in steroids and ALG. With the third rejection episode, however, serum creatinine did not decline. A renal allograft biopsy after seven doses of ALG showed persistent acute tubulointerstitial rejection. It was thought unsafe to give further antirejection therapy because of the risk of overimmunosuppression, and she was discharged on maintenance immunosuppression.

Persistent metabolic acidosis proved to be a major problem after the acute deterioration in renal function. Serum HCO₃ levels were consistently below 15 mmol/L, despite 20,800 mg NaHCO₃ daily (32 tablets), the maximum she could physically tolerate. She was admitted several times for intravenous alkaline therapy. In January 1987, 3 months after transplant, enteric conversion was done to a loop of jejunum. After the operation, NaHCO₃ replacement therapy was discontinued and serum HCO₃ levels were maintained >20 mmol/L even in the face of progressive uremia. In March 1987, maintenance hemodialysis was initiated. She remained on hemodialysis for 2 years. In March 1989, she received a second cadaver kidney transplant. One rejection episode of the renal allograft was successfully treated. Clinical rejection of the pancreas allograft has not occurred since the conversion. Currently, she is dialysis free and normoglycemic, 62 months after conversion, 65 months after pancreas transplantation.

Patient 2

A man diagnosed with diabetes in 1960 at age 11 received a BD pancreas transplant alone in May 1986. At discharge, he was normoglycemic, with a serum creatinine of 1.1 mg/dL. A pancreas rejection episode in December 1986 was reversed with a temporary increase in steroids and ALG. With continuous urine HCO₃ loss, 5200 mg oral NaHCO₃ daily was required to maintain a normal serum HCO₃. This dosage was the maximum he could physically tolerate.

Over the next 6 months, his serum creatinine increased from 1.1 mg/dL pretransplant to 1.9 mg/dL. Renal biopsy showed diffuse, mild diabetic nephropathy, interstitial fibrosis, and tubulitis consistent with cyclosporine toxicity. This deterioration in renal function coincided with several bouts of metabolic acidosis and dehydration.

In February 1987, he was admitted for dehydration and fatigue. His serum HCO₃ was 11 mmol/L, requiring intravenous correction. As an outpatient, he could not maintain serum HCO₃ levels above 20 mmol/L. In March 1988, 22 months after transplant, enteric conversion was done to a loop of jejunum. After this operation, oral NaHCO₃ was discontinued. He remained normoglycemic until he died at home of an analgesic overdose in November 1988, 8 months after conversion, 30 months after transplant.

Patient 3

A man diagnosed with diabetes in 1963 at age 12 received a BD SPK transplant in June 1988. At discharge, he was normoglycemic, with an average urine amylase of 9750 U/hour and serum creatinine of 1.3 mg/dL. He required 10,400 mg oral NaHCO₃ daily to maintain a normal serum HCO₃. One month after operation, urine amylase decreased to 3000 U/hour in association with a rise in serum creatinine to 3.5 mg/dL. Renal biopsy was consistent with acute rejection, and OKT3 treatment was instituted. Renal rejection reversed and urinary amylase returned to baseline.

No further rejection episodes occurred. The patient complained of severe dysuria and intractable burning pain, however, in the penis, testes, and suprapubic area, in the absence of positive urine cultures. Relief could only be obtained by Foley catheter placement. Cystoscopy showed only inflammation in the bulbous urethra. In October 1988, 5 months after transplant, enteric conversion was done to a loop of jejunum. His symptoms resolved immediately, and he was able to discontinue oral NaHCO₃. Currently, he is normoglycemic, 41 months after conversion, 46 months after transplant.

Patient 4

A woman diagnosed with diabetes in 1965 at age 13 received a cadaver kidney transplant in 1981 and a BD pancreas transplant in July 1986. At discharge, she was normoglycemic, with an average urine amylase of 2000 U/hour and serum creatinine of 1.6 mg/dL. She required 5200 mg oral NaHCO₃ daily to maintain a normal serum HCO₃.

She was readmitted for dysuria 1 month after transplant. Urine cultures were negative until 11 months after transplant in June 1987, however, when she had the first of several *Escherichia coli* UTIs, associated with fever and exacerbation of dysuria. With intravenous antibiotics, the infections resolved, but she continued to complain of dysuria, even though urine cultures remained sterile. Cystoscopic examination of the urinary tract failed to disclose pathology other than the presence of staples at the duodenocystostomy, which were removed. The dysuria was thought to be related to the effect of pancreatic enzymes on the urinary mucosa. In December 1988, 30 months after transplant, enteric conversion was done to a loop of jejunum. Dysuria immediately resolved, and oral NaHCO₃ was discontinued. She continues to be normoglycemic, 39 months after conversion, 69 months after transplant.

Patient 5

A man diagnosed with diabetes in 1969 at age 24 received a BD SPK transplant in February 1989. At discharge, he was normoglycemic, with an average urine amylase of 3000 U/hour and serum creatinine of 1.5 mg/dL. He required 7800 mg oral NaHCO₃ daily to maintain a normal serum HCO₃.

His course was complicated by constant dysuria and pelvic pain radiating into the penis, scrotum, and perineum, relieved only by Foley

catheter placement. Intermittently positive urine cultures were treated with antibiotics, and urologic consultation diagnosed prostatitis. Even during periods of sterile urine, however, the severe dysuria persisted. In August 1989, 6 months after transplant, enteric conversion was done to a loop of jejunum. His symptoms completely resolved, and he also was able to discontinue NaHCO_3 . He remains normoglycemic, 31 months after conversion, 37 months after transplant.

Patient 6

A woman diagnosed with diabetes in 1978 at age 24 received a BD SPK transplant in July 1989. At discharge, she was normoglycemic, with an average urine amylase of 5500 U/hour and serum creatinine of 1.9 mg/dL. She required 2600 mg oral NaHCO_3 daily to maintain a normal serum HCO_3 . Two episodes of pancreas and kidney allograft rejection were treated, once with ALG, and then with a temporary increase in steroids. Her serum creatinine subsequently remained elevated at 2.0 mg/dL, compounded by bouts of cyclosporine toxicity. She required increasing doses of oral NaHCO_3 to 18,200 mg daily to maintain a normal serum HCO_3 .

During the ensuing several months, she was admitted on multiple occasions because of dehydration and low serum HCO_3 levels, requiring intravenous hydration and HCO_3 replacement. In February 1990, 7 months after transplant, enteric conversion was done to a loop of jejunum. She was able to discontinue oral NaHCO_3 and has required no further admissions since the conversion, except for successful delivery of a baby. She remains normoglycemic, 25 months after conversion, 32 months after transplant.

Patient 7

A woman diagnosed with diabetes in 1969 at age 16 received a BD SPK transplant in February 1990. At discharge, she was normoglycemic, with an average urine amylase of 2100 U/hour and serum creatinine of 0.7 mg/dL. She required 60 mL Bicitra (Willen Drug Co., Baltimore, MD) four times daily to maintain a normal serum HCO_3 . A mild episode of renal allograft rejection 1 month after transplant was treated successfully with Solu-Medrol (Upjohn, Kalamazoo, MI) and a temporary increase in steroids. Her Bicitra dosage was increased, however, to 90 mL four times daily to maintain a normal serum HCO_3 .

An episode of abdominal pain and elevated serum amylase resolved with Foley catheter placement. Computed tomography scan and cystoscopy showed no evidence of a bladder leak, but the urinary catheter was left in place for 6 weeks, with no further such episodes. A severe CMV infection in June 1990 was treated with 14 days of ganciclovir (Syntex, Palo Alto, CA). Subsequently, she was admitted twice for episodes of severe dehydration, and profound metabolic acidosis, requiring intravenous hydration and HCO_3 replacement. Serum creatinine was 1.4 mg/dL after rehydration. In July 1990, 5 months after transplant, enteric conversion was done to a loop of jejunum. After operation, she initially was normoglycemic, and discontinued oral NaHCO_3 .

An episode of renal rejection, diagnosed by biopsy 1 month after conversion, was treated with OKT3. After this episode, her serum glucose slowly but progressively increased. Then, 6 months after conversion, 11 months after transplant, she had to resume exogenous insulin, presumably because of chronic pancreas rejection. Her renal allograft also showed evidence of chronic rejection by biopsy, with serum creatinine increasing slowly to 4.0 mg/dL. A second SPK transplant was done in May 1991. Exocrine drainage of the second pancreas allograft was enteric with a side-to-side duodenojejunostomy. Currently, she is normoglycemic, with a creatinine of 0.7 mg/dL, 10 months after the second transplant, with none of the early metabolic problems encountered after the first transplant.

Patient 8

A man diagnosed with diabetes in 1965 at age 9 had lost a previous renal allograft to rejection. He received a BD SPK transplant in October 1989. At discharge, he was normoglycemic, with an average urine amylase level of 3400 U/hour and serum creatinine of 2.0 mg/dL. He required 9750 mg oral NaHCO_3 daily to maintain a normal serum HCO_3 . An episode of acute renal rejection 1 month after transplant was treated with ALG. This renal injury was compounded by cyclosporine toxicity; his serum creatinine then stabilized at 2.1 mg/dL several months after operation. He required an increase in oral NaHCO_3 to 22,100 mg to maintain a normal serum HCO_3 level.

In September 1990, 11 months after transplant, he was admitted with severe dehydration and a profound loss of HCO_3 , requiring intravenous hydration and HCO_3 replacement. After fluid resuscitation and stabilization, enteric conversion was done to a loop of jejunum. Currently, he is normoglycemic, and has discontinued NaHCO_3 , 18 months after conversion, 21 months after transplant.

Patient 9

A man diagnosed with diabetes in 1964 at age 11 had lost a previous allograft to rejection. He received a BD SPK transplant in January 1990. At discharge, he was normoglycemic, with an average urine amylase of 9750 U/hour and serum creatinine of 1.1 mg/dL. He required 18,200 mg oral NaHCO_3 daily to maintain a normal serum HCO_3 .

His only complaint was severe dysuria. Several *E. coli* UTIs were successfully treated; however, he continued to be afflicted with dysuria even when urine cultures were sterile. In October 1990, 9 months after transplant, enteric conversion was done to a loop of jejunum. Dysuria immediately resolved, and he discontinued NaHCO_3 . Currently, he is normoglycemic, 18 months after conversion, 27 months after transplant.

Patient 10

A man diagnosed with diabetes in 1967 at age 12 had previously undergone a living related donor renal transplant in August 1987. He received a BD cadaver pancreas transplant in February 1990. At discharge, he was normoglycemic, with an average urine amylase of 2350 U/hour and serum creatinine of 1.3 mg/dL. He required 3900 mg oral NaHCO_3 daily to maintain a normal serum HCO_3 .

In May 1990, CMV gastritis was treated with 14 days ganciclovir. Several episodes of mild abdominal pain and elevated serum amylase were investigated by cystograms, which failed to show a urinary leak. Computed tomography scan showed an edematous pancreas allograft with loculated perigraft fluid, consistent with inflammation. The pain episodes rapidly resolved after Foley catheter placement, and serum amylase normalized. Multiple UTIs not associated with dysuria, but complicated by Foley catheter placement, were treated with intravenous antibiotics. Despite conservative therapy, he was admitted numerous times with repeated bouts of abdominal pain and elevated serum amylase. Recurrent graft pancreatitis was postulated as the cause of these symptoms, possibly due to reflux of urine through an incompetent sphincter of Oddi (not demonstrated on cystogram) during micturition, or stagnation of pancreatic exocrine secretions in a neurogenic bladder.

In September 1990, 7 months after transplant, enteric conversion was done to a loop of jejunum. During operation, extremely dense adhesions were encountered. An extensive lysis of fibrous tissue was required to isolate the duodenocystostomy and to procure an adequate segment of recipient jejunum before doing a side-to-side duodenojejunostomy. After removal of his nasogastric tube at 3 days after conversion, abdominal distention and low-grade fevers occurred. Computed tomography scan of the abdomen showed a fluid collection extending from midabdomen to pelvis. After computed tomography guided drainage of this collection,

cultures grew *Candida albicans*. The percutaneously placed drains proved to be inadequate. Therefore, laparotomy was done, purulent material evacuated from the peritoneal cavity, and large drains placed. A leak from the duodenojejunostomy could not be visualized during operation. Cultures taken at operation grew *Candida albicans*, *Candida glabrata*, and *Lactobacillus acidophilus*. Treatment with amphotericin B was initiated, and the patient was kept at bowel rest and given parenteral nutrition intravenously. Drains placed during operation leaked fluid high in amylase, although sinography through the fistula was unable to localize the enteric site. Over several weeks, the drainage diminished, the drains were removed, and the fistula resolved. He has had no further episodes of allograft pancreatitis since conversion, and remains normoglycemic 18 months after conversion, 25 months after transplant.

Patient 11

A woman diagnosed with diabetes in 1970 at age 19 received a BD SPK transplant in October 1986. At discharge, she was normoglycemic, with an average urine amylase of 2800 U/hour and serum creatinine of 1.3 mg/dL. She required 18,200 mg of oral NaHCO₃ daily to maintain a normal serum HCO₃.

Multiple episodes of renal allograft rejection were treated with temporary increases in steroids and ALG, and serum creatinine stabilized at 2.2 mg/dL. Several bouts of CMV infection also complicated the patient's clinical course. She could not tolerate increasing doses of NaHCO₃. Despite stable renal function, she had repeated bouts of metabolic acidosis and dehydration. In February 1991, 64 months after transplant, enteric conversion was done to a loop of jejunum. Currently, she is normoglycemic and has discontinued oral NaHCO₃, 13 months after conversion, 77 months after transplant.

Patient 12

A woman diagnosed with diabetes in 1963 at age 5 had lost a previous pancreas transplant to rejection. A second BD cadaver pancreas transplant was done in January 1989. At discharge after the second transplant, she was normoglycemic, with an average urine amylase of 6010 U/hour and serum creatinine of 0.9 mg/dL. She required 10,400 mg oral NaHCO₃ daily to maintain a normal serum HCO₃.

An episode of pancreas allograft rejection in January 1990 was successfully treated with ALG. A concomitant CMV infection responded to ganciclovir. She was readmitted in July 1990 with pancreatic ascites, and a leak from the duodenal segment of the allograft was demonstrated by cystogram. Laparotomy showed extensive CMV ulceration and tissue loss of the allograft duodenum, which could not be repaired. A graft duodenectomy was done, with ligation of the pancreatic duct. Initially, she did well; however, pancreatic ascites and severe abdominal pain recurred. Computed tomography scan showed what was interpreted as a large pseudocyst adjacent to the head of the pancreas. In December 1990, a drain was placed operatively in the cyst, and the pain and pancreatic ascites resolved. Output from the drain remained high (500 to 1000 mL daily), however, with an average amylase of 90,000 U/L. In March 1991, the pancreas allograft was operatively explored. The main pancreatic duct was found to be wide open, with the previously placed ligature lying free in the peritoneal cavity. A Roux-en-Y limb then was constructed, and the pancreatic duct anastomosed to the Roux limb using mucosa-to-mucosa approximation over an 8-F tube stent, buttressed by sutures from the pancreatic capsule to the bowel serosa. Currently, she is normoglycemic 12 months after conversion, 30 months after transplant.

Patient 13

A woman diagnosed with diabetes in 1970 at age 8 had previously received a living related segmental pancreas transplant from her sister

in March 1986. The graft was enterically drained through a Roux-en-Y pancreaticojejunostomy, and functioned for more than 3 years. In 1989, the graft was rejected, and the patient resumed exogenous insulin. She received a BD cadaver whole pancreaticoduodenal graft in November 1989. At discharge, she was normoglycemic, with an average urine amylase of 5000 U/hour and serum creatinine of 1.4 mg/dL. She required 10,400 mg oral NaHCO₃ daily to maintain a normal serum HCO₃.

Two rejection episodes of the second pancreas allograft occurred, in January and May 1990; both reversed with ALG treatment. She was placed on a higher dose of cyclosporine after the second rejection episode, and had no subsequent rejection over the next year. Her serum creatinine rose progressively to 1.9 mg/dL, however, and an increasing dosage of oral NaHCO₃ to 13,000 mg daily was required to maintain a normal serum HCO₃. Her average urine amylase remained stable at 6000 U/hour.

Because of recurrent episodes of acidosis and dehydration, enteric conversion was done in March 1991, 16 months after transplant. In this case, the previously created Roux limb was disconnected from the rejected segmental graft, the distal end of the limb oversewn, and the duodenal segment of the allograft anastomosed to the Roux limb just distal to the closed end. Four days after operation, she developed abdominal pain and distention. At abdominal exploration, a perforation of the proximal allograft duodenal segment was discovered, at a point where it had been separated from an adhesion. No anastomotic leak was evident, and the perforation was repaired. A subsequent intra-abdominal *Candida albicans* abscess was drained successfully, under computed tomography guidance. She discontinued oral NaHCO₃, and is currently normoglycemic, 12 months after conversion, 28 months after transplant.

Patient 14

A man diagnosed with diabetes in 1965 at age 6 received a BD SPK transplant in March 1991. At discharge, he was normoglycemic, with an average urine amylase of 1060 U/hour and serum creatinine of 1.2 mg/dL. He required 5200 mg oral NaHCO₃ daily to maintain a normal serum HCO₃.

His course was complicated by multiple episodes of severe dysuria. Urine cultures initially grew *Candida albicans*, for which he received oral fluconazole therapy. Subsequent cultures were sterile, but he continued to have debilitating dysuria. In May 1991, 2 months after transplant, enteric conversion was done to a loop of jejunum. After operation, oral NaHCO₃ was discontinued and dysuria resolved. He is currently normoglycemic, 10 months after conversion, 12 months after transplant.

Patient 15

A man diagnosed with diabetes in 1966 at age 13 received a BD SPK transplant in July 1990. At discharge, he was normoglycemic, with an average urine amylase of 6000 U/hour and serum creatinine of 1.1 mg/dL. He required 10,400 mg oral NaHCO₃ daily to maintain a normal serum HCO₃.

Three months after transplant, a renal rejection episode was diagnosed by biopsy and successfully treated with ALG. His clinical course was complicated by severe dysuria, despite sterile urine cultures. A 1.5 × 0.05 cm ulcer on the inferior aspect of the glans penis developed. Biopsy of this lesion showed only chronic inflammation. In July 1991, 12 months after transplant, cystoscopy showed an erythematous urethra, especially in the membranous portion. Enteric conversion was done to a loop of jejunum. After operation, his periurethral ulcer healed and dysuria resolved. Currently, he is normoglycemic, 8 months after conversion, 21 months after transplant. He is the only patient in our series who had a periurethral ulcer.

Patient 16

A man diagnosed with diabetes in 1956 at age 9 had previously undergone a coronary artery bypass and cadaver renal transplant, both in 1981. Because of chronic rejection of the first kidney, with his creatinine elevated to 4.5 mg/dL, he received a BD SPK transplant in June 1988. At discharge, he was normoglycemic, with an average urine amylase of 1860 U/hour and serum creatinine of 1.5 mg/dL. He required 19,500 mg oral NaHCO₃ daily to maintain a normal serum HCO₃.

In September 1988, his serum creatinine increased to 1.9 mg/dL. Renal biopsy indicated rejection, which was treated successfully with ALG and a temporary increase in steroids. His course was complicated by multiple episodes of dysuria and *Klebsiella* UTIs, which were treated with intravenous antibiotics. Cystoscopy on several occasions showed staples at the duodenocystostomy site, and many of these foreign bodies were extracted. He also complained of perineal pain; a urology consultation resulted in the diagnosis of prostatitis. Furthermore, the patient was chronically constipated, with a megacolon presumably secondary to autonomic neuropathy, and required daily enemas. He also complained of postprandial right upper-quadrant pain and was found to have gallstones by ultrasound examination. Because of persistent dysuria combined with multiple episodes of UTIs, enteric conversion was done to a loop of jejunum in January 1992, 43 months after transplant. He also underwent simultaneous subtotal colectomy with ileocolostomy and cholecystectomy. Since the operation, he has discontinued oral NaHCO₃, and has had no infections or dysuria; his other symptoms have also resolved. Currently, he is normoglycemic, 3 months after conversion, 46 months after transplant.

Patient 17

A woman diagnosed with diabetes in 1970 at age 8 received a BD SPK transplant in July 1991. At discharge, she was normoglycemic, with an average urine amylase of 4050 U/hour and serum creatinine of 1.4 mg/dL. She required 7800 mg oral NaHCO₃ daily to maintain a normal serum HCO₃.

She was admitted three times for metabolic acidosis and dehydration, each time corrected by intravenous hydration and HCO₃ replacement. Although her serum creatinine remained at 1.2 mg/dL and her oral NaHCO₃ dosage was doubled to 15,600 mg daily, she continued to have difficulties with metabolic acidosis. In January 1992, 6 months after transplant, enteric conversion was done to a loop of jejunum. She had no further episodes of dehydration and metabolic acidosis, and has discontinued oral NaHCO₃. Currently, she is normoglycemic, 2 months after conversion, 8 months after transplant.

Results

In our series, 17 patients (nine men, eight women; all Caucasian) underwent conversion from BD to ED of exocrine secretions, eight to correct chronic metabolic acidosis and associated dehydration, seven because of severe debilitating dysuria (six men, one woman), one because of persistent graft pancreatitis thought to be due to back pressure from the bladder, and one to treat a fistula occurring after graft duodenectomy and failed duct ligation for CMV-associated duodenal perforation. Although the patients were classified by these reasons for conversion, the spectrum of symptoms and presentations were quite variable. We were more liberal in the enteric conversion procedure for SPK recipients from the same donor ($n = 12$), compared with pancreas transplantation alone ($n = 3$) or pancreas transplantation after a kidney transplant ($n = 2$) recipients. In the SPK group, we could still monitor for rejection of both renal and pancreas allografts by serial measurement of serum creatinine.

The outcome after conversion from BD to ED is summarized in Table 1. The need for oral NaHCO₃ to replace HCO₃ lost by the bladder was relieved in all eight patients in whom metabolic acidosis was the primary cause for enteric conversion. Of these eight, seven also had recurrent dehydration episodes requiring fluid resuscitation before conversion; none had dehydration episodes after the conversion.

Dysuria was relieved in all seven patients in whom dysuria was the principal indication for conversion. All seven were also able to discontinue oral NaHCO₃.

The other two patients' underlying conditions (recurrent pancreatitis, pancreatic fistula) also were corrected successfully by conversion.

Fifteen conversions were done to a proximal loop of jejunum, and two to a Roux limb. Surgical complications (Table 2) occurred in two patients (anastomotic leak with fistula after abscess drainage, nonanastomotic perforation of the allograft duodenum with abscess after repair), an incidence of 12%. Although we could not monitor graft exocrine function after conversion, only one of 17 pancreases has been lost to rejection (follow-up, 2 to 62 months), an incidence of 6%. The only loss occurred in an SPK transplant recipient, who rejected the kidney as well; it is likely she would have lost both allografts even without conversion.

Of five patients without a kidney from the same donor (three pancreas transplants alone, two pancreas transplants after a kidney transplant), none have lost their graft to rejection (follow-up, 8, 12, 12, 18, and 39 months). These five all had stable exocrine and endocrine function for at least 2 months before conversion and were 7 to 30 months after transplant. Thus, they were past the period when most pancreas rejections occur.¹⁶

The human duodenum is known to secrete about 750 $\mu\text{mol/hour}$ HCO₃ at a basal state, which is similar to the resting pancreatic output.¹⁷ During stimulation, the output is even higher. This secretion is probably important in helping to neutralize gastric acid delivered to the proximal duodenum. Ordinarily, the fluid and electrolytes secreted by the pancreas and duodenum are reabsorbed by the rest of the gut. After pancreaticoduodenal transplantation with exocrine drainage into the bladder, however, there is an obligatory loss of HCO₃ and electrolytes. In our experience, the amount of exocrine drainage secreted by a BD segmental pancreas graft has not been enough to present problems with fluids and electrolytes. With a whole pancreaticoduodenal graft, however, these losses

Discussion

TABLE 1. Outcome After Conversion Procedure

Reason for Conversion Patient No.	Transplant Type	Serum Creatinine Value (mg/dL) Before Conversion	Complication	Follow-up
Acidosis				
1	SPK	4.4	None	Functioning graft 62 mo
2	PTA	1.9	None	Died with functioning graft 8 mo
6	SPK	2.0	None	Functioning graft 25 mo
7	SPK	1.4	Pancreas allograft lost, rejection 6 mo	Retransplant, functioning graft 10 mo
8	SPK	2.1	None	Functioning graft 18 mo
11	SPK	2.2	None	Functioning graft 13 mo
13	PTA	1.9	Allograft duodenal leak	Functioning graft 12 mo
Dysuria				
17	SPK	1.2	None	Functioning graft 2 mo
3	SPK	1.3	None	Functioning graft 41 mo
4	PAK	1.4	None	Functioning graft 39 mo
5	SPK	1.5	None	Functioning graft 31 mo
9	SPK	1.1	None	Functioning graft 18 mo
14	SPK	1.2	None	Functioning graft 10 mo
15	SPK	1.2	None	Functioning graft 8 mo
16	SPK	1.5	None	Functioning graft 3 mo
Graft pancreatitis				
10	PAK	1.3	Allograft duodenal leak	Functioning graft 18 mo
Loss of allograft duodenum				
12	PTA	1.4	None	Functioning graft 12 mo

SPK, simultaneous pancreas–kidney; PTA, pancreas transplant alone; PAK, pancreas after kidney.

cannot always be offset by oral replacement. It is also our impression that metabolic acidosis due to HCO_3^- loss after pancreas transplantation is more frequent when a large length of graft duodenum is transplanted. In our clinical experience, we have not seen metabolic acidosis in recipients of BD segmental grafts without the duodenum ($n = 11$), nor in recipients of BD whole pancreas grafts in which only a small patch of duodenum is retained for anastomosis to the bladder ($n = 5$).

This concept is supported by a recent report by Schang et al.¹⁸ on the role of electrolyte loss through BD in a dog and rat allogeneic pancreas transplant model. All dogs receiving whole duodenum-to-bladder anastomoses died of metabolic acidosis and hyponatremia at a mean of 6

± 2 days after operation. Dogs receiving duct-to-bladder anastomoses survived 10 ± 1.7 days until the grafts were rejected. In the rat model, a similar lethal functional outcome was noted if whole duodenum-to-bladder anastomoses were done. This lethal outcome could be delayed with intravenous replacement of sodium chloride and HCO_3^- . Rats receiving duct-to-bladder anastomoses survived >100 days, suggesting that they were able to compensate for electrolyte loss from the pancreas allograft alone. Because whole pancreaticoduodenal segments were poorly tolerated, the study concluded that the duodenal segment compounds metabolic wasting to such an extent that it could not be compensated for by the animals. The authors suggested that, in a clinical setting, the duodenal

TABLE 2. Complications After Conversion Procedure

	Patient No.	Transplant Type	Complication	Follow-up
Early (<1 mo) 2/17 (12%)	10	PAK	Enterocutaneous fistula	Closed spontaneously with total parenteral nutrition and bowel rest
	13	PTA	Enterotomy	Closed surgically
Late (>1 mo) 2/17 (12%)	2	PTA	Analgesic overdose	Death with functioning graft
	7	SPK	Loss of both pancreas and renal allografts to chronic rejection	Second SPK transplant; patient is insulin-independent and normoglycemic at 10 mo

PAK, pancreas after kidney; PTA, pancreas transplant alone; SPK, simultaneous pancreas–kidney transplant.

portion used for BD after pancreas transplantation should be kept as short as possible, to minimize the additional loss of HCO_3 from the allograft.

We also noted that patients who had difficulty controlling metabolic acidosis despite oral NaHCO_3 tended to have impaired renal function, with a mean serum creatinine before conversion of 2.14 ± 0.98 mg/dL. Most patients are able to compensate for HCO_3 loss through oral NaHCO_3 replacement, and through a renal mechanism that increases hydrogen ion secretion and conserves HCO_3 . If kidney function is impaired, by diabetic nephropathy, cyclosporine toxicity, or allograft rejection, the ability to compensate may be limited, and oral NaHCO_3 replacement may be inadequate. Indeed, many patients find ingestion of large amounts of NaHCO_3 difficult, although there is great variation in patients' tolerance to taking larger numbers of pills. Unmatched loss of HCO_3 results in metabolic acidosis, dehydration, hyponatremia, and hypokalemia, which may be life-threatening. Dehydration was also a recurrent theme in our patients. The average combined volume of secretions from a native pancreas and duodenum is estimated at 1500 to 3000 mL daily. Although this obligatory loss can be partially compensated for by increased fluid intake and conservation by a normal kidney, this was not the case in some of our patients in whom renal function was frequently diminished and fluid intake inadequate.

Activation of pancreatic enzymes resulting in urinary mucosal damage is a potentially serious complication of BD. In our series, however, only one patient was found to have gross anatomic changes that were consistent with enzymatic digestion. Therefore, this difficulty seems to be largely a symptomatic problem. Again, there is great variation in patients' tolerance to this irritation. We have not seen a case with urethritis as severe as the one described by Tom et al.¹² Their patient developed severe urethritis concomitant with inflammation of the glans penis after pancreaticoduodenal allotransplantation with BD. A urine sample from this patient showed elevated trypsin and chymotrypsin activity, in contrast to samples from three other pancreas transplant recipients without dysuria. In this case, the first to describe conversion from BD to ED, dysuria and urethritis were completely corrected by the conversion procedure. The clinical presentation of our pancreas transplant recipients with dysuria was less dramatic, yet clearly interfering with their day-to-day activities. Similarly, we found that all our patients with dysuria and perineal pain experienced symptomatic relief once converted to ED. Two patients consulted urologists, who diagnosed prostatitis; but this diagnosis may have been incorrect, because the symptoms resolved with conversion to ED. Even if prostatitis were a part of the syndrome, it is secondary to the effect of pancreas transplant secretions on the urinary tract, and in this setting, conversion from

BD to ED is the indicated treatment. Interestingly, in most of our patients, gross inflammation of the urinary tract could not be detected by external inspection or by cystoscopy. We had only one case of a periurethral ulceration of the glans penis similar to the case reported by Tom et al.¹² This ulceration resolved after enteric conversion.

One patient in our series (patient 10) was converted to ED because of possible recurrent graft pancreatitis. The pancreatitis could have been chemically induced by reflux of urine through an incompetent sphincter of Oddi into the pancreatic duct during micturition. Alternatively, stagnation of exocrine secretions in the pancreatic duct from the pressure in a chronically distended, neurogenic bladder could have been responsible. In any event, after the conversion, the episodes of allograft pancreatitis resolved.

The main drawback to conversion from BD to ED is loss of ability to monitor for early diagnosis of rejection episodes. For recipients of a pancreas transplant alone or after a kidney transplant, disconnection from the urinary tract means that rejection episodes will be diagnosed only when hyperglycemia occurs, decreasing the likelihood that treatment will be successful. For recipients of a simultaneous kidney from the same donor as the pancreas (the situation for 12 of our patients), however, monitoring for rejection before onset of hyperglycemia is still possible, because the serum creatinine will rise as a manifestation of kidney rejection before hyperglycemia occurs as an indicator of pancreas rejection. Only one of our 12 SPK recipients who converted from BD to ED lost pancreas allograft function to chronic rejection, 6 months after conversion. Her kidney allograft function also deteriorated rapidly, with biopsy evidence of chronic rejection. She has subsequently received another SPK transplant with BD of the pancreas allograft, and continues to be normoglycemic.

Recently, Elkhammas et al.¹⁹ discussed the use of acetazolamide in cases of intractable metabolic acidosis after pancreas transplantation. In their experience, four recipients of combined pancreas and kidney allografts with persistent metabolic acidosis, despite 2900 to 6000 mg oral NaHCO_3 daily, were treated with acetazolamide at a dosage of 250 mg twice daily. Increases in serum HCO_3 of 34%, 40%, and 50% were observed, with no deterioration of pancreas and kidney function. They did not report on any conversions in their series, having only short-term follow-up.

In converting exocrine drainage from the bladder to the bowel, Tom et al.¹² used a Roux-en-Y loop of recipient jejunum to anastomose to the graft duodenum. We avoided construction of a Roux loop when possible, to minimize the number of small bowel anastomoses required. In 15 cases, we divided the duodenocystostomy, closed the bladder in multiple layers, and anastomosed

the opening in the graft duodenum to the most convenient proximal loop of recipient jejunum (Fig. 2). One patient had a previous Roux loop created at an earlier operative procedure, which was available for use without the need for an additional anastomosis. Another patient underwent construction of a Roux loop, then pancreatic duct-to-jejunum anastomosis due to loss of the allograft duodenum. The Roux was created in this case because of the risk of a leak from a pancreatic duct-to-bowel anastomosis, the consequences of which would be less with a Roux.

Two early surgical complications occurred, the first in the group of 15 patients converted to a simple loop, and the second in the group of two patients converted to a Roux limb. The first patient presumably had a small leak from the duodenoenterostomy, which we were unable to detect after exploratory laparotomy, but which closed spontaneously with external drainage. The other patient had an iatrogenic perforation of the allograft duodenum at the site of enterolysis, which was easily repaired when diagnosed at reoperation.

Thus, we believe that simple conversion from a duodenocystostomy to a duodenoenterostomy without cre-

ation of a Roux-en-Y limb of recipient bowel is the procedure of choice. By performing a simple conversion, only one enteroenterostomy is needed. In contrast, the Roux procedure requires several small bowel anastomoses. Creation of a Roux-en-Y limb offers no advantages under most circumstances, and the risk of infection with a simple side-to-side duodenoenterostomy appears low.

In summary, either metabolic acidosis secondary to HCO_3^- loss from the graft exocrine and duodenal secretions, or dysuria and urethritis from pancreas graft exocrine enzymes, led us to divert exocrine secretion drainage from the bladder to bowel in 15 of 17 cases after pancreaticoduodenal transplantation. Of the remaining two conversions, one was performed to alleviate possible reflux allograft pancreatitis, and the other to re-establish internal drainage after removal of the duodenal portion of the allograft undergoing necrosis in association with CMV infection. All patients were relieved of their symptoms and discontinued oral NaHCO_3 . Patients with some element of renal dysfunction may be more prone to intractable acidosis, necessitating conversion to ED at a later date. There were two early complications of the conversion surgery in our series, both leaks from the allograft duodenum, and only one pancreas allograft was lost to chronic rejection. We have used this procedure only in the patients who had the most severe symptoms of dysuria or metabolic acidosis, but our favorable experience with conversion suggests that wider application may be indicated. Indeed, in SPK transplant recipients, the rationale for BD is questionable, because they can be monitored for rejection by measurement of serum creatinine.

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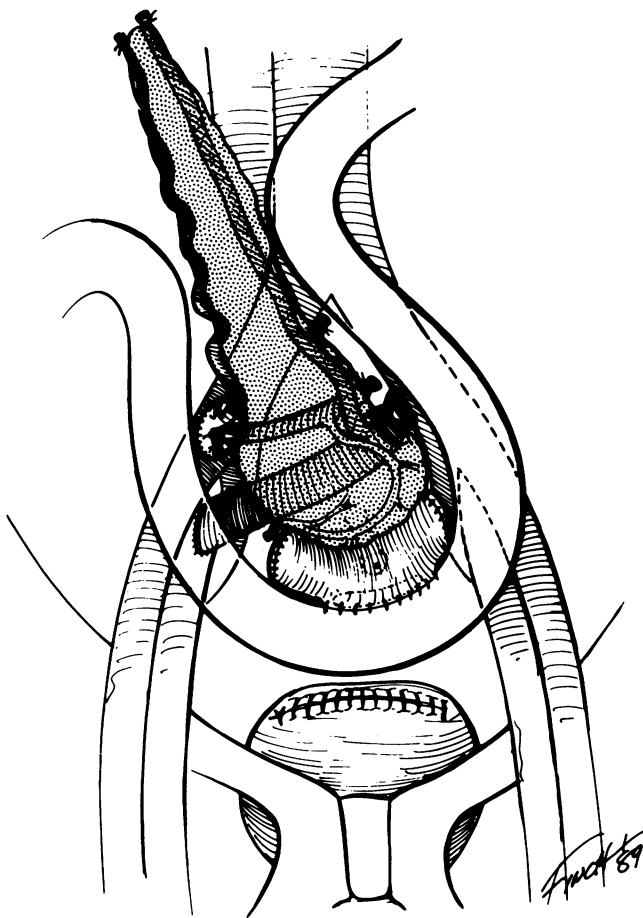


FIG. 2. Method for converting exocrine drainage from bladder to bowel for whole pancreaticoduodenal allografts.

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