In the United States, diabetes mellitus is the third most common disease and fourth leading cause of death from disease. Diabetes is the leading cause of blindness, the number one cause of amputations and impotence, and one of the most frequently occurring chronic childhood diseases. Diabetes is also the leading cause of end-stage renal disease in the United States, with a prevalence rate of 31% compared with other renal diseases. Diabetes is also the most frequent indication for kidney transplantation, accounting for 22% of all transplantation operations.

Increasingly, pancreas transplantation is being offered to patients who would benefit from kidney transplantation (called simultaneous pancreas-kidney transplantation) or who have had a previously successful kidney transplantation (called sequential pancreas after kidney transplantation). Relatively few transplantation centers are performing pancreas transplantation alone in patients with severe life-threatening complications of diabetes. Pancreas transplantation has been criticized because of the increased morbidity associated with the procedure and lack of controlled trials demonstrating significant benefit to the secondary complications of diabetes. However, many of these criticisms have been overcome with improvement in surgical techniques and pancreas transplantation preservation and with more potent immunosuppressive regimens. The relative frequency of pancreas transplantation, common surgical procedures, and outcomes of patients undergoing pancreas transplantation are discussed.
Transplantation as Treatment of End-Stage Renal Disease

**FIGURE 15-1**
Disease prevalence resulting in end-stage renal disease (ESRD) from the United States Renal Data Service (1993 to 1995). In the continental United States at the end of 1995, 257,266 patients had ESRD. Diabetes mellitus (DM) accounts for nearly one third of all patients newly diagnosed with ESRD who require kidney transplantation. GN—glomerulonephritis; HTN—hypertensive nephropathy; PCKD—polycystic kidney disease.

**FIGURE 15-2**
Kidney transplantations by diagnosis (October 1987 through December 1994). Approximately 10,000 patients receive kidney transplantations in a given year. Of the primary renal diseases requiring transplantation, diabetes accounted for 22% of all kidney transplantations performed in the United States. GN—glomerulonephritis; HTN—hypertensive nephropathy; PCKD—polycystic kidney disease.

**FIGURE 15-3**
Pancreas transplantations per year. The number of pancreas transplantations performed per year in the United States has been increasing. In 1995 and 1996, over 1000 pancreas transplantations were performed in the United States. A smaller number were performed outside of the United States.
Relative proportion of simultaneous pancreas-kidney (SPK) transplantations versus cadaveric kidney transplantations in the United States. Despite an increasing number of SPK transplantations over the past 7 years, pancreas transplantation is a less common procedure than is cadaveric kidney transplantation alone.

**FIGURE 15-5**
The inclusion criteria for pancreas transplantation are relatively few. Patients usually have type I diabetes mellitus and must have the physical stamina to undergo a major abdominal operation. The patient’s age is important, with 60 years of age usually being the cutoff. In some transplantation centers, the cutoff age is 50 years. The patient should demonstrate emotional and psychological stability, and significant secondary complications of diabetes must be present. Because Medicare does not pay for pancreas transplantations, recipients must use either private insurance or personal funds.

**FIGURE 15-6**
The exclusion criteria for pancreas transplantation include significant cardiac disease, substance abuse, psychiatric illness, and a history of noncompliance. Extreme obesity, active infection, and malignancy are relative contraindications to transplantation. Patients with few or very mild secondary complications of diabetes may be candidates for kidney transplantation alone.

**FIGURE 15-7**
Types of pancreas transplantation procedures and relative frequency per year (January 1988 through December 1996). Three different indications for pancreas transplantation exist. Patients with type I insulin-dependent diabetes who require kidney transplantation may undergo a simultaneous pancreas-kidney (SPK) transplantation or receive a kidney transplantation followed by a pancreas transplantation during a separate operation (called pancreas after kidney [PAK] transplantation). Patients without significant renal disease may undergo pancreas transplantation alone (PTA). The relative proportion of the types of transplantations is shown. Most pancreas transplantations performed in the United States are of the SPK type, followed by PAK transplantations. Presently, few PTA transplantations are performed.
Transplantation as Treatment of End-Stage Renal Disease

15.4

Transplantation Operation

Simultaneous pancreas-kidney allograft procedure. Most pancreas transplantations performed in the United States are whole organ pancreaticoduodenal allografts from cadaveric donors transplanted simultaneously with the kidney from the same donor [1]. Because the pancreas from a patient with diabetes still subserves digestive function, it is not removed. Therefore, the pancreaticoduodenal allograft is transplanted to an ectopic location, usually the right iliac fossa. Similarly, the kidney allograft is transplanted ectopically to the contralateral iliac fossa. The reconstructed arterial supply to the pancreas, as shown in Figure 15-9, is anastomosed to the common or external iliac artery. The portal vein of the allograft is anastomosed to the common iliac vein or distal inferior vena cava. Likewise, on the left side the renal artery and vein are anastomosed to the common iliac artery and vein, respectively. To restore the continuity of the urinary tract, a standard ureteroneocystostomy is constructed to the dome of the bladder.

Because the pancreas has dual endocrine and exocrine functions, it is necessary to perform another anastomosis to handle exocrine secretions. A variety of techniques to manage pancreatic exocrine secretions have been proffered over the years with less than satisfactory results. These include duct occlusion, open drainage into the peritoneal cavity, and creation of a button of duodenum and anastomosing this or the pancreatic duct directly to the bladder. Currently, the most commonly performed technique in the United States is drainage of pancreatic exocrine secretions into the bladder (bladder drainage, BD), as depicted [1]. The BD technique involves fashioning a short segment of donor duodenum, which is transplanted along with the pancreas. Then the donor duodenum is anastomosed to the dome of the recipient bladder in a side-to-side manner. In this way exocrine secretions, including enzymes, proenzymes, water, and sodium bicarbonate, are diverted into the urinary tract. This technique is safe, reliable, and well tolerated; however, it is associated with a number of specific urinary tract complications.

As a consequence of implantation into the iliac fossa, the pancreatic allograft is drained into the systemic venous circulation, as depicted. This results in systemic venous, rather than portal venous, insulin release and peripheral hyperinsulinemia. An alternative approach practiced by some surgeons is portal venous drainage. In this approach the portal vein of the allograft is anastomosed to the superior mesenteric vein of the recipient in an end-to-side fashion. This technique establishes drainage of insulin into the portal venous blood flow, perhaps a more physiologic situation (procedure not shown). The results of the two techniques are largely comparable. Fortunately, patients have suffered no adverse effects of systemic venous drainage and hyperinsulinemia.

Solitary pancreaticoduodenal allografts are implanted into either iliac fossa, at whichever point the iliac vessels permit vascular anastomoses. This procedure is done, usually and preferentially, on the right side. Otherwise, the operative sequence duplicates that of the combined procedure.
Kidney-Pancreas Transplantation

Ligated splenic A and V

Iliac "Y" graft

Ligated SMA and SMV

Ligated CBD

**FIGURE 15-9**

Preparation of the pancreaticoduodenal allograft and arterial reconstruction. The donor pancreas, duodenum, and spleen are perfused in situ with cold University of Wisconsin solution and harvested en bloc with the liver. The pancreaticoduodenal graft is separated from the liver graft and prepared on the surgical back table at 4°C. The spleen is first removed by ligating the splenic artery and vein. The duodenal segment is shortened to approximately 10 cm, and the suture lines are reinforced. The common bile duct (CBD) and the superior mesenteric artery and vein (SMA and SMV) have been ligated previously in the donor. A variety of techniques exist to reconstruct the dual arterial blood supply to the pancreas. In our experience, the most favorable approach entails using an iliac artery bifurcation graft harvested from the same donor. As shown, the external iliac arterial limb of the graft is anastomosed to the SMA, and the hypogastric arterial limb is anastomosed to the splenic artery. This technique is reliable and associated with a very low thrombosis rate. The venous anastomosis (portal vein to iliac vein or inferior vena cava) can be performed without tension by complete mobilization of both the donor portal vein and the recipient iliac vein. A venous extension graft is rarely necessary and probably increases the risk of thrombosis.

**FIGURE 15-10**

Enteric drainage (ED) technique. An alternative approach to bladder drainage, ED is, perhaps, a more physiologic method of handling pancreatic exocrine secretions. ED is the preferred method in Europe and is rapidly gaining popularity in the United States [1]. Most commonly, it is performed as depicted without a Roux-en-Y anastomosis. The donor duodenal segment is anastomosed in a side-to-side fashion to the ileum or distal jejunum. Long-term graft survival, thrombosis rates, and primary nonfunction rates are no different when comparing the two techniques [1–3]. Performed with expertise, both techniques should yield excellent results. Several significant advantages of the ED technique over bladder drainage make ED our technique of choice.
## COMPARISON OF BLADDER DRAINAGE VERSUS ENTERIC DRAINAGE TECHNIQUES

<table>
<thead>
<tr>
<th>Bladder drainage (BD)</th>
<th>Enteric drainage (ED)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>Ability to monitor urinary amylase levels as an indicator of rejection [6]</td>
<td>No need for enteric conversion in up to 25% of patients who have urologic complications</td>
</tr>
<tr>
<td>Decreased risk of perioperative intra-abdominal infections</td>
<td>Less metabolic acidosis and chronic dehydration [3]</td>
</tr>
<tr>
<td></td>
<td>Shorter length of hospital stay secondary to less dehydration</td>
</tr>
<tr>
<td></td>
<td>Early removal of urinary catheter and fewer UTIs</td>
</tr>
<tr>
<td></td>
<td>Ability to perform portal venous drainage, if desired</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>Risks of developing urologic complications in up to 25% of patients, including urethritis, urethral disruption, and hematuria</td>
<td>Increased risks of perioperative peripancreatic infections</td>
</tr>
<tr>
<td>Risk of recurrent UTIs greater for BD than for ED [3]</td>
<td>Difficult to diagnose pancreatic enzyme leaks</td>
</tr>
<tr>
<td>Prolonged urinary catheter drainage needed to decompress bladder anastomosis for healing</td>
<td></td>
</tr>
<tr>
<td>Frequent postoperative admissions for dehydration and metabolic acidosis and need for bicarbonate replacement</td>
<td></td>
</tr>
</tbody>
</table>

UTIs—urinary tract infections.

**FIGURE 15-11**

Early attempts using enteric drainage (ED) techniques resulted in prohibitively high rates of intra-abdominal abscesses, wound infections, and mycotic aneurysms threatening both graft and patient. Thereafter, bladder drainage (BD) via a duodenocystostomy evolved in the United States as the safest and most frequently performed exocrine drainage procedure. It has been suggested that BD affords the ability to monitor urinary amylase levels as an indicator of rejection, which may be useful in the setting of a solitary pancreas transplant. However, in recipients of simultaneous pancreas-kidney (SPK) transplant in whom kidney function serves as a marker of rejection monitoring of urinary amylase levels is not necessary to achieve excellent long-term graft survival.

As experience grew with BD, however, it was found that up to 25% of patients with BD developed a significant urologic or metabolic complication requiring surgical conversion of exocrine secretions to ED [4,5]. Renewed interest in primary ED has resulted. Several recent retrospective studies have compared BD pancreas transplants to ED transplants. These studies have demonstrated equivalent short-term graft survival rates without increased risks of infectious complications and pancreatic enzyme leaks [1–3]. ED is associated with fewer urinary tract infections (UTIs) and no hematuria. Patients who have ED experience less dehydration and metabolic acidosis and, as a result, a reduced need for fluid resuscitation and bicarbonate supplementation [3]. Finally, in patients who have ED the Foley catheter can be removed within several days, whereas patients who have BD require prolonged drainage (up to 14 days) to permit healing of the duodenocystostomy. Consequently, with ED, patients are able to leave the hospital sooner. ED has proved to be more physiologic and results in less morbidity compared with BD. Therefore, ED is rapidly gaining popularity as the method of choice for handling graft exocrine secretions in pancreas transplantation.
# Immunosuppression and Monitoring

## Immunosuppressive Protocols

<table>
<thead>
<tr>
<th>SPK</th>
<th>PAK and PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATGAM (20 mg/kg/d for 10 d)</td>
<td>ATGAM (20 mg/kg/d for 10 d) or OKT3 (5-10 mg/kg/d for 10 d)</td>
</tr>
<tr>
<td>MMF (3 g/d)</td>
<td>MMF (2 g/d)</td>
</tr>
<tr>
<td>Neoral® (8 mg/kg/d)</td>
<td>FK506 (8 mg/d)</td>
</tr>
<tr>
<td>Prednisone (500 mg intraoperatively; 250 mg on postoperative days 1 and 2; 30 mg/d thereafter)</td>
<td>Prednisone (500 mg intraoperatively; 250 mg on postoperative days 1 and 2; 30 mg/d thereafter)</td>
</tr>
</tbody>
</table>

ATGAM — antithymocyte globulin, polyclonal serum; FK506— tacrolimus, Prograf (Fujisawa USA, Inc., Deerfield, IL); MMF— mycophenolate mofetil, RS-61443, CellCept (Roche Laboratories, Nutley, NJ); OKT3— muromonab, murine antihuman CD3 monoclonal antibody; PAK— pancreas after kidney transplantation; PTA— pancreas transplantation alone; SPK— simultaneous pancreas-kidney transplantation.

**FIGURE 15-12**

Because the best treatment of rejection is prevention, the most efficacious regimen of immunosuppressive drugs should be used first. Quadruple-drug immunosuppressive regimens, including the use of antithymocyte globulin (ATGAM) or OKT3, have been accepted as standard at most pancreas transplant centers. Recent data from the United Network for Organ Sharing and several smaller retrospective comparative trials provide evidence that anti–T-cell antibody induction therapy may lessen the severity and delay the onset of rejection and may improve short-term graft survival in recipients of simultaneous pancreas-kidney (SPK) transplants [1,7,8]. This is the current practice. The development of newer, more specific immunosuppressive agents, however, has changed the face of modern immunosuppression in solid organ transplantation and raises the possibility of successful pancreas transplantation without induction therapy. Mycophenolate mofetil (MMF) has recently replaced azathioprine (AZA) as maintenance immunosuppressive therapy in kidney transplantation alone, SPK, and pancreas transplantation alone. MMF is a potent noncompetitive reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). IMPDH is an essential enzyme in the de novo purine synthetic pathway upon which lymphocyte DNA synthesis and proliferation are strictly dependent. Compared with AZA, MMF has no association with pancreatitis and has less association with leukopenia. Moreover, whereas AZA is not useful in treating ongoing rejection, MMF can salvage refractory acute renal allograft rejection in up to half of patients. By virtue of this mechanism of action, MMF provides more effective and specific immunosuppression with less risk compared with AZA.

Similarly, Neoral, a microemulsified formulation of cyclosporine (CsA) has replaced standard CsA therapy with Sandimmune (both drugs from Sandoz Pharmaceuticals, East Hanover, N J). Because of gastroparesis and autonomic dysfunction, patients with diabetes exhibit unpredictable absorption of CsA. The new formulation of CsA has an increased rate and extent of drug absorption with lower inter- and intra-individual pharmacokinetic variability than does Sandimmune, particularly in patients with diabetes. Improved bioavailability and more reliable pharmacokinetics may translate into fewer rejection episodes and improved graft survival. Experience with tacrolimus (FK506) in pancreas transplantation for induction, maintenance, and rescue therapy has demonstrated that it is safe, well tolerated, and has a low risk of glucose intolerance. Moreover, particularly for solitary pancreas transplants, strikingly improved short-term graft survival results have been reported [9,10]. The mechanism of action of FK506 as a calcineurin inhibitor is similar to that of CsA. FK506 has a better side-effect profile compared with CsA, causing less hirsutism, less hyperlipidemia, but somewhat more neurotoxicity. Unlike CsA, FK506 can rescue patients with refractory rejection and treat ongoing rejection. One caveat when using FK506 in combination with MMF is the risk of over-immunosuppression. Several studies have highlighted the fact that FK506 may increase blood levels of the active metabolite of MMF, mycophenolic acid, in a clinically relevant manner [11]. By reducing the incidence of rejection, these modern immunosuppressants have resulted in improved short- and long-term graft survival. Fewer rejection episodes will likely translate into an overall reduction in the glucocorticoid dosage being given in the perioperative period. This reduction may favorably impact short-term infectious complications and long-term steroid-related adverse side effects.
Pancreas transplantation biopsy. Pancreas allograft biopsy is the gold standard for evaluating pancreas allograft dysfunction and for diagnosing acute rejection. In a pancreas transplantation recipient, indications for the need of a biopsy to rule out rejection include elevated amylase or lipase levels, unexplained fever, and glucose intolerance. In patients with simultaneous pancreas-kidney (SPK) transplantation, pancreas rejection most commonly (about 90%) occurs simultaneously with kidney rejection. As a result, a diagnosis of rejection relies almost entirely on serum creatinine, \( \beta_2 \)-microglobulin, and renal allograft biopsy. However, in the setting of sequential pancreas after kidney transplantation or pancreas transplantation alone (PTA) in which isolated pancreas rejection occurs, predicting rejection with a serologic or urinary marker is more difficult. To date, no marker has been identified that can predict rejection accurately enough to warrant treatment without first performing a biopsy. Thus, the ability to perform pancreas allograft biopsy is essential in the postoperative care of recipients of PTA. In addition to a biopsy, radiologic evaluation of the allograft with ultrasonography (to evaluate vascular flow) and computed tomography (CT) scan (to rule out pancreatic enzyme leaks and fluid collections) are complementary studies that deserve consideration for all episodes of allograft dysfunction.

Percutaneous core biopsies of the pancreas allograft with real-time ultrasonography or CT guidance have been shown to be safe and reliable [12–14]. A and B, After the gland is assessed for vascular patency an appropriate portion of the pancreas is identified that is free of major vessels and overlying viscera (usually the body or tail). C, A 20-gauge automated biopsy needle is advanced into the pancreas graft under real-time ultrasonography, and a biopsy is obtained. In pancreaticoduodenal grafts with bladder drainage (BD) a cystoscopic transduodenal biopsy offers the opportunity to obtain biopsy specimens from both the pancreas and duodenum. Success rates for obtaining tissue for pathologic review in both techniques are 85% to 95%. Firm adherence of the pancreas to surrounding structures and use of real-time ultrasonography reduce the risks of complications related to biopsy. Overall, complications occur in 5% to 10% of patients, which can include bleeding, pancreatic duct leak, hematuria (in BD pancreas transplants), and asymptomatic transient hyperamylasemia. Rarely does a complication require a repeat operation or result in graft loss.
Management of Complications

A approach that balances aggressive immunosuppression against risks of infection. A diagnosis of rejection is dependent on biopsy of either the kidney or pancreas allograft in recipients of SPK transplantation or of the pancreas allograft in pancreas transplantation alone. Because of the double-edged sword of aggressive antirejection treatment, an episode of graft dysfunction should not be treated without biopsy-proven histopathologic evidence of immunologic graft injury. Ruling out infectious and anatomic causes of graft dysfunction with appropriate radiologic studies is equally important. Drachenberg and coworkers [15] and Nakhleh and Sutherland [16] have defined histologic criteria for grading pancreas allograft rejection that are practical from the standpoint of being able to prognosticate outcome and response to therapy. Serial histologic studies of pancreas rejection (as in this case) have shown that lymphocytic infiltrates initially involve the exocrine portion of the gland and that islet cell tissue becomes involved later [12]. As a result, exocrine dysfunction is frequently the first clinical sign of rejection (manifested by either elevated serum amylase or decreased urinary amylase levels). Consequently, early rejections without evidence of islet cell involvement usually can be treated successfully. On the contrary, the success of antirejection treatment is far less successful when initiated after the development of hyperglycemia [17].

A, Normal pancreas allograft core biopsy demonstrating an acinar lobule and preserved individual islet of Langerhans without inflammatory infiltrate (magnification × 200). B, Needle core biopsy demonstrating glandular architecture with fibrous septae interdigitating between acinar lobules. An infiltrate is present that can be described as mononuclear, predominantly lymphocytic, perivascular, and septal. Endothelialitis is seen in a medium-sized vein at the upper central edge of the biopsy specimen. These features are consistent with mild acute cellular rejection (magnification × 200). C, Needle core biopsy demonstrating intense septal inflammation with activated lymphocytes. Early acinar inflammation is present in the right upper lobule. Eosinophils also are present in the dense septal infiltrate. These findings also are consistent with mild acute cellular rejection (magnification × 200). Moderate rejection is characterized by significant acinar inflammation and arteritis. Severe rejection is suggested when, in addition to the features listed above, confluent acinar necrosis with extensive acinar inflammation and ductal epithelial necrosis are present.

Features indicating a poor prognosis include arteritis, confluent acinar necrosis, islet inflammation and necrosis, ductal epithelial necrosis, and fibrosis. Mild acute rejection usually is reversible with bolus corticosteroid therapy. In contrast to renal allograft rejections, however, most mild pancreas allograft rejections are somewhat recalcitrant to bolus steroid immunotherapy. Steroids may worsen potentially compromised glycemic control, thus complicating treatment. Therefore, significant rejection of the pancreas allograft may be best treated with antibody therapy, although a randomized control trial comparing the two treatment options has not been carried out. FK506 is commonly employed as rescue therapy in pancreas transplant episode recipients who are experiencing a significant acute rejection episode while on cyclosporine or Neoral (Sandoz Pharmaceuticals, East Hanover, NJ). Irreversible allograft rejection was a frequent occurrence several years ago. Today, it is unusual, occurring in less than 5% of patients.
Indications for enteric conversion (EC). A set of complications unique to pancreas transplantation arise as a consequence of urinary diversion of graft exocrine secretions. The development of one of these complications is the most frequent cause for re-admission to the hospital after pancreas transplantation with BD. These include the following: persistent gross hematuria, recurrent or chronic urinary tract infections (UTIs), urethritis, urethral stricture or disruption, urinary or pancreatic enzyme leak, graft (reflux) pancreatitis, and excessive bicarbonate loss and acidosis [18]. Surgical conversion to ED is indicated when these complications are incapacitating or refractory to conservative therapy. Except for leaks and pancreatitis, these complications are largely avoided in ED pancreas grafts.

Hematuria in the immediate postoperative period is usually mild and self-limited, occasionally requiring irrigation, cystoscopic fulguration, or both. Hematuria occurring late after transplantation (ie, months to years) may be caused by UTIs, suture granulomas, bladder stones, or ulceration of the duodenal segment. In total, hematuria occurs in 17% of patients. Conversion to ED is indicated when hematuria persists despite appropriate therapy and is required in up to a third of patients who present with late or chronic hematuria.

Pancreatic enzyme or urinary leaks also can occur in the early postoperative period or as late as several years after transplantation. Early leaks usually occur at the bladder-duodenum suture line, whereas late leaks occur most commonly at the lateral duodenal staple line or at the location of a duodenal ulcer. The cause is unclear. Whereas some early leaks may be technically related, late leaks are more likely a result of rejection, cytomegalovirus infection, ischemia, or a combination of all these. Patients usually present with sudden-onset lower abdominal pain, fever, leukocytosis, increased serum amylase and slightly increased creatinine. Diagnosis is confirmed by cystogram (see Fig. 15-17). Fortunately this complication is unusual, occurring in 10% to 15% of patients.

The most common infectious complication after pancreas transplantation is UTI, occurring in 63% of pancreas transplant recipients with BD. These recipients may be more predisposed to UTIs than are kidney transplant recipients because of the additive effect of several factors. These factors include alkalinization of the urine secondary to bicarbonate exocrine secretion, presence of a diabetic neurogenic bladder with incomplete emptying, mucosal injury at the bladder anastomosis, and prolonged catheter drainage. Occasionally, a cause for therapy-resistant or recurrent infections is found on cystoscopy and study of the upper tracts also is indicated. When no source is found, EC is indicated.

If persistent, urethritis may result in urethral stricture, disruption, or both. Although its exact cause is unclear, urethritis is most likely caused by the digestive action of pancreatic enzymes on the urothelium. Urethritis usually is manifested as perineal pain and discomfort during urination and seems to occur almost exclusively in males. Initially, conservative treatment with Foley catheter drainage for several weeks is recommended. When perforation occurs, it usually is in the membranous portion of the urethra and presents with perineal and testicular swelling. To avoid complications of urethral stricture and disruption, early enteric conversion is recommended when urethritis fails to respond to an initial short course of conservative treatment. Fortunately, these complications are unusual, occurring in only 5% of simultaneous pancreas-kidney (SPK) transplantation recipients.

Early postoperative hyperamylasemia, thought to be caused by preservation injury, is not uncommon and, fortunately, usually is asymptomatic and improves rapidly. Persistent or marked elevations of amylase indicate possible technical errors, including ductal ligation or leak. Graft pancreatitis (sometimes referred to as reflux pancreatitis) presents in a manner similar to that of a leak. Graft pancreatitis is further defined by absence of a leak on radiologic study; evidence of gland edema on CT scan, without evidence of abscess or fluid collections; and; most important, resolution of symptoms within 48 hours of Foley catheter drainage. Treatment with Foley catheter drainage for several days is usually successful. When an infection is found in the patient’s urine at this time, appropriate parenteral antibiotics may be beneficial.

Metabolic acidosis is present postoperatively in about 80% of patients after pancreas transplantation with BD and usually is due to excessive urinary loss of bicarbonate-containing exocrine fluids. Because urinary bicarbonate loss is accompanied by an obligate loss of fluid, low serum levels are associated with dehydration. Oral fluid replacement should be instituted to maintain a serum bicarbonate level of at least 20 to 25 mg/dL, and dehydration is treated appropriately. Fortunately, this problem usually stabilizes over time and infrequently requires conversion from bladder to enteric drainage.
Incidence and procedure in enteric conversion (EC). A, Surgical conversion of pancreatic exocrine secretions from bladder drainage to enteric drainage is necessary in many patients. Whereas half of patients receive EC within the first postoperative year, a significant percentage must undergo EC up to 5 years after transplantation. B, EC involves taking down the duodenocystostomy, repairing the bladder, and performing a simple side-to-side duodenoenterostomy. In our experience of performing 95 ECs over a 14-year period in 480 simultaneous pancreas-kidney (SPK) transplant recipients, only one graft was lost within 3 months of EC [5]. No differences were found in patient, kidney, or pancreas graft survival when comparing SPK transplant recipients who underwent EC with those who did not. The frequency of urologic complications and need for EC have prompted a changing trend toward performing primary enteric drainage; however, neither of these problems appears to impact negatively on graft survival.

Pancreatic enzyme and urinary leaks. A leak of urine, activated pancreatic enzymes, or both, is one of the most devastating and life-threatening infectious complications after pancreas transplantation. Patients exhibit sudden-onset lower abdominal pain, fever, leukocytosis, increased serum amylase levels, and increased serum creatinine levels. Diagnosis is confirmed by cystogram. When no leak is identified, voiding cystourethrography (VCUG) with gastrografin (panel A) or a VCUG using technetium (Tc99m) in normal saline is performed (panels B–E). (Continued on next page)
In our opinion, a $^{99m}$Tc-VCUG is the most sensitive test, because extravasation may occur only during the high-pressure phase of voiding [19]. B, This gastrograffin-VCUG demonstrates duodenal segment and anastomosis in the region of the dome of the bladder in an oblique anteroposterior projection. A leak of contrast is identified at the lateral duodenal segment staple line. B and C, Normal $^{99m}$Tc-VCUG scintigraphy is shown. Radioactive tracer is seen within the confines of the intact urinary tract, refluxing into the duodenal segment (large black arrow) and renal transplantation collecting system (small black arrow). D and E, $^{99m}$Tc-VCUG demonstrates spill of radioactive tracer outside of the bladder and duodenal segment (large white arrowhead). Later, radioactive tracer is also present in the pelvis and between loops of bowel throughout the peritoneal cavity (small white arrowheads).

For small leaks that are contained early, treatment consists of bladder decompression with a urinary catheter for 2 to 3 weeks. Large leaks and those that recur after conservative therapy require exploration, repair of the involved suture line, and enteric conversion.

Careful inspection of the duodenal segment is essential, and biopsy of the duodenal mucosa to search for rejection or cytomegalovirus pathology may be revealing in determining the cause. In most cases, however, the exact cause remains enigmatic despite careful investigation. In some cases, simultaneous diversion of the fecal stream with a Roux-en-Y anastomosis or proximal ileotransverse colostomy is advocated. Rarely is a urinary leak secondary to disruption of the ureteroneocystostomy. Enzyme leaks are more difficult to diagnose in enterically drained pancreata. A diagnosis in this setting relies on contrast-enhanced computed tomography (CT) scan, which usually demonstrates peripancreatic fluid collections. When drained percutaneously, these fluid collections reveal infection with enteric organisms and an elevated fluid amylase level. Surgical treatment of leaks in EDP pancreata requires an individualized approach that usually involves repair, drainage, and diversion of the fecal stream. An expeditious diagnosis, depending on a high index of suspicion, and aggressive surgical intervention are essential to manage these life-threatening complications.
Kidney-Pancreas Transplantation

**FIGURE 15-18**

Urethral disruption. When left untreated, urethritis usually progresses to urethral disruption. Retrograde urethrography in a recipient of a simultaneous pancreas-kidney transplant with bladder drainage demonstrates perforation of the membranous urethra with extensive extravasation of contrast. Immediate treatment is placement of a suprapubic cystostomy or, if possible, a Foley catheter. Enteric conversion follows, which is 100% successful. Sequelae of this process include stricture and bladder outlet obstruction.

**FIGURE 15-19**

Patient and graft survival rates for simultaneous pancreas-kidney (SPK) transplantations in the United States. The survival rates have improved over the past 10 years. The current 1-year patient survival rate for SPK is 94% (panel A), with an 89% kidney graft survival rate (panel B) and 82% pancreas graft survival rate (panel C). The differences over time are highly significant between all eras.
Patient (panel A) and graft (panel B) survival rates for sequential pancreas after kidney (PAK) transplantations. For patients with PAK, the survival rate is similar to simultaneous pancreas-kidney transplantations but graft survival has been poorer until very recently. The 1-year PAK graft survival rate has improved from 52% to nearly 70%. NS—not significant.

**FIGURE 15-21**
Graft (panel A) and patient (panel B) survival rates for pancreas transplantation alone (PTA). A much smaller number of PTAs have been performed in the United States compared with sequential pancreas after kidney (PAK) transplantations and simultaneous pancreas-kidney (SPK) transplantations. The patient survival rate for PTA is similar to those of SPK and PAK transplantation; however, the PTA graft survival rate has been closer to that of the PAK rate until the most recent transplantation era. Advancements in immunosuppressive therapy have improved the 1-year graft survival rate of PTA transplantations from 56% to 74%. NS—not significant.

**EFFECTS OF PANCREAS TRANSPLANTATION ALONE ON SECONDARY COMPLICATIONS OF DIABETES**

<table>
<thead>
<tr>
<th>Secondary Complication</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance of normoglycemia</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Stabilization and improvement</td>
</tr>
<tr>
<td>Prevention of recurrent nephropathy</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Major</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>None</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

Multiple studies have been performed on the effects of pancreas transplantation on the secondary complications of diabetes. Unfortunately, most of these studies were performed with small numbers of patients and were not randomized controlled studies. There are four major benefits of pancreas transplantation for the secondary complications of diabetes: 1) Normoglycemia has been demonstrated for an extended period of time as long as the pancreas is functioning; 2) nephropathy has been shown to improve; 3) pancreas transplantation appears to prevent recurrent diabetic nephropathy in the transplanted kidney; and 4) quality of life. Complete freedom from insulin injections, appears to be the major benefit of pancreas transplantation. Unfortunately, pancreas transplantation does not appear to reverse established diabetic nephropathy in patients with their own kidneys, and established retinopathy and vascular disease do not appear to improve.
**FIGURE 15-23**
Glycosylated hemoglobin before and after pancreas transplantation. All patients have an abnormal hemoglobin A1 value before pancreas transplantation. Most patients, however, maintain a normal hemoglobin A1C after successful pancreas transplantation. (From Morel and coworkers [20]; with permission).

**FIGURE 15-24**
Effects of pancreas transplantation on diabetic neuropathy. Careful studies of motor index (panel A), sensory index (panel B), and autonomic index (panel C) show a general trend of improvement over 42 months in patients who received pancreas transplantation compared with patients in the control group. In patients with pancreas transplantation, 70% had improved results on motor nerve tests, nearly 60% on sensory tests, and 45% on autonomic tests. In patients in the control group, only 30% had improved results on motor and sensory tests, 12% had improved autonomic tests, and nearly 50% had deterioration of neurologic function. (From Kennedy and coworkers [21]; with permission).

**FIGURE 15-25**
Effects of pancreas transplantation on diabetic retinopathy. Retinopathy does not appear to improve after pancreas transplantation. A similar rate of deterioration was observed in both patients who had successful pancreas transplantation compared with patients with diabetes who had kidney transplantation alone. (From Ramsay and coworkers [22]; with permission).
Transplantation as Treatment of End-Stage Renal Disease

**FIGURE 15-26**
Effects of pancreas transplantation on recurrent diabetic nephropathy. Pancreas transplantation appears to prevent the subsequent development of diabetic nephropathy in renal allografts [23]. Both mean glomerular volume (panel A) and mesangial volume (panel B) were significantly lower in patients with successful pancreas transplantation compared with recipients with diabetes who had unsuccessful pancreas transplantation.

**FIGURE 15-27**
Effects of pancreas transplantation on established diabetic nephropathy. Although there appears to be a benefit in the prevention of diabetic nephropathy, there does not appear to be a benefit in patients who undergo pancreas transplantation in reversing established diabetic glomerular lesions. In this study, mesangial fractional volume increased (panel A) and mean glomerular volume decreased (panel B) in pancreas transplantation recipients but no significant change in total mesangial volume (panel C) occurred over a 5-year follow-up. (From Fioretto and coworkers [24]; with permission).

**FIGURE 15-28** (see Color Plates)
Effects of pancreas transplantation on microvascular disease. The benefits of pancreas transplantation on vascular disease have been variable. A, In this study, thermography demonstrated a clear-cut improvement in diabetic microvascular disease after successful pancreas transplantation [25]. B, However, no evidence exists that successful pancreas transplantation results in the regression of established macrovascular disease.