Alimentary Tract Complications After Renal Transplantation

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A computer analysis of post renal transplantation gastrointestinal problems was performed to identify important associated clinical factors. Thirty-seven per cent of all transplant recipients developed one or more significant problems. Hemorrhage, nondiverticular intestinal perforation, and esophagitis occurred most frequently in hospitalized patients. Pancreatitis, diverticulitis, and gastroduodenal perforation occurred characteristically in long-term survivors with well functioning allografts. Eleven of 32 HLA identical recipients treated with maintenance corticosteroids during stable kidney function developed gastrointestinal disease while only one of 13 HLA identical recipients not given maintenance steroids developed a problem, which strongly suggests a causal role for steroids in the development of late complications. The association of preexisting peptic ulcer and diverticular disease with hemorrhage and perforation supports previous recommendations that documented peptic ulcer disease or diverticulitis should be corrected surgically prior to transplantation.

BECAUSE GASTROINTESTINAL DISEASE causes substantial mortality and morbidity among renal transplant recipients, identification of patients at risk for developing particular problems is important. Preexisting disease, uremia, and immunosuppression undoubtedly contribute to gastrointestinal complications following transplantation, but gastrointestinal disease also develops in the absence of antecedent symptoms and at unexpected times during otherwise successful care of the renal transplant recipient. Successful management of the problem, whenever it occurs, often depends upon early recognition of the cause and prompt, appropriate therapy. Therefore, a more complete knowledge of the clinical settings in which the various alimentary tract problems are likely to occur would be helpful. In this report we analyzed the relative incidences of major gastrointestinal problems after transplantation with particular attention to identification of associated clinical features.

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Methods

The medical records of the renal transplant recipients at Duke University Medical Center and the Durham Veterans Administration Hospital were reviewed, and surviving patients were interviewed. Patients with gastrointestinal problems excluding liver disease that developed after transplantation and before renal allograft nephrectomy were included in the study. Diagnostic evaluation included endoscopic, radiologic, bacteriologic and other studies as indicated, and original laboratory records were reviewed. Information relevant to the course and management of each complication was investigated by computer analysis. Frequencies and cross-correlations were obtained directly from the computer and checked manually against data sheets. Statistical tests were applied only when appropriate control groups were identified. Chi-square, Fisher exact probability, or unpaired tests were used,[29,32] and p values less than 0.05 considered significant.

Patient Population

From January, 1965 to March, 1978, 343 patients received 367 renal allografts. Fifty-six per cent of the kidneys originated from cadaveric donors and 44% from living related donors of which 34% were prospectively determined to be HLA-identical. Three-fourths of the recipients were male and 25% female. All patients were treated with standard immunosuppressive drugs consisting of azathioprine and/or cyclophosphamide and corticosteroids, and rejection episodes were treated by high dose intravenous steroids and local irradiation when necessary. After 1967, half the cadaveric and living related, HLA haploidentical recipients received additionally antithymocyte globulin

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TABLE 1. *Gastrointestinal Problems after Renal Transplantation*

	Number of Patients
Bleeding	81
upper	64
lower	17
Perforation	24
Esophagitis	24
Pancreaticobiliary	14
Miscellaneous	25
peptic ulcer disease without bleeding	5
abdominal abscess	2
appendicitis	2
bowel obstruction	2
inguinal hernia	2
incisional hernia	2
septic emboli to intestine	2
colitis	2
gastroenteritis	1
vascular dissection after arteriography	1
strongyloidiasis	1
rectal moniliasis	1
reticulum cell sarcoma of small bowel	1

(ATG), according to the protocol of a randomized, controlled study. HLA-identical recipients never received ATG, but were treated by the other immunosuppressive drugs. A group of 13 HLA identical patients who have been followed for three to 13 years, never received steroids except for treatment of acute rejection episodes. Patient and allograft survival has paralleled the experience of other major transplant centers and has been reported in part previously.[30,31]

Results

Incidence

Overall, 141 patients, 41% of the above evaluated population, developed one or more gastrointestinal problems after transplantation (Table 1). Twenty-five patients developed more than one problem resulting in a total of 168 complications. One hundred twenty-seven patients, 37% of all recipients, had one or more clinically significant problems. Gastrointestinal hemorrhage was most frequent, accounting for 48% of the complications. Perforation, esophagitis, and pancreaticobiliary disease were the other major categories. Nearly 20% comprised a group of miscellaneous problems that included gastritis or ulcer disease without hemorrhage, widespread infection or malignancy with incidental bowel involvement, herniae, appendicitis, bowel obstruction, and unusual problems such as strongyloidiasis and rectal moniliasis.

Forty per cent of cadaveric recipients developed gastrointestinal complications, which accounted for 92 of the 168 problems. Thirty-eight per cent of living related, HLA-haploidentical recipients and 29% of HLA-identical recipients had 57 and 19 problems respectively. Forty-eight per cent of patients on the ATG protocol who developed gastrointestinal problems received ATG and 52% did not. Fifteen of 43 HLA identical recipients who received maintenance steroids developed gastrointestinal problems. Only one of 13 HLA identical recipients who did not receive steroids developed gastrointestinal disease.

Chronological Distribution

Most of the gastrointestinal complications occurred after 1969, when the transplantation experience increased sharply (Fig. 1A). The number of patients with gastrointestinal disease per year has declined slightly from 1970 to 1977 despite a small, general increase in the number of allograft procedures performed

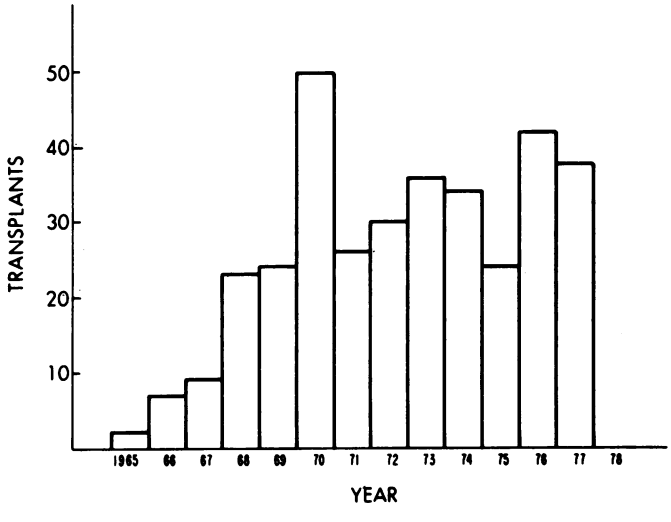

FIG. 1a. Number of transplants performed per year January, 1965–March, 1978.

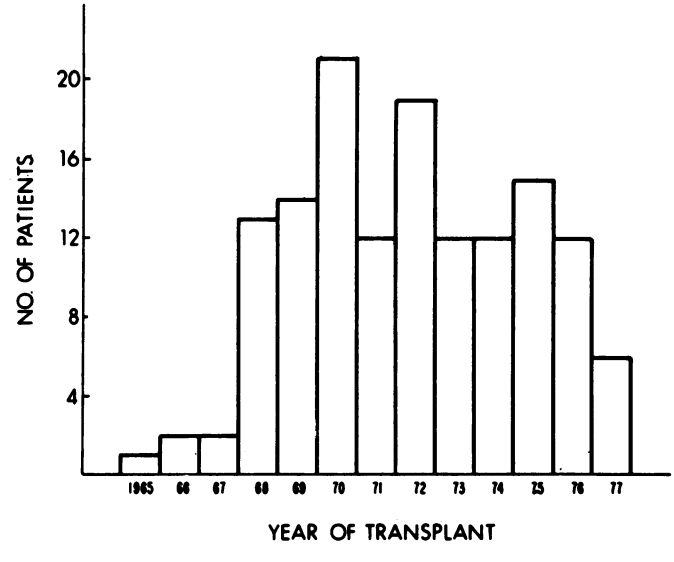

FIG. 1b. Number of gastrointestinal complications versus year of transplantation.

during that period (Figs. 1A and B). This decline in gastrointestinal complications is also evident when the number of patients is depicted against the year the difficulty was detected (Fig. 1C). An increasing number of late developing complications in long-term survivors is apparent from comparison of the slopes of Figures 1B and 1C. Approximately one-quarter of the gastrointestinal problems occurred greater than one year following transplantation. Within the major categories of posttransplantation problems, the only notable decline has been in gastrointestinal perforations, from 14 during 1970–1973 to seven during 1974–1978, which reflects a decrease in postoperative perforations; eight of the 14 perforations from 1970 to 1973 occurred prior to hospital discharge after the transplantation procedure, whereas six of the seven perforations in the past four years have been in patients who had been discharged and had a functioning allograft for more than six months.

Perforations

Twenty-four patients had gastrointestinal perforations, which were distributed anatomically as follows: six stomach or duodenum, four remainder of small intestine, and 14 colon or rectum (Fig. 2). Abdominal pain, of variable severity and character, was a prominent symptom in all 24 patients. Peak preoperative temperature was greater than 37.5° in 18, and a white blood cell count greater than 11,000 occurred in 14. However, in 15 of the 24 patients a diagnosis was not made until greater than 24 hours after the onset of symptoms. Diagnosis was established in 22 by plain or contrast roentgenographic examinations, in one patient at surgery, and in the other patient at autopsy. The overall mortality was 75% in this group. There was no apparent correlation between gastrointestinal perforations and age, sex, prior surgery, original renal disease, pretransplant peritoneal dialysis, the use of either pre- or postoperative steroids, azathioprine, radiation, or ATG.

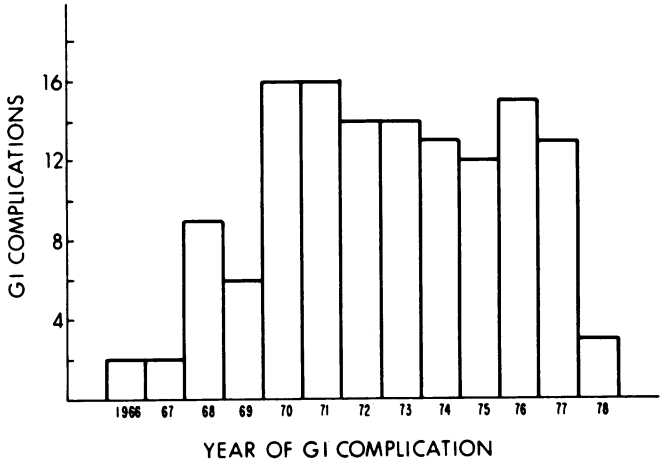

FIG. 1c. Number of gastrointestinal complications versus year of occurrence.

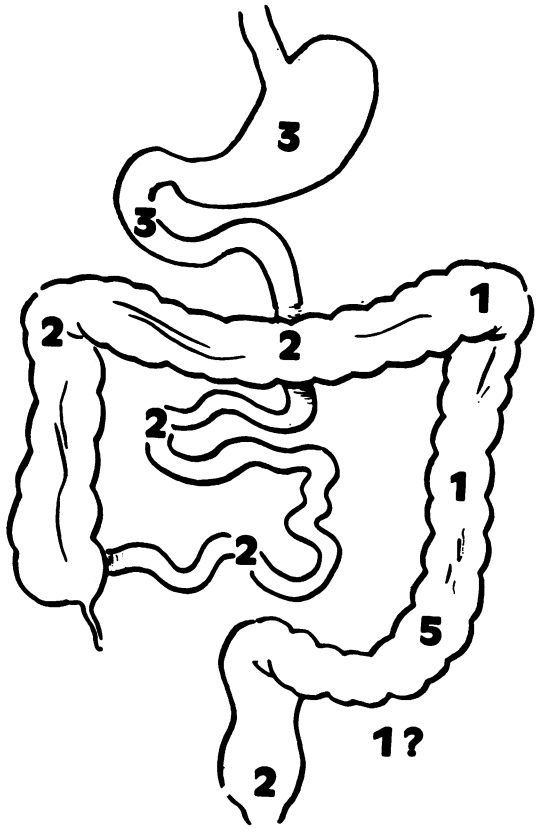

FIG. 2. Distribution of gastrointestinal perforations.

Small intestine and colon. Probable etiologies were determined for 15 of the 18 perforations that did not involve the stomach or duodenum. Three cases were clearly iatrogenic; one occurred after an overly vigorous Kayexolate enema for control of hyperkalemia, another from a percutaneous peritoneal dialysis trocar insertion, and a third in association with tube feeding a desperately ill patient. One perforation developed after impaction of the right colon, and another was caused by a closed loop obstruction. Five perforations occurred in juxtaposition to perinephric abscess cavities, and in each of these the abscess appeared to have eroded through bowel. Five patients had coincident diverticular disease, and in three of these cases the perforation was demonstrated pathologically to be through a diverticulum. Details of the clinical course and autopsy of an additional patient who had a

TABLE 2. *Upper Gastrointestinal Hemorrhage*

	Number of Patients	Died
Donor type		
HLA-identical	6	0
haploidential	16	4
cadaveric	42	15
Kidney function		
rejection	21	10
within two weeks of rejection	6	2
malfunction, other cause	12	4
stable, adequate renal function	25	3
Source		
discrete gastric ulcer	11	6
discrete duodenal ulcer	14	8
multiple superficial gastric ulcers	20	2
other	8	2
not determined	11	1

colon perforation at an outside hospital were not available for review.

Diverticular perforations. All five perforations in patients with diverticular disease occurred long after the transplantation procedure, mean day post transplantation (±SEM) being 892 ± 317. Three patients died from their perforations. Another patient perforated into the mesentery and was treated successfully with a three-staged resection procedure. The fifth developed a colovesical fistula, which was resected without further problem.

Nondiverticular perforations. Mean posttransplant day when these perforations of the distal small bowel, colon, and rectum occurred was 49 ± 16. This was significantly less than either diverticular or stomach and duodenal perforations. Mortality was 85%. One survivor's initial problem was a colocutaneous fistula which closed with conservative therapy. The other survivor had a free intraperitoneal perforation which was treated with the exteriorization of the bowel and extensive peritoneal irrigation.

Stomach or duodenum. Mean posttransplant day of occurrence of these perforations was 674 ± 434. Mortality was 67%; one of the survivors perforated his duodenum, the other his stomach.

Hemorrhage

Upper GI tract. The source of upper gastrointestinal bleeding was found in 53 of 64 patients: multiple superficial gastric erosions in 20 patients, 14 duodenal ulcer, 11 gastric ulcer, and eight from other sources. In addition, two of the patients with duodenal ulcer hemorrhages had experienced previous bleeding episodes from multiple superficial gastric ulcerations. Hemorrhage from all sources occurred at variable times after transplantation. Hemorrhage from each of the three principal sources, analyzed separately, did not occur at significantly different times after transplantation nor was any source associated with stable or unstable renal function. However, 61% of all cases occurred during unstable kidney function (deterioration in creatinine clearance); 21 (33%) with rejection, six (9%) within two weeks of a rejection episode, and 12 (19%) with renal malfunction from technical problems or undetermined factors. Despite the association with unstable renal function, neither occurrence nor severity of hemorrhage could be positively correlated with dosage of steroids, number of pulses of steroids during rejection episodes, time interval between last pulse of steroids and onset of bleeding, radiation, azathioprine or ATG. Eleven of 14 recipients with peptic ulcer disease documented prior to transplantation had at least one bleeding episode following transplantation; eight of these occurred greater than six months after transplantation. Recipients of cadaveric allografts bled nearly twice as often as recipients of living, related allografts (Table 2).

Initial detection of bleeding was by gross or occult blood from the rectum in 30 patients and by hematemesis or guaiac positive nasogastric aspirates in 34 of the 64 patients. Bleeding was suspected prior to documentation in ten patients with hematocrit decreases and two patients with sudden hypovolemia. Peptic ulcer disease had been unsuspected in one recipient in good health for four years who, while unattended at home, exsanguinated from a duodenal ulcer. Twenty-four patients (41%) had severe bleeding episodes, *i.e.*, required four or more units of blood, 19 (30%) required less than four units, and 17 of the 64 patients (27%) received no blood transfusion. Twelve patients underwent surgery to stop hemorrhage, and four patients received peripheral or selective vasopressin. Severity of bleeding was independent of the mode of initial recognition of the bleeding, *i.e.*, hematemesis, passage of gross blood per rectum, or detection of occult blood in stool.

Upper gastrointestinal bleeding was associated with a 29% mortality. Fourteen patients died as a direct consequence of blood loss, and five died of other principal causes. Survival was significantly better for patients with multiple superficial gastric erosions, stable kidney function or allografts from HLA-identical, living related donors (Table 2).

Lower GI tract. Various sources were determined for 13 of 17 patients with lower gastrointestinal bleeding; hemorrhoids in six patients, two with pseudomembranous colitis, extensive submucosal colonic hemorrhage in two, cecal ulcer in two, cecal polyp in

one patient. The other four patients developed hematochezia; however, no source from the upper or lower gastrointestinal tract of these patients was ever found.

Esophagitis. Twenty-four patients has esophagitis: 11 monilia, seven reflux, one herpes simplex, and five undetermined etiology. Twenty of the 24 cases were diagnosed by endoscopy, barium roentgenograms, and bacteriologic studies, while four severe cases which had produced minor symptoms were found at autopsy. Eighteen patients were hospitalized: nine for treatment of rejection and nine for other medical problems. All nine patients whose esophagitis occurred during or shortly after a period of rejection had received more than four pulses of steroid therapy for that rejection episode. Seventeen of the 24 patients had concurrent, clinically manifest ulcerations of the stomach or duodenum. No deaths occurred as a direct consequence of the esophagitis, but nine (38%) patients died of other causes during that hospitalization.

Seven of the 11 patients with monilia esophagitis complained of severe retrosternal pain with swallowing, and each had characteristic barium roentgenograms (Fig. 3). Candida was cultured from both esophagus and a gastric or duodenal ulcer in four of the 11 patients. A fifth patient perforated a gastric ulcer and candida was cultured from his peritoneal cavity.

Pancreaticobiliary. Nine patients had pancreatitis and five developed other pancreatic or biliary problems. In general, patients with pancreatic or biliary complications represented an older age group (Fig. 4A) than the total group of patients with gastrointestinal problems (Fig. 4B).

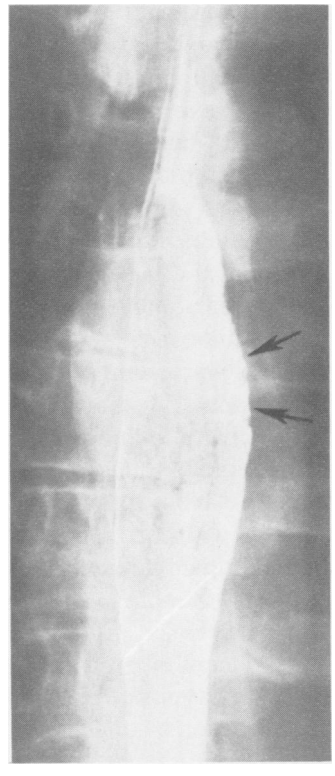

FIG. 3. Barium esophagogram of transplant patient with monilial esophagitis. Note irregular borders of esophagus on cone down film (arrows).

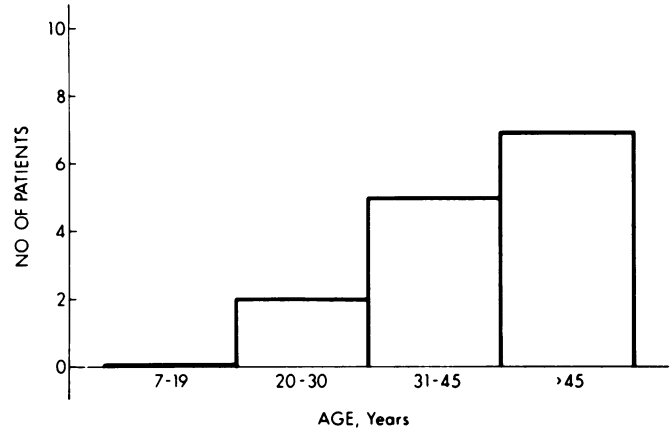

FIG. 4a. Distribution of pancreaticobiliary complications according to age of patient.

Six patients had clinically evident acute pancreatitis. Each case occurred at least four months following transplantation during stable and adequate renal function. Three of the six patients died from the pancreatitis. One of the three survivors had a history of alcohol abuse and pancreatitis documented prior to renal transplantation, and five months after transplantation he developed pancreatitis complicated by a pancreatic pseudocyst (Fig. 5), which was treated surgically by cystduodenostomy. Three patients had clinically insignificant autopsy findings of pancreatitis.

Two patients had acute calculus cholecystitis, one chronic calculus cholecystitis, one salmonella cholecystitis, and one pancreatic ascites. One of the two

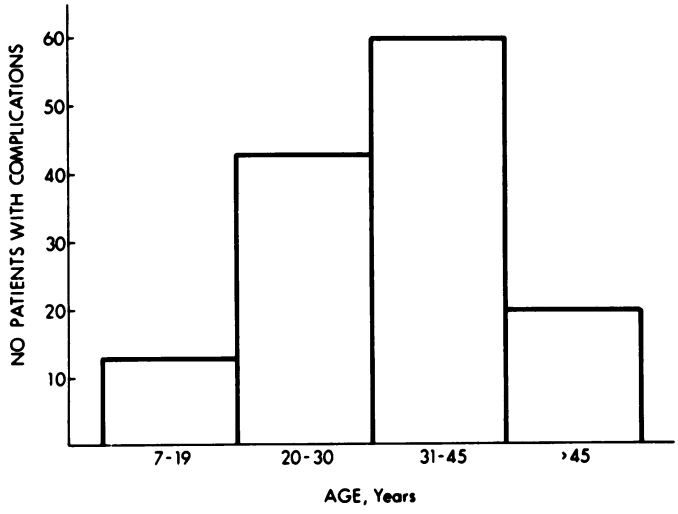

FIG. 4b. Distribution of all gastrointestinal complications according to age of patient.

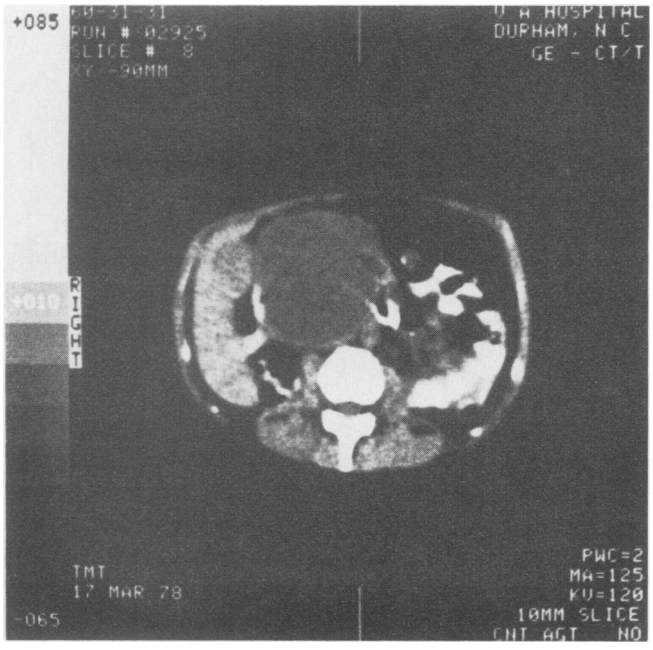

FIG. 5. CT scan of pancreatic pseudocyst in transplant recipient.

patients with acute cholecystitis had beryllium gallstones, which obstructed the cystic duct and caused rupture of the gallbladder. He underwent emergency cholecystectomy three years after transplantation and survived. Interestingly, the etiology of his renal failure had been chronic berylliosis.

Discussion

The incidence of gastrointestinal disease after renal transplantation and the associated mortality are clearly high. Previous studies have described complication rates between six and 34% in transplanted patients[1,13,15,21,23,25] and the 37% incidence of significant complications reported in the present series again illustrates the magnitude of this clinical problem. Mortality from certain complications was higher than estimated from similar problems in the general population. For example, the mortality from upper gastrointestinal bleeding from all sources was 29% in transplant recipients, whereas the mortality of all patients admitted to general hospitals with hematemesis or melena has been reported to be between 5 and 10%.[5,27] Also, the mortality from acute pancreatitis was 50% after transplantation compared to about a 10% overall mortality in the general population.[2] Perforations from diverticulitis after transplantation were frequently into the free, intraperitoneal cavity, causing a high mortality, while the vast majority of diverticulitis in the general population is a localized process with a considerably lower mortality.[19,24] The incidence of gastrointestinal disease, particularly peptic ulcer disease and bleeding, in chronic renal failure patients is also high, but the associated mortality is not as great as in transplantation patients.[10,20,28] Only one perforation has occurred in over 100 dialysis patients who underwent bilateral nephrectomies and no transplantation over the past ten years.

Many factors including uremia, steroids, cytomegalovirus, autoimmune disease, gastrointestinal hormones, hypercalcemia, and hyperparathyroidism have been implicated as causes of various gastrointestinal problems after transplantation,[7,8,14,22,36] but no cause and effect relationship has been demonstrated for any of these specific factors. The apparent association of hemorrhage with renal malfunction,[34] confirmed in this study, suggests that such bleeding is temporally related to the combination of uremia, "stress," and high dose steroids and not to maintenance immunosuppressive therapy, although stool guaiac examinations were not performed frequently during periods of stable renal function. In contrast, the association of pancreatitis with stable renal function suggests a relationship with maintenance therapy and/or autoimmune disease.

A primary goal of this analysis was to construct a patient profile for each major category of post transplant gastrointestinal complications, and certain general features of each category became apparent (Table 3). Upper gastrointestinal hemorrhage was the most common problem and occurred at varying time periods after transplantation. Hemorrhage was frequently severe and associated with renal malfunction. However, the site of the bleeding bore no significant relationship to periods of unstable kidney function. There was another group of patients whose bleeding occurred during stable, adequate renal function *i.e.* no rejection, normal BUN, and no deterioration in creatinine clearance. Nondiverticular perforations of the distal small bowel, colon, and rectum occurred early after transplantation and were often caused by iatrogenic factors or peritransplant infection. These perforations were usually fatal. Diverticular and gastroduodenal perforations occurred later and also had a high mortality. Esophagitis occurred most frequently in severely ill, hospitalized patients with coexistant gastric or duodenal ulcerations. Pancreatitis characteristically occurred long after surgery, in the presence of stable renal function, and was severe.

A concept emerges from this analysis that there are really two types of posttransplantation gastrointestinal complications: one that is associated with acute, physiologic change, for example from renal malfunc-

TABLE 3. *Characteristic Features of Some Major Complications*

Perforations	Hemorrhage	Esophagitis	Pancreatitis
Gastroduodenal—late	Renal malfunction	Hospitalized patient	Late
Diverticular—late	Ulcer patient at risk	Coincident ulcer disease	Stable renal function
Other—early	High mortality regardless of mode presentation		? older patient
Difficult diagnosis			
High mortality			

tion or infection, and another that occurs in periods of good health during chronic management of the recipient. The former complications were primarily postoperative or rejection-related problems, such as the majority of bleeding. The latter group which included pancreatitis and diverticulitis, and perhaps colitis, malignant disease, and other pancreaticobiliary problems, usually occurred at extended time periods after transplantation. A number of gastrointestinal problems, such as appendicitis, might have occurred had the patients never had renal failure nor undergone transplantation, and these patients would, of course, comprise a third, hard to discern, group of problems.

Perhaps the most tragic are the patients in the second group, who suddenly developed severe complications after doing well for months or years. Some insight into these complications is provided by a closer inspection of the data on the HLA-identical recipients. Forty-five of the 56 HLA-identical recipients had more than one year of stable kidney function. Of these 45, 32 received maintenance corticosteroids and 13 did not. Eleven of the 32 and one of the 13 patients treated without steroids developed gastrointestinal complications, a statistically significant difference and strong evidence that steroids are a causative factor in at least some of the chronic care complications. It should be pointed out that some bias is inherent in this data because the patients were not selected in a prospective randomized manner either to receive steroids, receive no steroids, or to be tapered from steroids. A large number of perforations and bleeding episodes during maintenance care of the recipients were associated with primary gastrointestinal pathology, which suggests that documented surgical disease should be corrected preoperatively. This analysis confirms previous reports[18,22,23] that documented peptic ulcer disease is likely to recur following transplantation. However, pretransplantation gastric analyses have been unsuccessful in predicting patients at risk.[6,9,11] Our current policy has been to perform prophylactic ulcer surgery prior to transplantation, usually proximal gastric vagotomy, for proven peptic ulcer disease. Because of the high incidence of diverticular disease with colon perforations, prophylactic colon resection for documented diverticulitis, as proposed by others,[26] also seems reasonable. However, whether or not colon resection is indicated for severe, asymptomatic diverticulosis depends upon further analysis of the incidence and natural history of diverticulosis in chronic renal failure patients.

Because hospitalized transplantation patients are clearly at risk to develop certain gastrointestinal complications, measures directed at reducing morbidity and mortality are appropriate. These may include prophylactic antacids, cimetidine, nystatin, close monitoring for occult bleeding, cautious enemas, early drainage of peritransplant infection, careful radiologic evaluation of abdominal pain, and reduction of steroids when possible. Avoidance of nonabsorbable antacid gels like aluminum hydroxide is recommended[4] because of the danger of fecal impaction, the cause of one perforation in our series. Caution is necessary when using cimetidine because of several reports of increasing serum creatinine.[3,12,16] Also, the efficacy of cimetidine in this group of patients has not been conclusively established. Expeditious endoscopy or contrast examinations are indicated for evaluating occult blood loss because subsequent mortality was shown to be high. Perforation should be suspected in patients with generalized abdominal pain and a peritransplant infection. Such infections occurred in about 5% of recipients and a higher percentage of patients with urinary fistulae.[6] Over the past five years, perforation in the postoperative period has decreased notably, perhaps due to better recognition of contributing iatrogenic factors.

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