Management of Necrotizing Pancreatitis

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A comprehensive management plan is presented for patients with severe acute pancreatitis. These patients may have pancreatic or peripancreatic necrosis or pancreatic fluid collections. Multiple organ failure often develops in patients with severe pancreatitis. We therefore recommend that all patients with acute pancreatitis be evaluated for pancreatic anatomy and function. If a patient is seriously ill, a computed tomographic (CT) scan with vascular enhancement should be done. Meanwhile, vigorous fluid replacement is necessary using Swan-Ganz monitoring. Patients with necrosis do not need surgical intervention unless the clinical course or CT scan-guided aspiration shows infection. The objective of an operation should be to remove all infected tissue and fluid. A preoperative CT scan with vascular enhancement should be used as a guide during the operation to ensure that all foci of infected necrosis or fluid are eliminated. We have found that open packing and irrigation with sodium oxychlorosene are helpful in patients with extensive necrosis or those who become infected early after the onset of symptoms. In all, 40% to 50% of patients treated by closed drainage will require reoperation because of incomplete debridement. Persistent sepsis is an indication for reoperation.

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About 80% of patients with acute pancreatitis have a mild form of the disease characterized by interstitial edema and often fat necrosis involving the pancreas and peripancreatic structures. Pancreatic and peripancreatic necrosis is rarely present and, if so, is limited to microscopic amounts. Local complications of necrosis, abscess or pseudocyst, or organ failure are absent. Most of these patients recover uneventfully after intravenous fluid replacement and the restriction of oral intake.

Patients with sterile or infected pancreatic or peripancreatic necrosis and those with sterile and infected pancreatic fluid collections have severe pancreatitis. Organ failure is frequently present. This report concerns the management of patients with severe pancreatitis.

In most patients, necrosis, when it occurs, develops within hours of the onset of symptoms, although there are a few patients in whom necrosis may develop as long as three to four days after symptoms begin. Necrosis of either the duct system or pancreatic parenchyma is the initiating event in most of the complications of acute pancreatitis[1,2] and occurs in the absence of bacteria.[3] As a result, about 10% of all patients with acute pancreatitis will have fluid collections due to the extravasation of fluid from the pancreatic ductal system. Another 10% with necrosis of more than 10% to 15% of the gland have a 40% to 70% chance of becoming infected.[4] Infection rarely occurs in the absence of pancreatic or peripancreatic necrosis. Consequently, pancreatic infections will develop in only 5% of all patients with acute pancreatitis, but 80% of all deaths from pancreatitis result from these infections. The other deaths are due, for the most part, to necrosis.[5,6] Much of the knowledge of the natural history of necrotizing pancreatitis is derived from the Ulm, Germany, group headed by Hans Beger.

The main factor that increases the likelihood of infection is the extent of pancreatic and peripancreatic necrosis. The more necrosis, the higher the incidence of infection. Infection can occur as early as two to three days after the onset of symptoms, but most cases occur later. The incidence of infection increases over the first three weeks, peaks during the third and fourth week, and then falls off rapidly. Whereas the incidence of infection is low the first week after symptoms begin, the mortality is in the range of 70% to 100%.[7] Each week thereafter, the mortality falls—to about 40% the second week, 27% the third week, and 13% the fourth week.[7,8]

The reasons for the high mortality associated with the early onset of infection are many. Patients infected early are physiologically sicker and have higher Ranson and APACHE [Acute Physiology and Chronic Health Evaluation] II signs of severity than those who become infected later.[9,10]* At an operation, the debridement of necrotic and peripancreatic tissue in those who become infected is more formidable not only because the patient is sicker, but because the operative procedure is technically more difficult. Debridement is often limited by the inability to distinguish viable from nonviable tissue. Frequently patent blood vessels traverse the necrotic areas in the pancreas and bleed during debridement. Fibrosis and granulation tissue do not begin to define and confine the areas

*See also the editorial by H. A. Reber, MD, and D. W. McFadden, MD, "Indications for Surgery in Necrotizing Pancreatitis," on pages 704-707.

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ABBREVIATIONS USED IN TEXT

APACHE II = Acute Physiology and Chronic Health Evaluation
CT = computed tomographic
UCD = University of California, Davis

of necrosis until the third week. Overall, patients infected early are more likely to require reoperation.

Unresolved Management Issues of Necrotizing Pancreatitis

Surgeons interested in this disease agree that when infection occurs, operative intervention is indicated. Surgeons disagree, however, as to whether patients with extensive sterile necrosis in whom there is a high probability of infection and in whom the mortality is high would benefit from a "preemptive operative strike," that is, removing all sterile necrosis before infection supervenes, as advocated by Rattner and co-workers.[6] They also disagree on whether the use of antibiotics will prevent or delay the occurrence of infections in patients with pancreatic or peripancreatic necrosis, as proposed by Bassi and colleagues.[11] Either outcome would be desirable. Few question the importance and necessity of vigorous fluid replacement in the resuscitation of patients with high Ranson or APACHE II scores and severe pancreatitis. The type of fluids and the goals of resuscitation, however, have not been defined.[5,12] The value of peritoneal lavage for 10 to 14 days—as opposed to 24 to 48 hours[13]—advocated by Ranson and Berman[14] is that it reduces the incidence of pancreatic and peripancreatic infection and mortality. This observation needs to be confirmed by others. The mechanism by which prolonged lavage might benefit a patient—by removing harmful substances from the abdominal cavity[15,16] or by providing improved fluid resuscitation[17]—is not known. There is also disagreement among surgeons as to how infected patients should best be managed—that is, open versus closed drainage or percutaneous versus operative drainage of infected fluid collections.[18,19]

University of California, Davis, Medical Center Approach

The approach of the University of California, Davis (UCD), Medical Center to patients with necrotizing pancreatitis has evolved from an experience with 90 patients (Figure 1). This is one of the world's largest experiences with necrotizing pancreatitis.

Basic Principles

The mortality of necrotizing pancreatitis can be reduced by using a comprehensive management plan. This plan includes the following:

- The rapid evaluation and assessment of the physiologic and anatomic derangements by the use of the APACHE II score and computed tomographic (CT) scan with vascular enhancement;
- The prompt institution of vigorous fluid resuscitation in which the cardiac index is maintained and monitored using Swan-Ganz techniques;
- Attempts to identify and document septic foci early by CT scan-guided aspiration for Gram's stain and culture; and
- Aggressive surgical debridement with open drainage in selected patients with extensive pancreatic and peripancreatic necrosis.

Physiologic Assessment of Severity

Most patients (75%) with severe pancreatitis presenting to the surgery service at UCD Medical Center are referred from other hospitals; therefore, the Ranson signs are not applicable for their assessment. (Ranson's signs are only applicable to patients during their first 48 hours of hospital stay and have not been validated for use days or weeks later at the time of hospital transfer.) We consider patients with more than two Ranson signs to be severely ill or to have the potential for a severe illness to develop. Only 28% of patients with pancreatic infections had severe pancreatitis at the initial hospital admission by the criteria of Ranson.[21] Ranson's signs are also inconvenient. Only five are available the day of admission, and the other six are calculated at 48 hours. We have found more useful the APACHE II classification of severity (Table 1),[10] which can be applied to patients coming to the intensive care unit from the emergency department and to those who are hospital transfers. The APACHE II is calculated the day of admission. The worst values obtained in a 24-hour period are used to calculate the severity of each sign or symptom on a scale of 1 to 4. The APACHE II also makes provisions for a patient's state of health at the time of illness—that is, a chronic health evaluation. Patients with an APACHE II of 7 or greater are severely ill or have the potential for a severe illness to develop. In our first 50 patients, we found the mean APACHE II score to be 33.6 for those who died and 14.9 for those who survived. There were no deaths in patients with an APACHE II score of 25 or less. There was only one survivor with an APACHE II score above 25.[5]

We also use the Ranson or APACHE II score to determine which patients are candidates for CT scan with

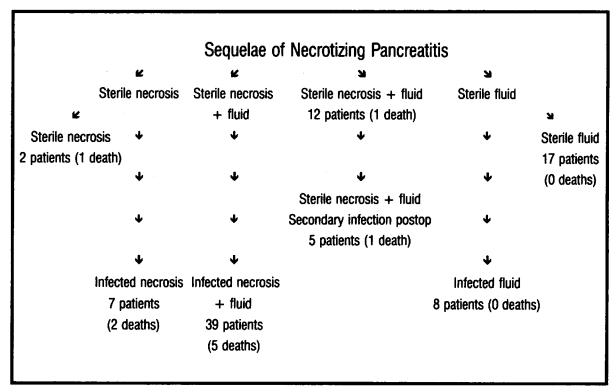

Figure 1.—The diagram outlines experience with 90 patients seen at the University of California, Davis, Medical Center with severe pancreatitis.

TABLE 1.—*APACHE II Severity of Disease Classification System*†

Physiologic Variable	High Abnormal Range, Points				Low Abnormal Range, Points				
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature, °C	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean arterial pressure, mm of mercury	≥160	130-159	110-129		70-109		50-69		≤49
Heart rate (ventricular response), beats per minute	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory rate (nonventilated or ventilated), breaths per minute	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation: A-aDo_2 or Pao_2, mm of mercury									
Fio_2 ≥ 0.5 record A-aDo_2	≥500	350-499	200-349		<200				
Fio_2 < 0.5 record only Pao_2					Po_2 >70	Po_2 61-70		Po_2 55-60	Po_2 <55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum sodium, mmol/liter	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum potassium, mmol/liter	≥7.0	6.0-6.9		5.5-5.9	3.5-5.4	3.0-3.4	2.5-2.9		<2.5
Serum creatinine, μmol/liter (mg/dl)‡	≥309 (≥3.5)	177-301 (2.0-3.4)	133-168 (1.5-1.9)		53-124 (0.6-1.4)		<53 (<0.6)		
Hematocrit	≥0.60		0.50-0.59	0.46-0.49	0.30-0.45		0.20-0.29		<0.20
Leukocyte count, × 10^9/liter	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1.0
Glasgow Coma Score§									
Total Acute Physiology Score (APS) II									
Serum bicarbonate, venous, mmol/liter¶	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

A-aDo_2 = alveolar-arterial Po_2 difference, APACHE = Acute Physiology and Chronic Health Evaluation, Fio_2 = fraction of inspired oxygen, Pao_2 = partial pressure of arterial oxygen, Po_2 = partial oxygen pressure

*From Knaus et al.[10]

†Definitions: Organ insufficiency or immunocompromised state must have been evident before this hospital admission and conform to the following criteria: *liver:* biopsy-proven cirrhosis and documented portal hypertension, episodes of past upper gastrointestinal tract bleeding attributed to portal hypertension, or previous episodes of hepatic failure, encephalopathy, or coma; *cardiovascular:* New York Heart Association Class IV; *respiratory:* chronic, restrictive, obstructive, or vascular disease resulting in severe exercise restriction: unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (≥40 mm of mercury), or respirator dependence; *renal:* receiving dialysis; *immunocompromised:* the patient has received therapy that suppresses resistance to infection—immunosuppression, chemotherapy, irradiation, long-term or recent high doses of steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, such as leukemia, lymphoma, or acquired immunodeficiency syndrome.

The APACHE II score is the sum of A + B + C:

A = APS points

B = age points: ≤44 yr, 0 points; 45 to 54 yr, 2 points; 55 to 64 yr, 3 points; 65 to 74 yr, 5 points; ≥75 yr, 6 points

C = Chronic Health points: If the patient has a history of severe organ system insufficiency or is immunocompromised, assign points as follows: for nonoperative or emergency postoperative patients, 5 points; for elective operative patients, 2 points.

‡Double-point score for acute renal failure.

§Score = 15 − actual Glasgow Coma Score.

‖Sum of the 12 individual variable points.

¶Not preferred; use if no arterial blood gas values.

vascular enhancement (Ranson: more than 2 signs of severity; APACHE II: 7 or above).

Anatomic Assessment of Severity

Although the Ranson and APACHE II scores are predictors of whether or not a patient survives, the CT scan with vascular enhancement is most useful as a predictor of those patients in whom the potential for infection exists. Between 40% and 70% of patients who have more than 30% necrosis of their pancreas will become infected.[4] Conversely, patients without pancreatic or peripancreatic necrosis will not become infected.

Those patients who have, on the basis of CT scan with vascular enhancement, 15% to 30% or more pancreatic necrosis, peripancreatic necrosis, or fluid collections in or around the pancreas are considered to have severe pancreatitis. A recent report by Foitzik and associates compared the effect of intravenous contrast medium on mortality in rats with exposure to pancreatitis of uniform severity and those in which no contrast was used.[22] The contrast was given within 24 hours of the pancreatitis being induced. If this report is confirmed, it would be advisable to delay CT scan with vascular enhancement until at least 24 hours after the onset of symptoms.

Fluid Resuscitation Therapy

Hemodynamic studies in humans have shown that there is a hyperdynamic cardiovascular state in patients with severe pancreatitis similar to that seen in patients with cirrhosis or septicemia. The exact mechanism whereby edematous pancreatitis evolves into necrotizing pancreatitis or perhaps begins de novo as necrotizing pancreatitis is not known.[23] Blood flow is known to be reduced to the pancreas during pancreatitis. In addition, patients are at risk of shock and the sequelae of shock and multiple organ failure as a result of a profound microvascular leak. Fluid is lost into interstitia, subcutaneous tissues, lungs, peritoneal cavity, and the pancreas, bowel, and retroperitoneum in severe pancreatitis. Pancreatic ascites and pulmonary effusion are common. The average positive fluid balance on the day of admission among our patients who died was 9.7 liters compared with 2.7 liters among survivors.[5] Patients with severe pancreatitis have diminished peripheral resistance and decreased intravascular volume. It is thought that trypsin released into surrounding tissues and the circulation triggers the complement cascade, kinins, prostaglandins, and eicosanoids, which has a profound effect on the integrity of the microvascular system.[12] To maintain circulation to the pan-

creas and other vital organs, we recommend a regimen of vigorous fluid resuscitation in patients with severe pancreatitis in whom the cardiac index is maximized to create a hyperdynamic circulation. Monitoring with a Swan-Ganz catheter is essential to achieve this goal. Special resuscitation regimens in animals using hypertonic saline-6% dextran 70 solutions produced marked improvement in cardiac contractility and pulmonary function over conventional resuscitation methods with electrolyte solution.[24] Schmidt and co-workers reported a decrease in mortality and in the incidence of pancreatic necrosis in rats using high-molecular-weight dextran 400 as the resuscitation solution.[25]

The use of furosemide to "maintain urinary output" in patients with severe pancreatitis is to be condemned. Organ hypoperfusion results, and multiple organ failure is the inevitable consequence. The hemodynamic phase of pancreatitis persists for four to six days when, if infection does not intervene, microvascular integrity returns and the patient's fluid requirements diminish.

Identifying Patients With Infection

Pancreatic necrosis and peripancreatic necrosis may cause leukocytosis, fever, and loss of microvascular integrity in the absence of infection. These manifestations of severe pancreatitis are difficult to distinguish from those of sepsis. Therefore, we use CT scan-guided aspiration to obtain Gram's stains and cultures in patients in whom there is any question of infection. This technique, described by Gerzof and associates,[26] is useful in patients in whom infection develops early after the onset of symptoms. We do not recommend operative intervention in patients with sterile necrosis early after the start of symptoms. Although this has been recommended by Rattner and colleagues,[6] their patients had a higher mortality than ours, 24% versus 14%. Of concern, in a substantial percentage of their patients, the sterile necrosis was converted to infected necrosis. Although their patients seemed to be less ill than ours by the APACHE II score, the comparison is not valid as our scores were obtained on admission to the UCD Medical Center's surgical intensive care unit and theirs on the day before operation.[6] Selected patients with sterile necrosis who remain ventilator-dependent or unable to eat after five to ten weeks require operative intervention.

The question of whether the use of antibiotics to prevent or delay infection is justified has not been completely settled. There is a high incidence of bacteremia during severe pancreatitis. Using imipenem in a multiinstitutional study in Italy, Bassi and co-workers noted a reduction in the incidence of infection in patients receiving presumptive antibiotic therapy.[11] There was no decline in mortality, however. Previous studies from the 1970s that concluded the presumptive use of antibiotics to be unhelpful used antibiotics ineffective against enteric organisms, the ones most frequently found in necrotizing pancreatitis. The antibiotics were administered to an unselected group of patients with acute pancreatitis, most of whom had no necrosis.

Operative Management

Once infection is identified on the basis of clinical evidence of sepsis or the results of CT scan-guided aspiration, the infected pancreatic and peripancreatic necrotic tissue should undergo vigorous debridement (Figure 2). The preoperative CT scan with vascular enhancement is used to locate and remove all infected tissue and fluid.

We favor a bilateral subcostal incision, which provides access to the lesser sac and allows the hepatic and splenic flexures of the colon to be mobilized. If there is CT scan evidence of extension inferiorly into the small bowel mesentery, a separate incision into the mesentery below the colon is necessary. If there is extensive necrosis behind either colon, a counterincision is made in the flank for bringing out drain tubes and assisting in the debridement of the necrosis. Should necrotic colon be present, a proximal colostomy is done and the distal colon irrigated until clear. If there is duodenal necrosis, the pylorus is stapled closed and a gastrojejunostomy performed. All necrotic tissue is weighed, and all the fluid removed is measured. Gram's stain and cultures are done for aerobic, anaerobic, and fungal organisms. After the debridement is completed, a decision is made as to whether to pack the surgical wound closed or open. The decision to pack open is influenced by the following: A large amount of necrotic pancreatic and peripancreatic tissue (more than 100 grams) is removed with the initial debridement; a preoperative CT scan shows more than 50% necrosis of the gland or extensive peripancreatic necrosis beneath the colon; and viable tissue is poorly delineated from nonviable tissue at the operation, which is usually seen in patients in whom infection intervened within the first several weeks after their symptoms began.

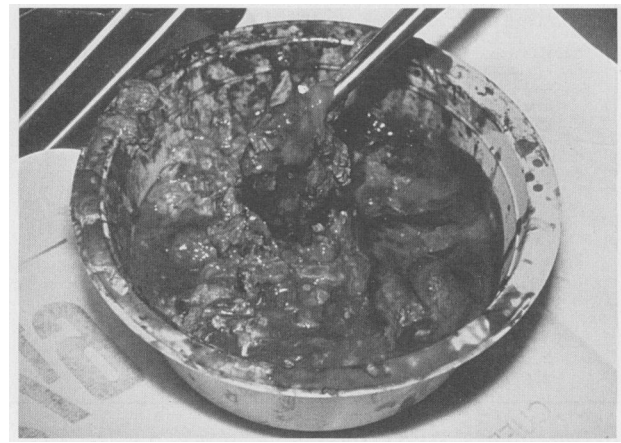

Figure 2.—Typical pancreatic and peripancreatic necrotic tissue was recovered at a necrosectomy.

Drainage and Irrigation

Whether the drainage is open or closed, triple-lumen Davol drains are used for irrigation with sodium oxychlorosene (Clorpactin) solution. Initially we irrigate at 250 ml per hour per drain. Dependent drainage is used, with #40 silicone chest tubes brought out beneath the

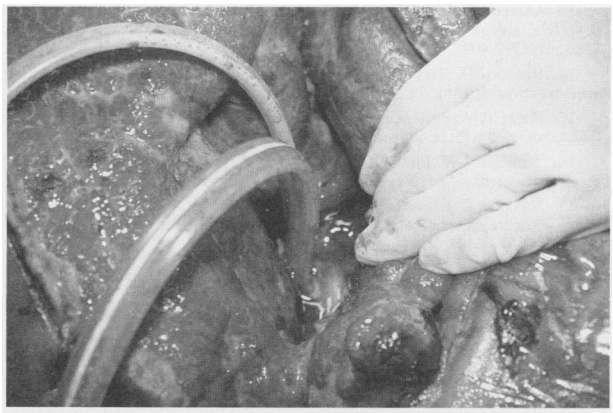

Figure 3.—Triple-lumen Davol drains are sutured to the skin at the edge of the incision for irrigation purposes.

colon in the flank. Suction is not used on the Davol drains because of bleeding complications that on two occasions necessitated a trip to the operating room for control.

At open drainage after placing the drains (Figure 3), the lesser sac is packed open with Kerlix rolls (Figure 4). There is no need to use Xeroform or Adaptic gauze to protect the bowel if irrigation is used. A space is thus created between the stomach and transverse mesocolon and colon that allows ready access to the anterior surface of the pancreas by simply removing the Kerlix rolls.

After the initial debridement, it is important to return on a regular basis every two to three days until all the infected necrotic tissue is debrided. After each debridement, a CT scan is done to determine if any pockets of infected necrosis remain. This process is repeated every two to three days until the abdomen is clean as observed at operation and by CT scan with vascular enhancement. The combination of infection and activated pancreatic enzymes may cause additional necrosis between debridement procedures.

If a patient has been treated by the closed or open technique and continues to have sepsis or does not improve, reoperation for what are inevitably pockets of undrained infected necrosis or fluid is mandatory. Frequently the major pancreatic duct is disrupted in the body of the pancreas so that the viable pancreatic tail continues to secrete pancreatic juice, creating a pancreatic fistula. The amylase levels in drain fluid should be measured, and if the volume of fluid and the amylase concentration are high, the drains should not be advanced. Some pancreatic fistulas will close as long as 8 to 12 months after they start.

Combined Therapy

We work closely with radiologists and often call on them to either drain isolated pockets of infected fluid as observed on CT scan or place a catheter into a collection. The catheter can also be used as an operative guide to locate pockets of infected necrosis in difficult-to-reach areas in the retroperitoneum. The percutaneous drainage of areas of infected necrosis, as a primary therapy, is an exercise in futility.[6]

Pancreatic Abscesses

Patients may develop a pancreatic abscess, which is a circumscribed intra-abdominal collection of pus containing little or no pancreatic necrosis. The abscess can best be drained operatively, although percutaneous drainage can be tried initially if a patient is a poor operative risk.

Fluid Collections

Large fluid collections can occur early in the course of acute pancreatitis, within days or weeks of the onset of symptoms following disruption of the main pancreatic duct or one of its branches. Usually there is some element of proximal ductal obstruction that leads to ductal hypertension and promotes the extravasation of pancreatic juice from the site of duct discontinuity. These fluid collections, unlike a pseudocyst, lack a wall of granulation or fibrous tissue. More than 50% of these collections will disappear spontaneously. Therefore, aspirating them before four to six weeks is meddlesome and unnecessary.

Our results in 90 patients observed from 1982 to mid-1992 show that patients with necrosis with or without associated fluid—as determined at the time of operative intervention—are at high risk of dying. Patients with fluid

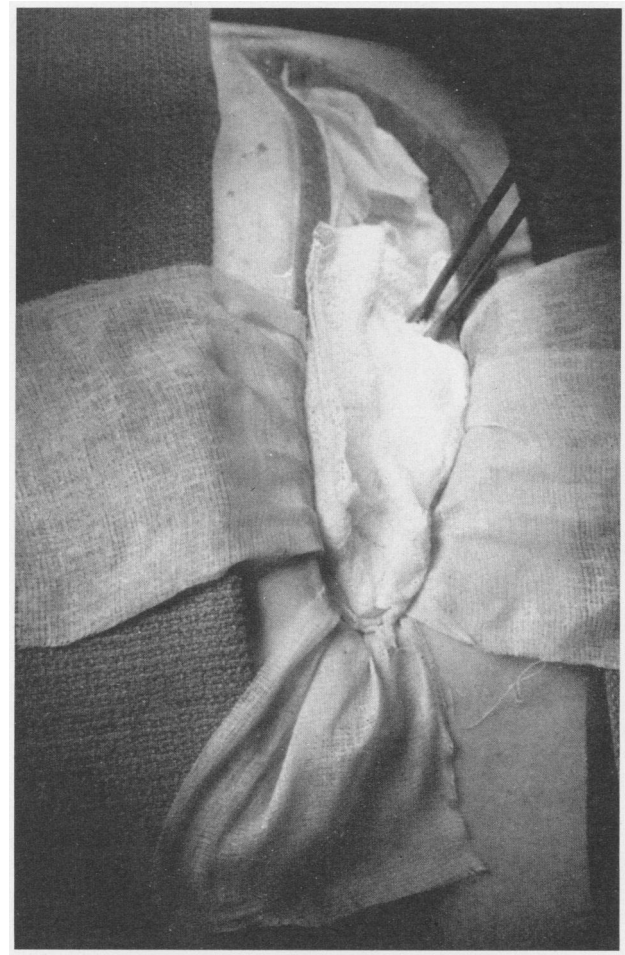

Figure 4.—The stomach is separated from the transverse colon and its mesocolon by Kerlix packing.

collections in the absence of necrosis, whether sterile or infected, all did well.

In summary, close adherence to the methods of care described herein has resulted in the mortality of necrotizing pancreatitis remaining at about 15%.

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