ACUTE PANCREATITIS

DIAGNOSIS AND TREATMENT

October 24, 1991

Katherine E. McArthur, M.D.
The University of Texas
Southwestern Medical Center at Dallas

INTRODUCTION

Acute pancreatitis is a discrete, individual episode of pancreatic inflammation which either occurs in isolation or as one of a series of recurrent attacks with clinical return to normal between episodes. Acute pancreatitis is often easily diagnosed and generally responds to symptomatic treatment. However, sometimes the diagnosis is difficult and confusion and delay prevent optimum care of the patient. In other cases, patients with acute pancreatitis develop a rapidly life-threatening illness or suffer complications which require aggressive intervention.

ETIOLOGY AND PATHOGENESIS OF ACUTE PANCREATITIS

Exocrine Pancreatic Physiology

The pancreas has two major functions, endocrine secretion of insulin and other hormones, and exocrine secretion of fluid and digestive enzymes. Acute pancreatitis is caused by the activation of these enzymes within the pancreas itself with subsequent autodigestion. This concept was first suggested by Chiari in 1896 (1).

The development of the pancreas occurs quite early in the fetus. Dorsal and ventral pancreatic buds arise from the junction of the primitive foregut and midgut (Fig. 1). Each of these buds has its own duct, the dorsal duct arising from the duodenal wall and the ventral duct from the common bile duct. As the ventral bud rotates, in the 7th week of development it is brought together with the dorsal system and the two ducts fuse. The major pancreatic duct is formed proximally from the ventral duct of Wirsung, and thus empties with the common bile duct into the duodenum at the papilla of Vater. In about 30-40% of normal individuals, the major pancreatic duct and common bile duct fuse before entering the papilla and share a short common channel. The minor pancreatic duct is formed from the proximal portion of the dorsal duct of Santorini, and in about 70% of normal individuals travels through the head of the pancreas separately from the major duct, emptying into the duodenal wall proximal to the ampulla of Vater.

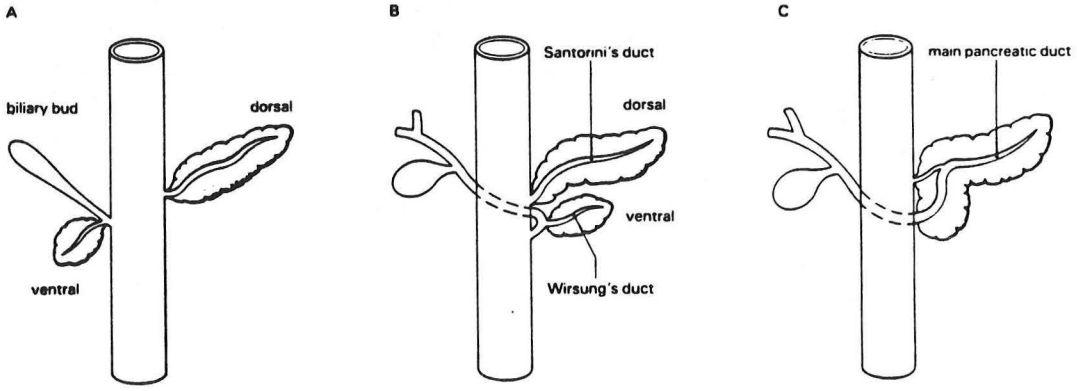

Fig. 1. Developmental anatomy of the pancreas. (From Ref. 2.)

In about 5-7% of the normal population, the dorsal and ventral buds of the pancreas fail to fuse, producing pancreas divisum, which is generally not associated with any symptoms or pathophysiologic aberrations. In the fully developed individual, the pancreas is a retroperitoneal organ which lies across the spine (Fig. 2).

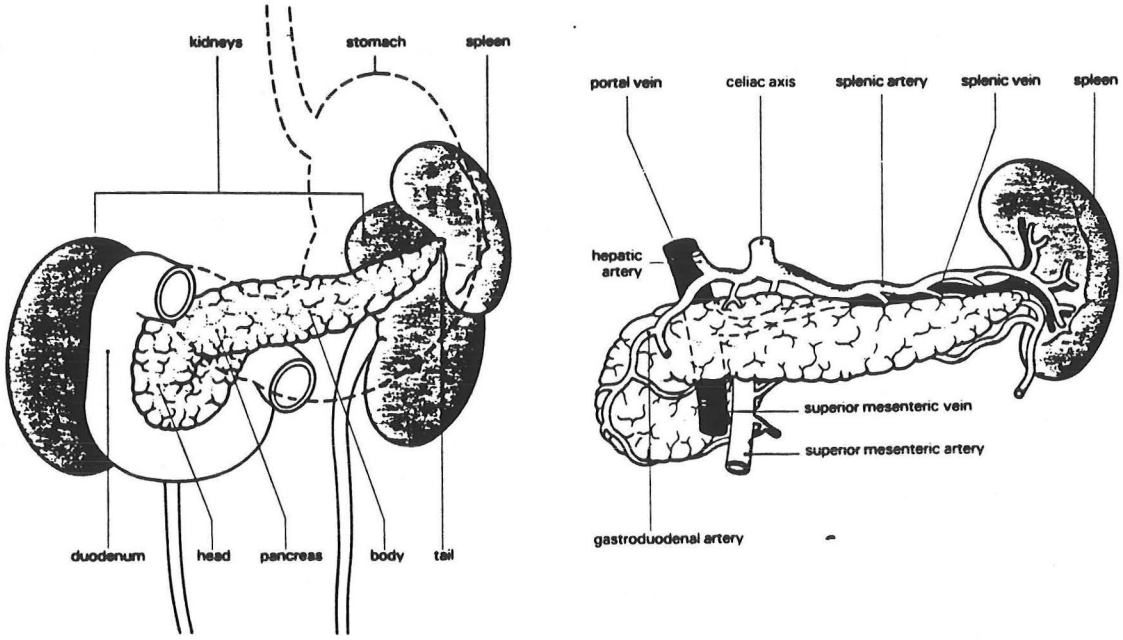

Fig. 2. Anatomical relationships of the pancreas. (From Ref. 2.)

The head and uncinate process, making up about 30-35% of the gland, lie in the duodenal curve while the body and tail extend up to the hilum of the spleen. The close juxtaposition of the pancreas to the duodenum, gastric antrum and sometimes transverse colon can produce secondary inflammation of these organs in pancreatitis.

A normal healthy individual secretes from 1500 to 3000 ml of pancreatic fluid each day, containing from 6 to 20 g of at least 20 digestive enzymes. Pancreatic fluid is rich in bicarbonate and chloride; at maximum flow rates bicarbonate concentrations reach almost 150 meq/L while chloride secretion is reciprocally decreased. Bicarbonate secretion probably comes principally from the duct cells while chloride is secreted from the acinar cells. The alkaline pancreatic fluid (pH ~ 8.3) neutralizes gastric acid stimulated by a meal so that intestinal pH is normally greater than 4.0 distal to the duodenal bulb. This is important in preventing acid inactivation of pancreatic enzymes as well as being a protective factor against duodenal ulcer disease.

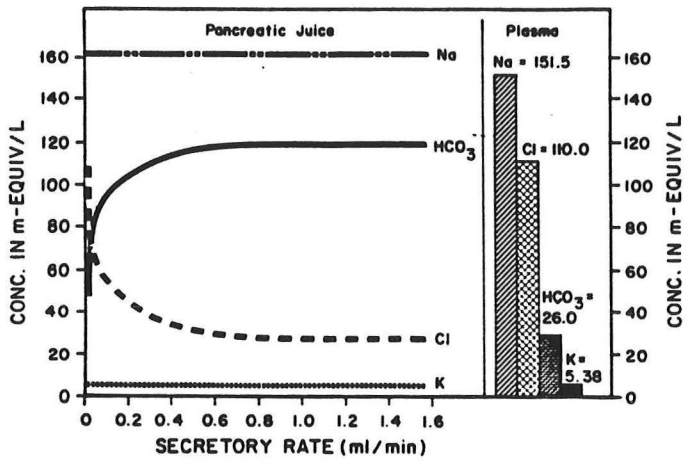

Fig. 3. Pancreatic electrolyte secretion as a function of secretory rate (Ref. 3).

Pancreatic enzymes are secreted by acinar cells which are arranged in small secretory lobules around an acinar lumen. The digestive enzymes are synthesized in the rough endoplasmic reticulum and then packaged together in zymogen granules near the apex of the cells. In response to stimulation, the zymogen granules move to the surface where their membranes fuse with the apical cell membrane, releasing the contents of the granule. When secretion is rapid and prolonged, the zymogen granules become depleted and newly synthesized proteins can be secreted without going through the packaging step. Most enzymes are secreted as proenzymes which are activated in the intestinal lumen. The proportion of different types of digestive enzymes secreted by the pancreas is primarily regulated by long term changes in enzyme synthesis in response to diet composition, however, there is some evidence that there are subpopulations of acinar cells in the pancreas which contain different proportions of enzymes. Different sensitivities to stimulation thus may produce some regulation of pancreatic enzyme composition on a short term basis.

Basal pancreatic secretion is only a few percent of maximal secretion. The major stimulus to pancreatic secretion is ingestion of a meal. Pancreatic secretion, like gastric secretion, has cephalic, gastric and intestinal phases. Secretion continues for about five hours after a meal. Although pancreatic acinar cells have receptors for a large number of hormones, paracrine substances and neurotransmitters, the three most important physiologic stimulants of secretion are acetylcholine (Ach), released by vagal stimulation, secretin, released in the small intestine by gastric acid, and cholecystokinin (CCK), released in the small intestine primarily by fatty acids, small peptides and some amino acids. The mechanisms of control of pancreatic secretion are summarized in Table 1.

Table 1. Stimulation of Pancreatic Secretion.

Level	Pathway	Effect
Cephalic	Vagus (Ach, VIP?)	↑ Enzymes
Sight, taste, smell, swallowing		
Gastric	Reflexes	
Food in stomach	(Ach, VIP?)	↑ Enzymes
Distension	Gastrin	↑ Enzymes
H^+ Secretion	Secretin	↑ Enzymes and HCO_3
Intestinal		
distension	Reflexes (Ach, VIP?)	↑ Enzymes
acid	Secretin	↑ HCO_3
proteins	CCK	↑ Enzymes
fats	CCK	↑ Enzymes

- Modified from Reference 4.

Recently, considerable evidence has accumulated that pancreatic secretion can regulate itself to some extent by a feedback loop (5). Pancreatic proteases in the intestine suppress CCK release and thus enzyme secretion by inactivation of a CCK-releasing factor. After a meal, proteases attack the meal components, freeing up this CCK-releasing factor which then stimulates CCK release. Bile salts also play a role in this feedback regulation (6).

Etiologic Factors in pancreatitis.

Pancreatitis has many possible etiologies but the underlying mechanisms that produce cellular injury are poorly understood. In all cases of pancreatitis, proteases are activated either with the cells themselves or within the intrapancreatic ducts. Normally, there are several mechanisms that protect against intrapancreatic activation (7): 1. Enzymes are synthesized in an inactive form (proenzymes); 2. The zymogen granules that contain the proenzymes are separated from the rest of the cell by a membrane; 3. The pH inside the zymogen granule is acidic, preventing activation; and 4. A trypsin inhibitor is secreted into the intrapancreatic ducts along with the enzymes which slows activation until the intestinal lumen is reached.

The most widely accepted theories of the pathogenesis of pancreatitis are that obstruction to pancreatic outflow or reflux of bile and duodenal contents into the pancreatic duct lead to pancreatic inflammation. At least some types of pancreatitis are due to direct toxic effects, nutritional deficiencies, vascular insufficiency or allergic reactions. Despite much interest in this area, each proposed theory has serious defects.

Experimental pancreatitis can be produced by a variety of diets, drugs or surgical manipulations but these models do not closely approximate the development of pancreatitis in humans. Premature activation of trypsin, lipase and phospholipase A_2 have all been shown in experimental models to be important in producing pancreatitis.

Table 2. Enzymatic mechanisms of pancreatitis.

Enzyme	Mechanisms of Injury
Trypsin	1. Releases histamine and kallikrein which increase vascular permeability. 2. Directly damages blood vessel walls. 3. Converts pancreatic proenzymes to active enzymes.
Lipase	1. Hydrolyzes triglycerides to fatty acids which destroy pancreatic cell membranes.
Phospholipase A	1. Converts biliary lecithin to lysolecithin which breaks down membranes of cells and organelles. 2. Causes both pancreatic and sometimes systemic coagulation necrosis.

In the United States, *excessive alcohol consumption* and *gallstones* cause about 65% of cases of acute pancreatitis while no cause is found in another 20% of cases referred to as *idiopathic pancreatitis*. Therefore, all other causes of pancreatitis are relatively rare but should be sought because they are potentially treatable. These less common causes include *drugs, infections, trauma including surgery and endoscopic retrograde cholangiopancreatigram (ERCP), renal transplant, hyperlipidemia, hypercalcemia, penetrating ulcer, cancer, hereditary causes, and perhaps rarely anatomic or functional problems such as pancreas divisum and sphincter of Oddi dysfunction*.

The epidemiology of *alcoholic pancreatitis* mirrors the epidemiology of excessive alcohol consumption. Men outnumber women by 3 to 1. Patients are generally between 30 and 45 years of age. The younger age of the patients may explain the lower mortality of alcoholic pancreatitis compared to biliary pancreatitis or idiopathic pancreatitis. In general, the initial episode of alcoholic pancreatitis will be the most severe. Technically speaking, all patients with acute alcoholic pancreatitis already have chronic pancreatitis histologically, and although the patient may return to normal clinically after the episode has resolved, permanent pancreatic damage exists.

Gallstone pancreatitis occurs in the patients most likely to have cholesterol gallstones. Thus this form of pancreatitis is more common in women than men by 2 to 1, and occurs in a somewhat older age group, peaking between ages 50 and 70. Again, the initial episode of pancreatitis is most likely to be the worst. Fifty percent of patients with gallstone pancreatitis will have repeated attacks if left untreated while cholecystectomy prevents recurrent episodes in virtually all patients. Small gallstones are more dangerous than large ones, which generally cannot pass into the cystic duct but remain in the gallbladder.

Idiopathic pancreatitis clinically resembles gallstone pancreatis in its patient population and mortality. However, the recurrence rate is less than half of that seen in gallstone pancreatitis.

Drug-induced pancreatitis is actually quite uncommon in light of the very large number of drugs taken in our society. Although pancreatitis has been reported in association with a very large number of drugs, the evidence that a specific drug is actually causative is difficult to obtain since rechallenging the patient is generally felt to be dangerous and contraindicated. *Azathioprine* and its metabolite, *6-mercaptopurine*, cause a generally mild pancreatitis in about 3-6% of patients who take these drugs (8), most commonly given for inflammatory bowel disease or after organ transplant. This pancreatitis is felt to be a hypersensitivity reaction. *Thiazide diuretics* occasionally cause pancreatitis, which can be fatal (9). The risk of pancreatitis increases with dose and duration of treatment. Its incidence is quite low considering the frequency with which these drugs are prescribed. *Sulfonamides* rarely produce pancreatitis, probably by an allergic mechanism since symptoms of vasculitis occur in most patients (10). *Tetracycline*, like thiazide diuretics, causes pancreatitis in relation to increasing dose and duration of use. The pancreatitis is complicated by simultaneous liver disease, and prognosis is quite serious, with a high mortality rate. *Estrogens* produce pancreatitis by elevating serum triglycerides, usually to greater than 3,500 mg/dl (10). In patients with normal triglycerides, estrogens are not associated with pancreatitis. *Valproic acid* (11) and *sulindac* have both been associated with cases of pancreatitis. Drugs which probably cause pancreatitis include *chlorthalidone, ethacrynic acid, L-asparaginase, phenformin, methyldopa*, and rarely, *steroids*.

A list of other uncommon but documented causes of pancreatitis appears in Table 3.

Table 3. Uncommon, non-drug related causes of pancreatitis.

• Trauma	• Infections
• Hyperlipidemia	• Ascaris
• Hypercalcemia	• Hereditary
• Penetrating ulcer	• Pancreas divisum
• Cancer	• Sphincter of Oddi dysfunction

The most simple pathological form of pancreatitis is edematous pancreatitis. Symptoms and pancreatic swelling resolve without sequelae. The pancreas is pale and boggy with fluid between the pancreatic lobules. Acinar cell necrosis does not occur but fat necrosis may be present.

More severe pancreatic injury results in necrosis and/or hemorrhage of the pancreas, leading to severe systemic symptoms and local complications such as phlegmons, pseudocyst, abscess, fistula, pancreatic ascites or structuring of the pancreatic duct, duodenum or even colon. After an acute attack of pancreatitis is over, it takes weeks or months for endocrine and exocrine pancreatic function to return entirely to normal.

CLINICAL PRESENTATION OF ACUTE PANCREATITIS

Symptoms and Signs.

The *diagnosis* of pancreatitis rests principally on its clinical features of epigastric pain often radiating to the back, nausea and vomiting, fever, and volume depletion. Jaundice may occur but hematemesis is much more unusual. Some slow GI bleeding occurs in about 10% of patients due to gastric or duodenal inflammation secondary to the contiguous inflamed pancreas; these patients rarely require transfusion.

Serum Amylase

Elevated serum amylase concentrations are quite useful in confirming the clinical diagnosis, but both false negatives and positives occur (12-14). When serum amylase is normal, serum lipase will usually be elevated, but about 5% of patients with clinical symptoms and CT findings of acute pancreatitis will have normal serum concentrations of both amylase and lipase (15,16). Amylase may be elevated by many problems other than pancreatitis, as listed in Table 4. It has been proposed that the amylase-creatinine clearance ratio (ACR) can help differentiate pancreatitis from these other conditions, because amylase is more rapidly cleared than creatinine in the early stages of acute pancreatitis due to decreased renal tubular reabsorption of amylase. The normal ACR ranges from 1-4%, and is calculated as follows:

$$ACR = \frac{Amylase_{urine} \times Creatinine_{serum}}{Amylase_{serum} \times Creatinine_{urine}} \times 100.$$

Table 4. Causes of Hyperamylasemia.

Condition	ACR
Chronic pancreatitis	N
Pancreatic pseudocyst	N
Carcinoma of pancreas	N
Common bile duct obstruction	N
Peptic ulcer penetrating into pancreas	N
Peptic ulcer perforation	N
Mesenteric infarction	N
Salivary adenitis	N
Acute alcoholism	N
Hepatocellular disease	N
Opiate administration	N
Ovarian neoplasm	N
Macroamylasemia	N
Acute pancreatitis	↑
Postoperative state	↑
Burns	↑
Diabetic ketoacidosis	↑
Chronic renal insufficiency	↑
Pancreatic duct rupture	?
Acute cholecystitis	?
Afferent loop obstruction	?
Salpingitis	?
Ruptured ectopic pregnancy	?
Post ERCP	?

- From Ref. 10.

Calculation of the ACR is simple and may occasionally be helpful, but is often unable to distinguish mild pancreatitis from other conditions. In most cases, it is not helpful to determine ACR.

The *differential diagnosis* of acute pancreatitis includes several serious problems that require urgent surgical management, thus the importance of early and accurate assessment of the patient. The major serious illnesses that can mimic acute pancreatitis include perforated peptic ulcer, acute cholangitis, and mesenteric infarction. *Perforated peptic ulcer* generally has a very abrupt onset of severe and is associated with prominent peritoneal signs such as abdominal rigidity. In at least 75% of cases, free air

in the abdomen is apparent on chest radiograph or plain film of the abdomen. Perforations into the lesser sac or retroperitoneal tissues may be more difficult to detect. *Acute cholangitis*, like pancreatitis, has an onset over minutes to a few hours. Temperature elevations may be higher in cholangitis, and pain is more likely to be localized to the right upper quadrant. *Mesenteric infarction* is almost always difficult to diagnosis, but should be considered in older patients or those with a history of vascular disease. The pain of mesenteric infarction is generally more gradual in onset than that of pancreatitis. An important clinical clue is that the patient's pain is often out of proportion to the relatively normal abdominal examination. In a very ill patient in whom the diagnosis is in doubt, surgery is indicated.

The clinical evaluation of acute pancreatitis has been greatly aided by the establishment of specific criteria such as those of Ranson (Table 5) which allow for planning therapy and evaluating treatments in clinical trials. Not only initial clinical features are important but progression over the first 48 hours of the illness.

Table 5. Poor prognostic factors in acute pancreatitis.

On admission	After 48 hours
Age > 55 yrs	Hct ↓ > 10%
WBC $\geq$ 16,000	BUN ↑ > 5
Glucose > 350	Calcium < 8
LDH > 350	pO_2 < 60
AST 250	Base deficit > 4 mEq
	Fluid sequestration > 6L

- Ranson, Ref. 17.

Ranson's criteria accurately distinguish patients with an excellent prognosis (0 - 2 factors present) to those with a poor prognosis (5 - 6 factors present). When a patient has greater than 6 poor prognostic factors present, his disease is almost uniformly fatal.

Because Ranson's criteria are somewhat difficult to remember, others have attempted to simplify these prognostic signs. One such simplified scheme is shown in Table 6. It is not yet clear whether such a scheme will have the accuracy of Ranson's criteria in correctly predicting outcome.

Table 6. Simplified list of poor prognostic factors in acute pancreatitis.

System	During initial 48 hours
Cardiac	BP < 90 mm Hg Tachycardia > 130/min
Pulmonary	Dyspnea pO_2 < 60 mm Hg
Renal	Urinary output < 50 mL/h
Metabolic	Calcium < 8 mg/dl Albumin < 3.2 g/dL

- From Ref. 18.

MANAGEMENT OF ACUTE PANCREATITIS

When pancreatitis is mild to moderate, treatment generally involves little more than volume repletion and pain control with nasogastric suction as needed for vomiting. Patients should be given sufficient medication to relieve pain. Meperidine hydrochloride is preferable to morphine because it has less tendency to cause spasm of the sphincter of Oddi. Fluid sequestration can be considerable even in mild pancreatitis; up to 30% of the circulating plasma volume may form a peripancreatic exudate. Some physicians suggest that a unit (12.5 g) of albumin should be given for each liter of fluid for deficits greater than 2 or 3 L (Ref. 10.) Symptoms will resolve in about four to seven days; persistence of symptoms or recurrent symptoms when the patient begins eating again may suggest the development of a complication such as a pseudocyst or abscess although it occurs in 10 - 20% of patients. Amylase elevations may persist up to two weeks in about 10% of patients, but should prompt a search for pseudocyst formation. Routine treatment with antibiotics should not occur; many patients will have low-grade temperature elevations and leukocytosis without bacterial infection.

Severe pancreatitis is less common than mild to moderate pancreatitis, and has a high morbidity and mortality. Hospital stays of up to 60 days are common with about half this time spent in intensive care. Mortality results from a variety of complications, summarized in Table 7, which will be discussed in more detail later.

Table 7. Causes of Death in Acute Pancreatitis.

First Week	After First Week
Cardiovascular collapse	Generalized sepsis
ARDS	Pneumonitis
Intraabdominal hemmorhage	Pancreatic abscess
Acute renal failure	
Acute cholangitis	

Patients with severe pancreatitis generally are hypotensive and need large volume resuscitation. If this is not sufficient to stabilize blood pressure, then pressor agents should be added in as low a dose as possible, with dopamine as a first choice to protect renal blood flow. Oxygen by nasal cannula is routinely required and many patients eventually require ventilator support.

In addition to intensive support with fluids, oxygen and pressor agents as needed, modalities such as antibiotics and lavage with or without added protease inhibitors are often tried. Progress in clinical research is handicapped by the relative rarity of severe cases which makes it difficult to accumulate cases for statistical analysis. Peritoneal lavage has not been clearly shown to affect mortality in well-designed trials (Table 8).

Table 8. Complications and Outcome in Patients with Severe Pancreatis Treated with Peritoneal Lavage.

Complication	Lavage N = 45	Control N = 46
Fatal	12	13
Major	32	25

- From Ref. 19.

Modification such as prolonged lavage in severe cases may decrease some of the infectious complications, although this has not been borne out in initial studies by Ranson's group (Table 9).

Table 9. Outcome in Patients with Acute Pancreatitis Treated with Long Versus Short Lavage.

	All	3 - 4 Signs	≥ 5 Signs
Long Lavage			
Patients	21	5	16
Deaths	6	0	6
Abscess	4	0	4
Short Lavage			
Patients	18	8	10
Deaths	5	0	5
Abscess	6	2	4

- From Ref. 20.

Protease inhibitors probably should be considered experimental at this point, although pancreatitis in animal models is ameliorated with their use.

In general, *surgery for acute pancreatitis* is rarely needed (21). Indications are pancreatic sepsis with infected pseudocysts or abscesses, rare gastrointestinal perforations, unresolved mature pancreatic pseudocysts, and very rarely protracted pancreatitis with necrosis (22) or when the diagnosis is unclear and the patient is deteriorating.

Biliary pancreatitis forms a special category of cases of acute pancreatitis. If underlying gallbladder or common duct stones are not dealt with reasonably soon, the incidence of recurrent pancreatitis in the next six weeks to six months is quite high. The more widespread use of endoscopic sphincterotomy has increased interest in using nonoperative intervention in at least some of these cases. A controlled trial by Neoptolemos and others found that in *severe* cases of biliary pancreatitis, ERCP to extract stones within three days resulted in fewer complications and shorter hospital stays than when patients were treated with conventional therapy (23). In contrast, early surgery (less than 48 hours) results in increased mortality in severe pancreatitis, and should be delayed (24).

Table 10. Preoperative Endoscopic Sphincterotomy Versus Surgery Alone for Common Bile Duct Stones in the Absence of Pancreatitis.

	N	Duct Cleared	Major Complications
ERCP + Surgery	55	91%	16%
Surgery Alone	60	92%	16%

- From Ref. 25.

Table 11. Complications in Patients with Pancreatitis Treated with Endoscopic Sphincterotomy.

	Mild		Severe	
	ES	Control	ES	Control
	N = 34	N = 34	N = 25	N = 28
Pseudocyst	3	4	3	8
Endoscopic Complications	1	0	3	12
Death	0	0	1	2

- From Ref. 26.

The issue of whether all patients with biliary pancreatitis must undergo definitive operative treatment is unclear at present. In the absence of pancreatitis, ERCP with sphincterotomy to clear the common duct followed by simple cholecystectomy appears about equal in efficacy and safety to surgery alone. Although surgery or endoscopic therapy is clearly indicated to prevent recurrent pancreatitis, selection of therapy should be guided by the ability of the patient to withstand surgery and the relative technical abilities and experience of the physicians and surgeons caring for the patient. The current accepted approach to therapy of biliary pancreatitis is outlined in the following flow diagram.

Table 12. THERAPEUTIC APPROACH TO BILIARY PANCREATITIS

MILD	SEVERE
Supportive	Short trial of supportive care
↓	↓
Resolution	Nonresolution
↓	↓
↓	ERCP with sphincterotomy
↓	↓
Elective surgery ± ERCP with sphincterotomy	Elective surgery

IMAGING STUDIES IN ACUTE PANCREATITIS

Imaging studies in acute pancreatitis are not as important for diagnosis as for detection of complications and to look for treatable problems such as gallstones. The chest radiograph is important to assess baseline status of the heart and lungs, since patients with severe pancreatitis may develop cardiac or respiratory complications. Some patients develop pleural effusions. Atelectasis is common. In addition to the chest radiograph, the three major studies which can be useful are the plain film of the abdomen, the abdominal sonogram and the abdominal CT scan.

Plain Film of the Abdomen

All patients with suspected acute pancreatitis should have plain films of the abdomen, with both an anterior-posterior view and either an upright film or a left lateral decubitus. In general, these patients will have normal radiographs or nonspecific findings such as an ileus or gastric dilatation. Rarely a mass will be seen in patients with pseudocyst or abscess. In patients with suspected alcoholic pancreatitis, calcifications of the pancreas support the diagnosis of chronic pancreatitis with an acute episode superimposed. An important reason to order abdominal films is to detect pathology other than pancreatitis such as free air from a perforated viscus.

Abdominal Sonogram

The great usefulness of the abdominal sonogram in patients with acute pancreatitis is in detecting *gallstones* with or without ductal dilatation and later in the course identifying and following pseudocysts. The *sonogram* is both sensitive and specific for these purposes (27), and has the advantages of being safe, relatively inexpensive, and widely available. In mild pancreatitis, the sonogram may be normal, but in more advanced cases, the pancreas will often appear enlarged and hypoechogenic. Hemorrhage in and around the pancreas causes increased echoes. The sonogram unfortunately is frequently limited by the presence of small bowel dilatation which may obscure the pancreas. All new cases of pancreatitis should be evaluated with sonography, but in patients with multiple, clinically similar admissions for acute alcoholic pancreatitis, frequently repeated sonography is not indicated.

Abdominal CT Scan

The abdominal CT scan is rarely useful in uncomplicated acute pancreatitis. It is best reserved for diagnosis and treatment of complications such as abscesses which may occur late in the course of acute pancreatitis. In early pancreatitis, like the sonogram, the abdominal CT scan will show either no abnormalities or a diffusely enlarged gland. The head of the gland is sometimes particularly enlarged, which may raise the question of pancreatic cancer. Follow-up examination generally shows resolution after several weeks or months. In more severe cases of pancreatitis, the peripancreatic fat often develops a streaky appearance due to fat necrosis. When intravenous contrast material is given, necrotic areas of the pancreas will not perfuse well, allowing visualization of phlegmons (exudates), pseudocysts or hemorrhage (28). A very important use of the CT scan is to allow direct visualization and aspiration of these collections when sepsis is suspected (29), as discussed in more detail later. Occasionally, pseudocysts can be drained by placing drainage catheters under CT guidance.

COMPLICATIONS OF ACUTE PANCREATITIS

Complications of acute pancreatitis can be either systemic, occurring generally earlier in the course, or localized to the pancreas and surrounding organs.

Systemic complications

Systemic complications tax the best efforts of physicians and intensive care nursing units, involving often total body failure. The most common of these complications are hypovolemia and shock, hypocalcemia, hyperlipidemia, hyperglycemia, coagulation abnormalities, respiratory complications, renal problems and less often arthritis, bone and skin lesions (30).

Hypovolemia and shock with cardiac decompensation is the cause of the majority of deaths in acute pancreatitis. As in sepsis, the cardiac index increases and the systemic vascular resistance increases (31-34). There are probably both cardiac and

peripheral vascular depression due to multiple metabolic agents released in severe pancreatitis. The kinin system is activated, there is an increase in prostaglandins. and trypsin in the pancreas initiates bradykinin that increases vascular permeability. The pancreatic acinar cells release a myocardial depressant factor (35) which has not been structurally characterized. Fluid sequestration due to increased vascular permeability is a major factor in the pathophysiology of shock, but aggressive fluid replacement and even administration of fresh plasma does not reverse hypotension in some patients.

Hypocalcemia less than 8.0 mg/dl is seen in a large proportion of patients with acute pancreatitis (30 - 60%) (36-39) and denotes a poorer prognosis. Hypocalcemia is generally worst in the first several days of the illness (38). There are several explanations for the hypocalcemia of pancreatitis: 1. Total calcium measurements are falsely low due to commonly occurring hypoalbuminemia. Either ionized calcium should be corrected or total calcium concentrations corrected for decreased serum albumin. When this is done, true hypocalcemia probably occurs in only 10 -15% of patients (38). 2. Calcium forms a soap in areas of fat necrosis, sequestering large amounts of calcium (36). 3. Hormonal abnormalities may contribute to hypocalcemia (hyperglucagonemia (39,40), failure of PTH secretion (41,42), hypomagnesemia (43), hydrolysis of circulating PTH (44). 4. Increased free fatty acids released in acute pancreatitis bind to albumin and calcium and then are cleared from the circulation into fat, muscle and liver (45). On a practical clinical level, hypocalcemia and hypomagnesemia must be corrected. Hypokalemia should be corrected at the same time to prevent cardiac arrhythmias.

Hyperlipidemia may be either the cause or consequence of acute pancreatitis. About 20% of patients with acute pancreatitis have hyperlipidemia (46). High triglyceride concentrations may occur with normal cholesterol concentrations. It is important to recognize hyperlipidemia for several reasons: 1. In a minority of patients, hyperlipidemia may be the primary cause of pancreatitis, so should be treated appropriately when the patient recovers to prevent recurrences. 2. Patients who develop acute respiratory distress syndrome are more likely to have hypertriglyceridemia (47). 3. Hyperlipidemia can lead to fat embolization in the brain and other organs. 4. Serum amylase may be falsely depressed in patients with hyperlipidemia, confusing the diagnosis of acute pancreatitis.

Hyperglycemia is another poor prognostic sign in acute pancreatitis. As many as 2 - 10% of patients may develop diabetes after an episode of severe acute pancreatitis (49). Although more studies are needed, it appears that patients with acute pancreatitis have increased concentrations of glucagon and cortisol as well as inappropriately low insulin concentrations. During the acute illness, it is generally not necessary to treat hyperglycemia unless it is severe since patients may be quite sensitive to insulin and develop hypoglycemia.

Coagulation abnormalities in acute pancreatitis can cause disseminated intravascular coagulopathy (DIC), bleeding and intravascular thrombosis. Patients with acute pancreatitis and DIC do not respond well to heparin therapy. Although 5 - 10% of patients may have some upper gastrointestinal hemorrhage from inflammation of the stomach and duodenum, transfusion is rarely necessary. More rarely, pancreatic

inflammation causes erosion of a major intraabdominal vessel with internal hemorrhage. Angiography is the best method for diagnosing this, and in centers equipped to do so, embolization may obviate the need for surgery.

Respiratory complications in acute pancreatitis are commonly organized into three categories (30): 1. About 60% of patients have mild respiratory insufficiency with arterial hypoxemia but no clinical or radiographic abnormalities in the first few days of illness. These patients need to be given oxygen and monitored for response with blood gas determinations but rarely need other treatment. 2. About one-third of patients have not only hypoxia but demonstrable abnormalities such as pleural effusions, atelectasis, elevation of the diaphragm, or pulmonary infiltrates. 3. About 10 - 15% of patients with acute pancreatitis develop adult respiratory distress syndrome, with ventilation/perfusion mismatch, severe hypoxia, and fluffy pulmonary infiltrates. Patients require close attention to fluid balance and intubation and ventilatory assistance with positive end-expiratory pressures. Steroids are often given, but probably are not beneficial (50). Proposed mechanisms for pathogenesis include decreased trypsin inhibitors with increased circulating trypsin which damages the lungs, increased lecithinase in the serum which may degrade pulmonary surfactant, toxic levels of circulating free fatty acids, and generation of biologically active complement-derived peptides.

Renal complications in acute pancreatitis are serious, and are due primarily to shock and tubular necrosis. Patients also may develop deposits of fibrin and fibrinogen in the glomerular capillaries. Acute renal failure in conjunction with acute pancreatitis carries a mortality rate of 80% (51,52).

Arthritis, bone and skin lesions are generally due to metastatic fat necrosis from circulating pancreatic lipase. Skin lesions appear like erythema nodosum, but are found on the thorax, buttocks and thighs as well as on the pretibial and malleolar areas.

Local complications

Local pancreatic and peripancreatic fluid collections can be divided into *pseudocysts, phlegmons*, and *abscesses*. Sonography and abdominal CT scanning are essential for good diagnosis and management of these problems. The distinctions between these three categories can be quite blurred. The *pseudocyst* is an encapsulated collection of fluid arising initially from the pancreas. There is no true wall composed of cells, thus the name pseudocyst. The pseudocyst contains pancreatic enzymes and debris. Although most pseudocysts are in or near the pancreas, frequently in the lesser sac, they may track through the retroperitoneal tissues into distant locations such as the pelvis or mediastinum. Frequent use of the sonogram in patients with acute pancreatitis has shown us that pseudocysts are exceedingly common; most are small are resolve without sequelae and require no specific treatment. Up to 50% of patients with severe pancreatitis may develop pseudocysts (53). Continuing abdominal pain in a patient with acute pancreatitis after a week of therapy may indicate pseudocyst formation. In patients with elevated amylase concentrations after three weeks of observation, 50% have pseudocysts. However, it should be noted that half of patients with pseudocysts have normal amylase concentrations. Pseudocysts larger than 5 cm

generally require surgical treatment. Generally the patient should be observed for four to six weeks to allow the wall, composed of fibrous tissue, to form. Then the patient should have either excision of the cyst (usually technically not feasible) or internal drainage into the stomach, duodenum or jejunum (54). External surgical drainage should be avoided except in critically ill patients, since about 30% will develop pancreatic fistulas. As mentioned earlier, in some centers percutaneous drainage with CT-placed catheters is tried initially and surgery performed only if the procedure is unsuccessful

Pancreatic phlegmons are poorly localized collections of necrotic material, fluid and pancreatic enzymes. Sometimes phlegmons form a fibrous wall and then are referred to as pseudocysts. Phlegmons do not need particular treatment, but clinically are quite difficult to distinguish from pancreatic abscesses.

Pancreatic abscesses occur when pseudocysts or more commonly phlegmons become infected. Eventually frank pus will form. This complication is more frequent by far in patients with necrotic, hemorrhagic pancreatitis. As many as 9% of these patients develop an abscess. Sonography and CT scan cannot distinguish between sterile and infected fluid collections. Recent studies have shown that CT scan can be used to predict patients with a high chance of developing abscess (Table 13).

Table 13. Relationship Between Initial CT Grade and Incidence of Pancreatic Abscess and Related Death.

	Initial CT Grade				
	A	B	C	D	E
Number of Patients	12	19	17	12	23
Number of Abscesses	0	0	2 (12%)	2 (17%)	14 (61%)
Number of Abscess Deaths	0	0	0	1 (8%)	4 (17%)
Average Hospital Stay (days)	13	17	25	30	52

- Ref. 55.

Abscesses occur relatively late in the course of acute pancreatitis, often two to three weeks after diagnosis. The most common clinical findings are fever, leukocytosis and clinical deterioration. These symptoms occur very frequently in patients with severe sterile pancreatitis as well, as shown in Table 14.

Table 14. Temperature and Leukocyte Count 24 Hours Before Aspiration of the Pancreas.

	N	Temperature	WBC X 10^3
Sterile	50	101.3 ± 1.5	20.8 ± 9.9
Infected	42	102.1 ± 2.1	20.7 ± 8.0

- From Ref. 29

Early diagnosis and surgical treatment of pancreatic abscess is essential for the patient's survival, but surgery itself has a high morbidity and mortality in these critically ill patients, so should be avoided unless necessary. When a pancreatic abscess is suspected on clinical grounds, CT scan with aspiration of any fluid collections should be performed to obtain material for culture and to make the correct decision regarding surgical management. This aspiration is done with a 20 gauge needle, and in experienced hands appears to be quite safe. Gerzof et al. reported that a wide variety of organisms caused pancreatic abscess, and that abscesses occurred earlier than generally suspected purely on clinical grounds (Table 15).

Table 15. Interval between Onset of Pancreatitis and Documentation of Pancreatic Sepsis by Guided Aspiration in 36 Patients.

Days	Patients
1-7	8
8-14	12
15-21	8
22-28	3
29-35	2
>35	3

- From Ref. 29.

Guidelines for CT-guided aspiration of pancreatic fluid collections are summarized in Table 16.

Table 16. CT-guided Aspiration of Pancreatic Fluid Collections.

- Aspirate for combination of fever, leukocytosis and (+) CT scan.
- Pseudocysts and phlegmons should be aspirated promptly due to high risk of infection.
- Extrapancreatic fluid collections usually sterile and may be observed a few days.
- Recurrence of symptoms after treatment warrants a repeat aspiration.

Pancreatic fistulas remain an unusual but difficult management problem (56). Pancreatic fistulas are frequently a complication of trauma or pancreatic surgery with associated pancreatitis. Prolonged total parenteral nutrition with resulting pancreatic rest sometimes allows fistulas to close. Repeated surgeries may be required. Use of injectable somatostatin analog (octreotide) is theoretically appealing and sometimes done although there is still primarily anecdotal evidence to support this therapy (57,58).

Pancreatic ascites is another fairly rare complication of acute pancreatitis. It represents a leaking pancreatic duct or pseudocyst, and occurs much more often in chronic pancreatitis than acute pancreatitis. The characteristics of ascitic fluid in pancreatic ascites and several other common forms of ascites are shown in Table 17.

Table 17. Characteristics of Ascitic Fluid.

Disease	Protein Content	White Cells	Amylase	Serum/Ascites Albumin Gradient
Pancreatic Ascites	High	Low	High	< 1.1
Malignancy	High	Low	Low	< 1.1
Cirrhosis	Low	Low	Low	> 1.1
Cirrhosis with SBP*	Low	High	Low	> 1.1

* SPB = spontaneous bacterial peritonitis

- From Ref. 59

Most patients will spontaneously close these leaks with total parenteral nutrition and require no specific treatment other than paracentesis as needed for comfort. Octreotide has also been suggested for use in refractory pancreatic ascites. If ascites continue to accumulate after more than three or four weeks, then ERCP to detect the location of the leak followed by surgery is indicated.

ADDENDUM

The following case illustrates some of the problems encountered in diagnosing and caring for a patient with acute pancreatitis.

W. J. was a 42 y.o. white male who presented to the emergency room complaining of several hours of severe epigastric pain radiating into the back. This severe pain was of fairly sudden onset, but the patient had noticed similar and less severe pain partially relieved by antacids and food for the last two weeks. He was unable to take antacids on the day of admission due to severe nausea and vomiting. The patient had a history of duodenal ulcer disease diagnosed by UGI series 15 years ago, and had experienced at least five clinical episodes of recurrent ulcer symptoms which responded to either antacids or H_2-blocker therapy. During the last episode about a year ago, his family doctor had ordered a sonogram which showed probable gallstones but no ductal dilatation. The patient had a history of heavy alcohol intake until that time; he then stopped drinking until a month ago when he lost his job. He then began drinking up to a quart of whiskey daily. Past medical history was otherwise negative except for a history of hypertension treated for the last two years with a thiazide diuretic.

On physical examination, the patient had a temperature of 100.1 ° F, blood pressure was 90/50, pulse was 122 and respiratory rate was 22. The patient was in obvious pain and appeared agitated. Positive findings on physical examination included dry mucous membranes and decreased skin turgor, decreased breath sounds and dullness to percussion over the left lower chest, decreased bowel sounds and diffuse guarding and abdominal tenderness most marked in the epigastrium.

On initial laboratory studies, sodium was 134, potassium was 3.1, chloride was 92 and bicarbonate was 24. Glucose was slightly elevated at 161, BUN was 47 and creatinine was 2.3. Amylase was 388, alkaline phosphatase was 180, calcium was 8.9, AST was 267, LDH was 327, albumin was 3.2, bilirubin was 2.2 , and WBC was 17,200. A plain film of the abdomen showed several dilated loops of small bowel with air/fluid levels.

W.J. was admitted to the ward and started on intravenous fluids and nasogastric suction. He was given meperidine with an antiemetic intramuscularly for pain. After several hours, he was noted to be quite restless and tachypneic. Arterial blood gas determination showed pH 7.34, pO_2 62 and pCO_2 25. Oxygen was started at 4 L/min by face mask. Due to continued restlessness and hypotension, the patient was transferred to the intensive care unit six hours after admission. He did poorly, requiring intubation and ventilation with positive end-expiratory pressures. Despite aggressive management, after 48 hours he was still hypotensive on a

dopamine infusion. Repeat laboratory tests showed pO_2 was 58, BUN had risen to 63, calcium was 7.8, the patient was still acidotic with a bicarbonate of 15, hematocrit had fallen to 34 from admission value of 46, and fluid sequestration was estimated to be about 4 liters.

After five days in the intensive care unit, W.J. expired from prolonged and profound cardiovascular collapse. Autopsy showed severe hemorrhagic pancreatitis, a normal heart, pulmonary congestion compatible with adult respiratory distress syndrome, acute tubular necrosis, and several areas of fat necrosis on the lower extremities. Despite several days of fever and leukocytosis, no evidence of sepsis was found. The gallbladder was distended but no stones were found.

REFERENCES

1. Chiari H. Untitled. Z. Heilk 1896;17:69-96.

2. Misiewicz JJ, Bartram CI, Cotton PB, Mee, AS, Price AB, Thompson RPH. Normal pancreas and pancreatic disease. In Slide Atlas of Gastroenterology. Gower Medical Publishing, London, 1984.

3. Bro-Rasmussen F, Kilman SA, Thaysen, JH. Acta Physio. Scand. 1956;37:97.

4. Valenzuela JE. Pancreatic physiology. In Medical and Surgical Diseases of the Pancreas. Ed. Valenzuela JE, Reber HA, Ribet A. Igaku-Shoin, New York, 1991.

5. Slaff J, Jacobson D, Tillman CR, et al. Protease-specific suppression of pancreatic exocrine secretion. Gastroenterology 1984;87:44-52.

6. Gomez G, Upp JR, Lluis F, et al. Regulation of the release of cholecystokinin by bile salts in dogs and humans. Gastroenterology 1988;94:1036-1046.

7. Valenzuela JE, Ribet A. Pathogenic mechanisms of pancreatitis. In Medical and Surgical Diseases of the Pancreas. Ed. Valenzuela JE, Reber HA, Ribet A. Igaku-Shoin, New York, 1991.

8. Sturdevant RAL, Singleton JW, Deren JJ, Law DH, McLeery JL. Azathioprine-related pancreatitis in patients with Crohn's disease. Gastroenterology 1979;77:883-886.

9. Cornish AL, McClellan JT and Johnston DH. Effect of chlorothiazide on the pancreas. J. Engl. J. Med. 1961;265:673-675.

10. Soergel KH. Acute pancreatitis. In Gastrointestinal Disease. Ed. Sleisenger MH, Fordtran JS. Third edition. W.B. Saunders Co., Philadelphia, 1983.

11. Parker PH, Helinek GL, Ghishan FK and Greene HL. Recurrent pancreatitis by valproic acid. A case report and review of the literature. Gastroenterology 1981;80:826-828.

12. Agarwal N, Pitchumoni CS, Sivaprasad AV. Evaluating tests for acute pancreatitis. Am. J. Gastroenterol. 1990;85:356-366.

13. Kolars JC, Ellis CJ, Levitt MD. Comparison of serum amylase, pancreatic isoamylase and lipase in patients with hyperamylasemia. Dig. Dis. Sci. 1984;29:289-293.

14. Collen MJ, Ansher AF, Chapman AB, Mackow RC, Lewis JH. Serum amylase in patients with renal insufficiency and renal failure. Am. J. Gastroenterol.

1990;85:1377-1380.

15. Spechler SJ, Dalton JW, Robbins AH, Gerzof SG, Stern JS, Jjohnson WC, Nabseth DC, Schimmel EM. Prevalence of normal serum amylase levels in patients with acute alcoholic pancreatitis. Dig. Dis. Sci. 1983;28:865-869.

16. Clavien P-A, Robert J, Meyer P, et al. Acute pancreatitis and normoamylasemia. Not an uncommon combination. Ann. Surg. 1989;210:614-620.

17. Ranson JHC. Etiologic and prognostic factors in human acute pancreatitis: a review. Am. J. Gastroenterol 1982;77:633-667.

18. Agarwal N, Piitchumoni CS. Simplified prognostic criteria in acute pancreatitis. Pancreas 1986;1:69-73.

19. Mayer AD, McMahon MJ, Corfield AP, et al. Controlled clinical trial of peritoneal lavage for the treatment of severe acute pancreatitis. N. Engl. J. Med. 1985;312:399-438.

20. Ranson JHC, Berman RS. Long peritoneal lavage decreases pancreatic sepsis in acute pancreatitis. Ann. Surg. 1990;211:708-718.

21. Ranson JH. The role of surgery in the management of acute pancreatitis. Ann. Surg. 1990;211:382-392.

22. Kivilaakso E, Lempinen M, Makelainen A, Nikki P, Schroder T. Pancreatic resection versus peritoneal lavation of acute fulminant pancreatitis. A randomized prospective study. Ann. Surg. 1984;199:426-431.

23. Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet 1988;2:979-983.

24. Kelly TR, Wagner DS. Gallstone pancreatitis: A prospective randomized trial of the timing of surgery. Surg. 1988;104:600-605.

25. Neoptolemos, JP, Carr-Locke, DL, Fossard, DP. Prospective randomised study of preoperative endoscopic sphincterotomy versus surgery alone for common bile duct stones. Br. Med. J. 1987;294:470-474.

26. Neoptolemos, JP, Carr-Locke, DL, London, N, Bailey I, Fossard, DP. ERCP findings and the role of endoscopic sphincterotomy in acute gallstone pancreatitis. Br. J. Surg. 1988;75:954-960.

27. Scholmerich J, Gross V, Johannesson T, et al. Detection of biliary origin of acute pancreatitis. Comparison of laboratory tests, ultrasound, computed tomography,

and ERCP. Dig. Dis. Sci. 1989;34:830-833.

28. Freeny PC. Angio-CT: Diagnosis and detection of complications of acute pancreatitis. Hepato-gastroenterol. 1991;38:1009-115.

29. Gerzof SG, Banks PA, Robbins AH, Johnson WC, Spechler SJ, Wetzner SM, Snider JM, Langevin RE and Jay ME. Early diagnosis of pancreatic infection by computed tomography-guided aspiration. Gastroenterology 1987;93:1315-20.

30. Pitchumoni CS, Agarwal N, Jain NK. Systemic complications of acute pancreatitis. Am. J. Gastroenterol. 1988;83:597-606

31. Cobo JC, Abraham E, Bland RD et al. Sequential hemodynamic and oxygen transport abnormalities in patients with acute pancreatitis. Surgery 1984;95:324-330.

32. Beger HG, Bittner R, Buchler M et al. Hemodynamic data pattern in patients with acute pancreatitis. Gastroenterology 1986;90:74-79.

33. Ito K, Ramirez-Schon G, Shah PM et al. Myocardial function in acute pancreatitis. Ann Surg. 1980;194:85-88.

34. Bradley EL, Hall JR, Lutz J et al. Hemodynamic consequences of severe pancreatitis. Ann Surg. 1983;198:130-133.

35. Lefer AM, Glenn TM, O'Neill TJ et al. Inotropic influence of endogenous peptides in experimental hemorrhagc pancreatitis. Surgery 1971;69:220-228.

36. Edmondson HA, Fields IA. Relation of calcium and lipids to acute pancreatic necrosis: Report of fifteen cases, in one of which fat embolism occurred. Arch. Intern. Med. 1942;69:177-190.

37. Ranson HC, Rifkind KM, Roses DF, et al. Objective early identification of severe acute pancreatitis. Am. J. Gastroenterol. 1974;61:443-451.

38. Imrie CW, Allam B, Ferguson JC. Hypocalcemia of acute pancreatitis. The effect of hypoalbuminemia. Curr. Med. Res. Opin. 1976;4:101-116.

39. Paloyan E, Paloyan D, Harper PV. The role of glucaogn hypersecretion in the relationship of pancreatitis and hyperparathyroidism. Surgery 1967;62:167-173.

40. Bierge SJ, Avioli LV. Glucagon-induced hypocalcemia in man. J. Clin. Endocrinol. Metab. 1969;29:213-218.

41. Roberston GM, Moore EW, Switz DM, et al. Inadequate parathyroid response in acute pancreatits. N. Engl. J. Med. 1976; 294:512-516.

42. Drew SI, Joffe B, Vinik A, et al. The first 24-hours of pancreatitis. Changes in biochemical and endocrine homeostasis in patients with pancreatitis compared with those in control subjects undergoind stress for reasons other than pancreatitis. Am. J. Med. 1978;64:795-803.

43. Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. Clin. Endocrinol. 1976;5:209-224.

44. Hermon-Taylor J, Majee AI, Grant DAW, et al. Cleavage of peptide hormones by beta 2-macroglobulin-trypsin complex and its relation to the pathogenesis and chemotherpay of acute pancreatits. Clin. Chim. Acta. 9181;109:203-209.

45. Warshaw AL, Lee KH, Napier TW, et al. Depression of serum calcium by increased plasma free fatty acids in the rat: A mechanism for hypocalcemia in acute pancreatits. Gastroenterology 1985;89:814-820.

46. Cameron JL, Capuzzi DM, Zuidema GD, et al. The incidence of lipid abnormalities in acute pancreatitis. Ann. Surg. 1973;177:483-489.

47. Warshaw AL, Lesser PB, Rie M, et al. The pathogenesis of pulmonary edema in acute pancreatitis. Ann. Surg. 1975;182:505-510.

48. Lesser PB, Warshaw AL. Diagnosis of pancreatitis masked by hyperlipemia. Ann. Intern. Med. 1975;82:795-798.

49. Kasper H, Sommer H. Klinik der akuten pankreatits. In: Forrell MM, ed. Handbuch der Inneren Medizin, Band 3, Teil 6. Pankreas. 5. Auflage Berlin, Heidelberg, New York: Springer Verlag, 1976.

50. Raffin TA. Novel approaches to ARDS and spesis. In: Chernow B, Shoemaker WC, eds. Critical care state of art, vol. 7. The society of critical care medicine. 1986:247-280.

51. Frey CE. Pathogenesis of nitrogen retention in pancreatitis. Am. J. Surg. 1965;109:747-755.

52. Balslov JT, Jorgensen HE, Nielsen R. Acute renal failure complicating severe acute pancreatitis. Acta. Chir. Scand. 1962;124:348-354.

53. Kolars JC, Allen MO, Ansel H, Silvis SE, Vennes JA. Pancreatic pseudocysts: clinical and endoscopic experience. Am. J. Gastroenterol. 1989;84:259-264.

54. Warshaw AL, Rattner DW. Timing of surgical draining for pancreatic pseudocyst. Clinical and chemical criteria. Ann. Surg. 1985;202:720-724.

55. Ranson JHC, Balthazar E, Caccavale R, Cooper M. Computed tomography and

the prediction of pancreatic abscess in acute pancreatitis. Ann. Surg. 1985;202:656-663.

56. Warshaw AL, Moncure AC, Rattner DW. Gastrocutaneous fistulas associated with pancreatic abscesses. An aggressive entity. Ann. Surg. 1989;210:603-607.

57. Kwan D, Aufses AH Jr. Short-term administration of SMS 201-995 in the management of an external pancreatic fistula. Am. J. Gastroenterol. 1989;84:326-328.

58. Prinz RA, Pickleman J, Hoffman JP. Treatment of pancreatic cutaneous fistulas with a somatostatin analog. Am. J. Surg. 1988;155:36-42.

59. Reber HA, Cryer HG. Local complications of pancreatitis including pseudocyst and ascites. In Medical and Surgical Diseases of the Pancreas. Ed. Valenzuela JE, Reber HA, Ribet A. Igaku-Shoin, New York, 1991.